2022 Qualifying Condition Form

Upon petition, the State Medical Board of Ohio has the authority to approve and designate conditions or diseases as qualifying medical conditions for treatment with medical marijuana. For the calendar year of 2022, the board will accept petitions for consideration between November 1, 2022 and December 31, 2022.

The following conditions are already part of the program: AIDS, amyotrophic lateral sclerosis, Alzheimer's disease, cachexia, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy or another seizure disorder, fibromyalgia, glaucoma, hepatitis C, Huntington's disease, inflammatory bowel disease, multiple sclerosis, pain that is either chronic and severe or intractable, Parkinson's disease, positive status for HIV, post-traumatic stress disorder, sickle cell anemia, spasticity, spinal cord disease or injury, terminal illness, Tourette syndrome, traumatic brain injury, and ulcerative colitis.

The board's Medical Marijuana Committee determined that the following are considered to be covered by an existing qualifying condition.

- Arthritis (determined to be covered by pain that is either chronic or intractable, February 2021)
- Chronic Migraines (determined to be covered by pain that is either chronic or intractable, February 2021)
- Complex Regional Pain Syndrome (determined to be covered by pain that is either chronic or intractable, February 2021)
- Degenerative Disc Disease (determined to be covered by pain that is either chronic or intractable, February 2022)
- Lupus where pain is present (determined to be covered by pain that is either chronic or intractable, February 2022)

You do not need to submit a petition for any of these conditions. Click here to read the board's position statement.

The petition will not be considered if:

- Received after December 31, 2022
- It seeks to add a broad category of diseases or conditions
- The condition that has been previously reviewed by the board and rejected unless new scientific research that supports the request is offered

If you are petitioning for a previously considered condition:

- Do not resubmit documents which have already been reviewed by the board
- Only new scientific research should be submitted for previously rejected petitions
- A catalogue of submitted research and documents can be found here

Most information submitted as part of a petition is public record and may be posted on the Medical Board's website at med.ohio.gov. This includes the submitter's name provided contact information, and responses.

Instructions:

- All sections below are required to be completed per Ohio Administrative Code 4731-32. All text boxes are required. Applicants may type "see attached" or "previously submitted" in the required fields.
- If you would like for the Medical Board to consider multiple conditions, please complete a separate submission for each one.
- Please refrain from providing personal medical information as all submissions are subject to public record requests.

First Name *	Last Name *	Email *
Pete	Nischt	pete.nischt@klutchusa.com
Address *	**City ***	**State ***
1055 Home Ave	Akron	OHIO
Zip Code *	**County ***	**Specific Disease or Condition ***
44310	SUMMIT	Irritable Bowel Syndrome (IBS)

1) Information from experts who specialize in the disease or condition *

Please see attached documents

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 1 Attachments

File Name	Size
Section 1 - Irritable Bowel Syndrome QC Petition - OMCIA.pdf	161.26 kB
Chey W D et al - Irritable bowel syndrome - a clinical review.pdf	210.67 kB
Abdul - Irritable bowel syndrome and inflammatory bowel disease overlap syndrome.pdf	316.36 kB
Ford A C et al - Irritable bowel syndrome.pdf	322.60 kB
Enck P - Irritable Bowel Syndrome - Enck P. et al.pdf	2.69 MB
Johnson - Prior Stressor Exposure Sensitizes LPS-Induced Cytokine Production.pdf	98.46 kB
Irritable Bowel Syndrome Issue Brief - October 2022 - Minnesota Department of Health.pdf	208.04 kB
Fagundes C P et al - Depressive symptoms enhance stress-induced inflammatory responses.pdf	327.65 kB

Links will not be reviewed

2) Relevant medical or scientific evidence pertaining to the disease or condition *

Please see attached documents

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 2 Attachments

File Name	Size
Section 2 - Irritable Bowel Syndrome QC Petition - OMCIA.pdf	183.85 kB
Chey W D et al - Irritable bowel syndrome - a clinical review.pdf	210.67 kB
Irritable Bowel Syndrome Issue Brief - October 2022 - Minnesota Department of Health.pdf	208.04 kB

3) Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition *

Please see attached documents

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 3 Attachments

File Name	Size
Section 3 - Irritable Bowel Syndrome QC Petition - OMCIA.pdf	157.89 kB
Chey W D et al - Irritable bowel syndrome - a clinical review.pdf	210.67 kB
van Lanen et al - Efficacy of a low-FODMAP diet in adult irritable bowel syndrome.pdf	2.07 MB
Consumer Health Group Warns of Loperamide Abuse, Misuse _ AAFP.pdf	148.58 kB
Lucak SL - Optimizing outcomes with alosetron hydrochloride in severe diarrhea-predominant irritable bowel syndrome.pdf	168.64 kB
Lacy Chey - Lubiprostone chronic constipation and irritable bowel syndrome with constipation.pdf	434.60 kB
Ford A C et al - American_College_of_Gastroenterology_Monograph_on.2.pdf	388.88 kB
Dekel R. et al - The_use_of_psychotropic_drugs_in_irritab.pdf	204.85 kB
Manheimer et al - Acupuncture for irritable bowel syndrome.pdf	1005.18 kB
Menees - The_Efficacy_and_Safety_of_Rifaximin_for_the.10.pdf	313.42 kB
HUSSAIN - Systematic review_ complementary and alternative medicine in the irritable bowel syndrome.pdf	652.49 kB
Irritable Bowel Syndrome Issue Brief - October 2022 - Minnesota Department of Health.pdf	208.04 kB

4) Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation *

Please see attached documents

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 4 Attachments

File Name	Size
Section 4 - Irritable Bowel Syndrome QC Petition - OMCIA.pdf	179.98 kB
Irritable Bowel Syndrome Issue Brief - October 2022 - Minnesota Department of Health.pdf	208.04 kB
Hill - Medical cannabis for the treatment of chronic pain and other disorders.pdf	104.52 kB
Storr - Neurogastroenterology Motil - 2008 - Storr - The role of the endocannabinoid system in the pathophysiology and treatment of.pdf	190.92 kB
Hasenoehrl - The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease.pdf	781.92 kB
Brugnatelli - Irritable Bowel Syndrome_ Manipulating the Endocannabinoid System as First-Line Treatment.pdf	283.35 kB
Vianna CR - Cannabinoid receptor 1 in the vagus nerve is dispensable for body weight homeostasis.pdf	4.31 MB
Choi - Cannabis_Use_is_Associated_With_Reduced_30_Day.25.pdf	158.30 kB
Wong et al - Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit.pdf	979.88 kB
WONGET~1.PDF	984.21 kB
Desai P et al - Association Between Cannabis Use and Healthcare.pdf	123.93 kB
Minnesota's medical cannabis program adds new qualifying medical conditions - MN Dept. of Health Press Release.pdf	398.46 kB

5) Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable. *

Please see attached documents

Please do not include any links in the text field. All materials submitted for review must be attached in the format of a Microsoft Word document or PDF

Question 5 Attachments

File Name	Size
IBS Support Letter_ Dr. Dunne copy.pdf	105.86 kB

1. **Information from experts who specialize in the disease or condition.**

Content for this section was borrowed heavily from the Minnesota Department of Health's Issue Brief on Irritable Bowel Syndrome, which was published in October 2022 in support of its decision to add Irritable Bowel Syndrome to the state's list of Qualifying Conditions for Medical Marijuana. For more information, we encourage you to contact the Minnesota Department of Health's Office of Medical Cannabis at:

Minnesota Department of Health Office of Medical Cannabis PO Box 64882 St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, along with irregular bowel movements that can result in diarrhea, constipation, bloating, or a combination thereof. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Further, IBS is often associated with additional somatic comorbidities, psychiatric conditions, and visceral sensitivity.[1] For many who suffer from it, IBS is a lifelong disorder that can be extremely confusing, debilitating, and embarrassing.

IBS is currently understood to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the digestive system, which leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both.[2]

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes: IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools are loose, or watery and more than a quarter of a patient's stools are hard and lumpy.[3]

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis in Ohio and many other states is irritable bowel disease (IBD), along with subcategories of IBD like Crohn's disease and Ulcerative colitis. Unlike IBS, which is characterized by a gut-brain disorder, IBD is characterized by chronic relapsing inflammation and immune activity.[4] However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological

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[1] Enck, P., Aziz, Q., Barbara, G., Farmer, A. D., Fukudo, S., Mayer, E. A., Niesler, B., Quigley, E. M., Rajilić-Stojanović, M., Schemann, M., Schwille-Kiuntke, J., Simren, M., Zipfel, S., & Spiller, R. C. (2016). Irritable bowel syndrome. *Nature reviews. Disease primers*, *2*, 16014. https://doi.org/10.1038/nrdp.2016.14

[2] Ford, A. C., Sperber, A. D., Corsetti, M., & Camilleri, M. (2020). Irritable bowel syndrome. *Lancet (London, England)*, *396*(10263), 1675–1688. https://doi.org/10.1016/S0140-6736(20)31548-8

[3] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

[4] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

comorbidities, specifically depression and anxiety.[5] Further, studies have found that depression can increase a patient's probability for developing increased inflammation.[6] [7] Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development.[8] However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent.[9] Finally, both IBD and IBS patients experience abnormal gut microbiota.[10] However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease.[11] Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks.

[5] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

[6] Fagundes, C. P., Glaser, R., Hwang, B. S., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2013). Depressive symptoms enhance stress-induced inflammatory responses. *Brain, behavior, and immunity*, *31*, 172–176. https://doi.org/10.1016/j.bbi.2012.05.006

[7] Johnson, J. D., O'Connor, K. A., Deak, T., Stark, M., Watkins, L. R., & Maier, S. F. (2002). Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain, behavior, and immunity*, *16*(4), 461–476. https://doi.org/10.1006/brbi.2001.0638

[8] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

[9] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

[10] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

[11] Abdul Rani, R., Raja Ali, R. A., & Lee, Y. Y. (2016). Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. *Intestinal research*, *14*(4), 297–304. https://doi.org/10.5217/ir.2016.14.4.297

Irritable Bowel Syndrome: a clinical review

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Review

Irritable Bowel Syndrome
A Clinical Review

William D. Chey, MD; Jacob Kurlander, MD; Shanti Eswaran, MD

IMPORTANCE Irritable bowel syndrome (IBS) affects 7% to 21% of the general population. It is a chronic condition that can substantially reduce quality of life and work productivity.

OBJECTIVES To summarize the existing evidence on epidemiology, pathophysiology, and diagnosis of IBS and to provide practical treatment recommendations for generalists and specialists according to the best available evidence.

EVIDENCE REVIEW A search of Ovid (MEDLINE) and Cochrane Database of Systematic Reviews was performed for literature from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*.

FINDINGS The database search yielded 1303 articles, of which 139 were selected for inclusion. IBS is not a single disease but rather a symptom cluster resulting from diverse pathologies. Factors important to the development of IBS include alterations in the gut microbiome, intestinal permeability, gut immune function, motility, visceral sensation, brain-gut interactions, and psychosocial status. The diagnosis of IBS relies on symptom-based criteria, exclusion of concerning features (symptom onset after age 50 years, unexplained weight loss, family history of selected organic gastrointestinal diseases, evidence of gastrointestinal blood loss, and unexplained iron-deficiency anemia), and the performance of selected tests (complete blood cell count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate colorectal cancer screening) to exclude organic diseases that can mimic IBS. Determining the predominant symptom (IBS with diarrhea, IBS with constipation, or mixed IBS) plays an important role in selection of diagnostic tests and treatments. Various dietary, lifestyle, medical, and behavioral interventions have proven effective in randomized clinical trials.

CONCLUSIONS AND RELEVANCE The diagnosis of IBS relies on the identification of characteristic symptoms and the exclusion of other organic diseases. Management of patients with IBS is optimized by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral interventions.

JAMA. 2015;313(9):949-958. doi:10.1001/jama.2015.0954

CME Quiz at jamanetworkcme.com and **CME Questions** page 965

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal condition. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits, in the absence of any other disease to cause these sorts of symptoms. Pooled population-based prevalence estimates of IBS vary globally, in part related to differences in study populations, diagnostic criteria, and study methodology. In North America, the population prevalence of IBS is approximately 12%.[1] IBS is most prevalent in South America (21.0%) and least prevalent in Southeast Asia (7.0%).[1] In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent among women than men, whereas there appears to be greater parity in Asia.[2] Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea.[2] It appears that IBS prevalence decreases with age. In the United States, patients are equally distributed among IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), whereas in Europe, IBS-C or IBS-M may be more prevalent.[3]

This clinical review covers the epidemiology, natural history, pathophysiology, diagnosis, and management of IBS.

Methods

Evidence to support this clinical review was obtained from searches performed by a medical librarian of MEDLINE and the Cochrane Database of Systematic Reviews from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*. This search strategy yielded 1303 articles after limiting to the English language. We selected 139 articles for inclusion. When available, systematic reviews and meta-analyses were used to summarize the available evidence.

FODMAP *fermentable oligosaccharides, disaccharides, monosaccharides, and polyols*

IBS *irritable bowel syndrome*

IBS-C *IBS with constipation*

IBS-D *IBS with diarrhea*

IBS-M *IBS with a mixed bowel pattern*

Burden of Illness and Natural History

Multiple comorbidities are associated with IBS, including somatic pain syndromes (fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain),[4] other gastrointestinal disorders (gastroesophageal reflux disease[5] and dyspepsia[6]), and psychiatric disorders (major depression, anxiety, and somatization),[7] raising the possibility of shared pathogenesis.

In most patients, IBS is a chronic relapsing disease in which symptoms may vary over time. A systematic review showed that during long-term follow-up of clinic-based IBS patients, 2% to 18% worsened, 30% to 50% remained unchanged, and 12% to 38% improved.[8] Previous surgery, longer duration of disease, higher somatic scores, and comorbid anxiety and depression all predicted worse outcomes. After a negative diagnostic evaluation result, a patient receiving a diagnosis of IBS has a less than 5% risk of receiving an alternative organic diagnosis in the future.[8]

Over time, patients may migrate between different IBS subtypes,[9] most commonly from IBS-C or IBS-D to IBS-M; switching between IBS-C and IBS-D occurs less commonly.[10] Many of the "natural history" studies in IBS are affected by treatments introduced by the patient or clinician. Thus, it is difficult to know how much symptom variation is the consequence of medical intervention vs the true natural history of IBS.

IBS significantly reduces health-related quality of life and work productivity.[11] Among patients with IBS, 13% to 88% seek care. Individuals who seek care have more distress and less social support than those who do not.[12] In the United States, IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually, with total direct and indirect expenditures exceeding $20 billion.[13,14]

Pathophysiology

The pathogenesis of IBS, like the clinical phenotype, is heterogeneous (**Box 1**). IBS likely encompasses a number of diseases with distinct pathophysiology that present with similar symptoms. During the past 40 years, a number of factors that contribute to the pathophysiology of IBS have emerged. Traditionally, the pathogenesis of IBS has focused on abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress. Although one or more of these abnormalities are demonstrable in the majority of IBS patients, none can account for symptoms in all of them. More recently, altered gut immune activation, intestinal permeability, and intestinal and colonic microbiome have been identified in some IBS patients.[15,16]

Box 1. Pathophysiology of Irritable Bowel Syndrome (IBS)

Environmental Contributors to IBS Symptoms

Early life stressors (abuse, psychosocial stressors)

Food intolerance

Antibiotics

Enteric infection

Host Factors Contributing to IBS Symptoms

Altered pain perception

Altered brain-gut interaction

Dysbiosis

Increased intestinal permeability

Increased gut mucosal immune activation

Visceral hypersensitivity

Supporting a role for these factors is the increased prevalence of IBS symptoms in inflammatory conditions such as celiac disease[17] and inflammatory bowel diseases[18] and following severe acute gastroenteritis.[19] The intestinal mucosa of some IBS patients shows increased activation of the innate and adaptive immune systems.[20,21] Increased small bowel and colonic permeability has also been observed in patients with IBS-D[22] and is associated with visceral hypersensitivity.[23] The fecal microbiota of IBS patients differ significantly from that of controls, likely reflecting the influence of genetics, diet, stress, infection, and drugs or antibiotics.[24]

IBS symptoms that arise after acute gastroenteritis or so-called postinfectious IBS present an interesting developmental model. Host factors such as genetics, immune function, microbiome, and psychological status, as well as environmental factors such as stress, severity of infection, or treatment with antibiotics, could predispose to the development of chronic IBS symptoms.[25] It is important to identify patients with postinfectious IBS because, unlike typical IBS, which tends to be a chronic relapsing condition, it spontaneously resolves in roughly half of patients within 6 to 8 years of the index infection.[25]

Many patients identify food as a trigger for their IBS symptoms. Various reviews of how specific dietary constituents can cause gastrointestinal symptoms are available.[26-29] The contribution of true food allergies to IBS is small.[30] Conversely, food intolerances are common in IBS patients. Increasingly, rapidly fermentable, osmotically active, short-chain carbohydrates (including fructose, lactose, fructans and galactans, and sugar alcohols) have been recognized as an important trigger of IBS symptoms. Poorly absorbed carbohydrates can exert osmotic effects and lead to increased fermentation in the small bowel or colon, which can exacerbate symptoms

Box 2. Features of Irritable Bowel Syndrome

Typical Features

Loose/frequent stools

Constipation

Bloating

Abdominal cramping, discomfort, or pain

Symptom brought on by food intake/specific food sensitivities

Symptoms dynamic over time (change in pain location, change in stool pattern)

Concerning Features for Organic Disease

Symptom onset after age 50 y

Severe or progressively worsening symptoms

Unexplained weight loss

Nocturnal diarrhea

Family history of organic gastroenterological diseases, including colon cancer, celiac disease, or inflammatory bowel disease

Rectal bleeding or melena

Unexplained iron-deficiency anemia

Box 3. Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes[a]

Recurrent abdominal pain or discomfort[b] at least 3 d/mo in the last 3 mo associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Subtyping IBS by Predominant Stool Pattern

1. IBS with constipation—hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements
2. IBS with diarrhea—loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Mixed IBS—hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

[a] Criterion fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.

[b] "Discomfort" means an uncomfortable sensation not described as pain.

in IBS patients who have underlying abnormalities in gut function and sensation.[29] On the other hand, healthy individuals with normal gut function and sensation rarely experience symptoms after a meal.

Psychosocial factors may also predispose to the development of IBS. Women with IBS are more likely to have experienced verbal, sexual, or physical abuse, which can contribute to the development of the disease through brain-gut and mucosal immune dysfunction.[31] For some IBS patients, recurrent abdominal pain may begin in childhood and reflect learned-illness behaviors.[32] These experiences may lead to persistent changes in the brain-gut axis, resulting in the perception of otherwise unconscious interoceptive input from the gastrointestinal tract.[33] A subset of IBS patients have hypersensitivity to rectal balloon distention and increased activation of brain regions associated with emotional arousal and endogenous pain modulation.[34] In another subset of IBS patients, hypervigilance and catastrophizing are important features that lead to gastrointestinal and nongastrointestinal symptom amplification.[35]

Diagnosis

The diagnosis of IBS is based on the presence of characteristic symptoms and the exclusion of selected organic diseases (**Box 2**). The cardinal features of IBS according to the current diagnostic standard, the Rome III criteria, include abdominal pain or discomfort and altered bowel habits (**Box 3**). IBS patients can experience constipation, diarrhea, or both. Identification of a patient's predominant bowel complaint plays an important role in both the selection of diagnostic testing and treatment. The Rome III criteria emphasize the importance of stool consistency to distinguish between the 3 subtypes of IBS (Box 3)[36] because it correlates with patients' complaints of constipation or diarrhea and colonic transit better than stool frequency.[37] It can be assessed with the Bristol Stool Form Scale, a validated instrument that allows reporting of stool appearance from a score of 1 (hard and lumpy stool) to 7 (entirely liquid).[38] Bloating (subjective sensation of abdominal fullness) and distention (objective increase in abdominal girth) are also common and bothersome complaints reported by more than 80% of IBS patients.[39] However, many individuals without IBS also report these complaints.[40]

Although identifying patients with IBS-D or IBS-C is straightforward, patients with IBS-M present unique challenges. A detailed history can help determine whether a mixed bowel pattern represents the underlying disease state or is the consequence of medical intervention. It is important to consider all prescription and over-the-counter medications and supplements that could affect IBS symptoms (**Box 4**). A stool diary can help identify patterns among the chaotic bowel habits that many IBS patients report. Many IBS-M patients report periods without a bowel movement or with only small, hard stools, followed by periods of multiple stools of variable consistency that they interpret as "diarrhea." Most of these patients actually have IBS-C, with periods of progressive stool accumulation culminating in bowel purging. A radiograph demonstrating fecal loading can help confirm this clinical suspicion.

Along with an assessment of symptom-based criteria, one should be conducted for the presence of concerning features that identify patients who should undergo a more detailed evaluation to exclude organic disease[41] (Box 2, **Box 5**). Although the presence of concerning features may identify patients more likely to have an organic disease, most patients will ultimately have a negative evaluation result. Thus, the value of concerning features lies in their negative, rather than their positive, predictive value. Evidence suggests that a diagnosis of IBS can be confidently made for patients who fulfill symptom-based criteria and have no concerning features because the yield of extensive diagnostic testing is low.[42] Nonetheless, most health care professionals view IBS as a diagnosis of exclusion[43] and are uncomfortable relying solely on symptoms to diagnose it.

There are several diseases that should be considered in patients with IBS symptoms. A meta-analysis of 5 studies found a 4-fold

Box 4. Commonly Used Treatments That Can Exacerbate Irritable Bowel Syndrome Symptoms

Over-the-Counter
Antihistamines
Calcium
Iron
Magnesium
Nonsteroidal anti-inflammatory drugs
Wheat bran

Prescription
Antibiotics
Antidepressants
Antiparkinsonian drugs
Antipsychotics
Calcium-channel blockers
Diuretics
Metformin
Opioids
Sympathomimetics

Box 5. Diagnostic Testing for Patients With Suspected Irritable Bowel Syndrome (IBS) and No Concerning Features

All IBS Subtypes
Complete blood cell count
Age-appropriate colorectal cancer screening

IBS With Diarrhea
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
When colonoscopy performed, obtain random biopsies
SeHCAT, fecal bile acids, or serum C_4 where available

IBS, Mixed
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
Stool diary
Consider abdominal radiography to evaluate for stool accumulation

IBS With Constipation
If severe or medically refractory, refer to gastroenterology specialist for physiologic testing

Abbreviations: SeHCAT, tauroselcholic (selenium 75) acid; TtG, tissue translutaminase.

increased likelihood of biopsy-proven celiac disease in patients with IBS symptoms.[44] The prevalence of celiac disease in these patients varies by region, and although studies from Europe have demonstrated a higher prevalence of the disease, those from the United States have not.[45] Decision analysis suggests that routine screening for celiac disease in IBS patients becomes cost-effective at a prevalence of greater than or equal to 1%.[46] Given the potential long-term consequences of missing celiac disease, clinicians caring for patients with IBS should have a low threshold to screen for it, particularly in individuals with IBS-D.[41]

Recent literature has identified that a small subset of patients with suspected IBS-D have microscopic colitis. A recent case-control study found that age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new drugs, and comorbid autoimmune diseases were associated with an increased risk of microscopic colitis (Box 2).[47] When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be performed to rule out microscopic colitis (Box 5).[41]

Inflammatory bowel diseases, including ulcerative colitis and Crohn disease, are of concern when a patient with IBS symptoms is evaluated. Even low-grade inflammation could alter permeability and sensitize visceral afferent neurons, leading to alterations in motility and visceral sensation.[18] Studies suggest that more than a third of patients with inflammatory bowel disease fulfill the Rome criteria for IBS.[18] It is unclear how many patients with inflammatory bowel disease and overlapping IBS symptoms have concerning features (Box 2). From a pragmatic standpoint, the important question is how often inflammatory bowel disease is ultimately identified in patients who have typical IBS symptoms and no concerning features. A prospective US study that included more than 900 nonconstipated IBS patients and healthy controls undergoing colonoscopy found inflammatory bowel disease in less than 1% of IBS patients and none of the controls.[48] These data argue against routine colonoscopy in patients with typical IBS symptoms and no concerning features. Noninvasive biomarkers may provide a more cost-effective means by which to screen for inflammatory bowel disease than colonoscopy. A recent systematic review and meta-analysis suggested that fecal calprotectin, a biochemical assay for intestinal inflammation, was effective and cost-effective in identifying inflammatory bowel disease.[49] Another systematic review and meta-analysis found that a C-reactive protein level of less than 0.5 mg/dL or fecal calprotectin level of less than 40 µg/g conferred a less than 1% risk of inflammatory bowel disease in patients with typical IBS symptoms.[50]

Perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit.[51] Evidence of bile acid malabsorption may be present in up to a third of patients with IBS-D symptoms.[52] At present, clinicians can assess for bile acid malabsorption by instituting an empirical trial with a bile acid sequestrant. Several tests have been developed to identify such malabsorption, including the SeHCAT (tauroselcholic [selenium 75] acid) retention test, serum C4 measurement, and fecal bile acid measurement. However, these tests are not widely available in the United States. It is hoped that eventually bile acid malabsorption testing will identify IBS-D patients more likely to benefit from a bile acid sequestrant.

For IBS-C patients, colorectal cancer is a common concern. A meta-analysis that included 8 cross-sectional surveys found that constipation was actually associated with a lower prevalence of colorectal cancer (odds ratio, 0.56; 95% CI, 0.36-0.89). This analysis also found no significant increase in colorectal cancer risk among constipated patients vs nonconstipated controls in 3 cohort studies (odds ratio, 0.80; 95% CI, 0.61-1.04).[53] However, a more recent case-control study found that patients with chronic constipation have a significantly higher prevalence and incidence of colorectal cancer and benign colorectal neoplasms.[54] The limited prospective literature suggests that the risk of colorectal cancer is less than 1% in patients

Table. Summary of Therapies for Irritable Bowel Syndrome[a]

Treatment	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Over-the-Counter			
Fiber: psyllium	Moderate	Best suited for IBS-C	Bloating, gas
Laxatives: polyethylene glycol	Very low	Beneficial for constipation but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidiarrheals: loperamide	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Low	Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics	Similar to placebo
Antispasmodics: peppermint oil	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription			
Antidepressants: TCAs, SSRIs, SNRIs	High	TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents			
Linaclotide	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Lubiprostone	Moderate	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaximin	Moderate	Improves global symptoms, pain, and bloating in nonconstipated IBS patients	Similar to placebo
5-HT_3 receptor antagonists: alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other Therapies			
Psychological/behavioral therapy	Very low	Benefits for global IBS symptoms in all subgroups	Similar to placebo

Abbreviations: GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Quality of Evidence were taken from Ford et al.[59] Quality of the evidence was reported as very low, low, moderate, or high based on the number and quality of available clinical trials and reproducibility of the results. Evidence judged to be of very low quality was from case series and nonrandomized trials while evidence judged to be of high quality was taken from randomized placebo-controlled trials with reproducible results.

with typical IBS symptoms and no concerning features and not increased compared with that in healthy controls. As such, in patients with typical IBS symptoms and no concerning features, age-appropriate colorectal cancer screening is the most logical recommendation.

An underrecognized condition in patients with IBS-C symptoms is dyssynergic defecation, a constipation-associated condition that arises from the inability to coordinate the abdominal wall, anal sphincter, and pelvic floor muscles in a way that enables normal defecation.[55] Although a sense of incomplete evacuation after a bowel movement or the need for digital maneuvers to facilitate defecation may increase the likelihood of dyssynergia, symptoms generally do not accurately identify affected patients.[56] Dyssynergia can cause abdominal symptoms such as pain, discomfort, and bloating, which are relevant to IBS-C. Preliminary data suggest that correction of dyssynergia with biofeedback can improve both bowel and abdominal symptoms.[57] Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia with a digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging.

Management

General Management Recommendations

A trusting patient-physician relationship is the cornerstone of managing IBS patients. Actively listening, not interrupting, using empathy, setting realistic expectations ("helping" rather than "curing"), and using nonverbal techniques such as making eye contact, nodding, leaning forward, and using open body posture can help build this relationship.[58] The clinician must understand the patient's goals for the visit and avoid focusing only on the gastrointestinal symptoms. Performing a physical examination establishes the ritual of touch, which many patients identify with a thorough and caring physician. It is critical to assign a confident diagnosis and provide education regarding the causes, natural history, and treatment of IBS.

Because IBS is a symptom-based disorder, treatments can address abdominal symptoms such as pain, cramping, bloating, or bowel symptoms, including diarrhea and constipation (Box 2). Traditionally, first-line IBS therapies have focused on over-the-counter medications aimed at improving diarrhea (eg, loperamide, probiotics) or constipation (eg, fiber supplements, laxatives). Benefits of this strategy include improving altered bowel habits, widespread availability, low cost, and an excellent safety record. However, over-the-counter medications offer little benefit for global, or overall, IBS symptoms or abdominal symptoms such as pain and bloating. The **Table** provides a summary of commonly used IBS treatments, along with recently published recommendations and evidence quality assessments from the American College of Gastroenterology Functional Bowel Disorders Task Force.[59] During the last 5 years, lifestyle and dietary interventions have become an increasingly important first-line treatment option.

Exercise

Physically active individuals move their bowels more often and have more rapid colon transit than sedentary individuals.[60] Further-

more, a randomized clinical trial found that a structured exercise intervention led to greater improvements in overall IBS symptoms than usual care.[61] Thus, IBS patients should be encouraged to increase their physical activity. A simple recommendation is to take a 20-minute walk (roughly 1 mile) each day. Distance and pace can be gradually increased as tolerated.

Diet

Patients often associate their IBS symptoms with eating a meal. Up to 90% of IBS patients restrict their diet to prevent or improve their symptoms.[62] True food allergies are uncommon in IBS. On the other hand, food intolerances or sensitivities are frequently reported. At present, there is emerging evidence that supports diets for IBS patients that are gluten free and low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).

The effect of gluten was assessed by a randomized, double-blind, placebo-controlled, rechallenge trial in 34 IBS patients with a history of gluten sensitivity.[63] During 6 weeks, overall IBS symptoms were not adequately controlled in 68% of patients receiving gluten vs 40% receiving a gluten-free diet ($P < .001$). Gluten worsened pain, bloating, and stool consistency, as well as "tiredness." Another study in IBS-D patients reported increased stool frequency, as well as altered gut permeability and immune activation, in the presence of gluten.[64] These data have led some to conclude that gluten is the primary cause of symptoms after ingestion of wheat. However, wheat contains fructans and other proteins that might also cause symptoms in IBS patients. In a recent Australian study of 37 IBS patients with wheat sensitivity, symptom relief was more closely associated with exclusion of poorly absorbed carbohydrates than gluten.[65] It is also likely that widespread negative media reports about gluten have increased the chance of a "nocebo" response, contributing to the perceived negative effects of eating gluten-containing foods.

Short-chain, poorly absorbed, highly fermentable carbohydrates are collectively known as FODMAPs and are found in such foods as wheat, onions, some fruits and vegetables, sorbitol, and some dairy. FODMAPs lead to increased small intestinal and colonic water secretion and fermentation, which causes increased production of short-chain fatty acids and gas.[66] Aside from increased flatulence, FODMAPs do not cause gastrointestinal symptoms in healthy adults.[67] Conversely, FODMAPs are an important trigger of meal-related symptoms in IBS patients, possibly as a consequence of underlying abnormalities in gut physiology and visceral sensation.[29] A randomized clinical trial in 30 IBS patients found lower overall symptom scores on the low-FODMAP diet vs a typical Australian diet ($P < .001$).[67] Seventy percent of IBS patients felt better while receiving the low-FODMAP diet regardless of IBS subtype. Responders to full FODMAP exclusion should gradually reintroduce FODMAP-containing foods to identify the level of dietary restriction needed to maintain symptom benefit. There are currently few long-term efficacy or safety data for the low-FODMAP diet.

Given the rapidly expanding role of dietary intervention in the primary management of IBS and other gastrointestinal conditions, it is becoming increasingly important for clinicians to become educated and to integrate a trained registered dietitian into the health care team.

Medical Treatments for IBS-D

Antidiarrheals

Antidiarrheal medications such as loperamide inhibit peristalsis, prolong gut transit, reduce fecal volume, and are often used as first-line agents in patients with IBS-D. Two randomized trials enrolling IBS-D and IBS-M patients found no benefit of loperamide over placebo for overall IBS symptoms.[59] However, loperamide reduces stool frequency, increases stool consistency, and can be used prophylactically when a patient anticipates diarrhea. When used long term, loperamide is preferred to diphenoxylate or atropine because it does not cross the blood-brain barrier and thus is less subject to habituation. In practice, many gastroenterologists use bile acid sequestrants such as cholestyramine and colesevelam to treat diarrhea. These agents have not been evaluated in rigorous, randomized trials with IBS patients.

Serotonin Agents: 5-HT_3 Receptor Antagonists

The gut hormone serotonin influences gastrointestinal motility and visceral sensation.[68] Alosetron is a 5-HT_3 antagonist approved in the United States for treating women with severe, disabling IBS-D that has not responded to traditional medical therapies. Alosetron (0.5-1 mg once to twice per day) improves global and individual IBS-D symptoms in women and men for up to a year, with a therapeutic gain over placebo of approximately 15%. Dose-dependent constipation and idiosyncratic ischemic colitis are potential adverse effects of alosetron that have led to a risk management plan requiring US patients and prescribers to acknowledge the risks before dispensation of the medication.[69]

Ondansetron, a 5-HT_3 antagonist that is less potent than alosetron, has been shown to benefit IBS-D in a recent randomized, double-blind, placebo-controlled, crossover study.[70] Ondansetron (4-8 mg 1-3 times per day) significantly improved stool consistency, global IBS symptoms, urgency, stool frequency, and bloating (all comparisons, $P \leq .002$) but not pain.

Antispasmodics

Antispasmodics include drugs with anticholinergic or calcium-channel blocking properties that may improve IBS symptoms by relaxing gut smooth muscle. Acknowledging the poor quality of many trials, a 2011 Cochrane review reported benefits of antispasmodics over placebo for abdominal pain and global assessment.[71] The American College of Gastroenterology Functional Bowel Disorders Task Force recently concluded that "certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS."[59] Because some IBS patients have an exaggerated gastrocolonic reflex that is in part cholinergically mediated,[72] these drugs may be best suited for postprandial abdominal cramping and loose stools. Dose-dependent adverse events, including constipation, fatigue, dry mouth, dizziness, and blurred vision, may occur. Anticholinergics should be avoided in the elderly.

Peppermint oil, which is available over the counter, possesses calcium-channel blocking properties and thus is classified as an antispasmodic. A number of small clinical trials suggest that enteric peppermint oil (187-225 mg 3 times daily) benefits some IBS patients.[73] Although peppermint oil is typically well tolerated, some patients may experience reflux symptoms.[73]

Medical Treatments for IBS-C

Fiber Supplements

The efficacy of fiber for treating IBS has been summarized in recent reviews.[26,74] The most recent meta-analysis reported modest benefits with fiber for global IBS symptoms (relative risk, 0.86; 95% CI, 0.80-0.94; number needed to treat, 10).[74] In a subgroup analysis, soluble fiber (psyllium and ispaghula husk; relative risk, 0.84; 95% CI, 0.73-0.94) but not insoluble fiber (wheat bran) was associated with improved IBS symptoms. Benefits of fiber appear most robust in patients with IBS-C rather than IBS-D. Fiber, which is often used as a first-line therapy, should be started at a nominal dose and gradually titrated upward during weeks to a total daily intake of 20 to 30 g. Wheat bran contains fructans, which, like other FODMAPs, can exacerbate IBS symptoms; thus, wheat bran should be avoided in IBS patients.[26]

Laxative Agents

Osmotic laxatives such as polyethylene glycol are frequently recommended as first-line therapy for IBS-C patients. Clinical trials have demonstrated that it improves bowel complaints, including stool frequency and consistency, but does not reliably improve abdominal pain or bloating.[75] The usual starting dose is 17 g in juice or water, with dose escalation dictated by clinical response. Polyethylene glycol is typically well tolerated but can cause dose-dependent bloating, gas, and loose stools.

Stimulant laxatives are also commonly used in IBS-C patients. Although efficacy has been demonstrated in patients with chronic constipation,[76] to our knowledge there are no randomized, controlled trials in IBS-C patients. Relevant to IBS, the most common adverse effects are abdominal pain and cramping.

Prosecretory Agents

Luminally acting prosecretory agents have been evaluated in IBS-C patients. Lubiprostone is a chloride-channel (ClC-2) activator that stimulates intestinal fluid secretion and improves global, bowel, and abdominal symptoms in IBS-C patients.[77] In 2 phase 3 trials (1711 IBS-C patients), a significantly higher percentage of patients treated with lubiprostone 8 µg twice daily responded compared with those treated with placebo (17.9% vs 10.1%; $P = .001$).[78] A higher dosage of 24 µg has proven effective in patients with chronic idiopathic constipation. To limit dose-dependent nausea (8% with an 8-µg dose and 33% with a 24-µg dose), lubiprostone should be received with food.

Linaclotide is a guanylate cyclase-C agonist that increases production of cyclic guanosine monophosphate. Intracellularly, cyclic guanosine monophosphate increases intestinal chloride secretion via the cystic fibrosis transmembrane regulator, whereas extracellularly it reduces firing of visceral afferent pain fibers.[79] A 2013 meta-analysis that included 3 rigorous randomized clinical trials in IBS-C patients reported a relative risk for response to linaclotide (290 µg once daily) vs placebo of 1.95 (95% CI, 1.3-2.9) and a number needed to treat of 7 (95% CI, 5-11).[80] The maximum benefit for stool frequency occurs within a week of treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks to maximally improve. Diarrhea is the most common adverse effect with linaclotide, reported by 20% of patients.[81] Linaclotide should be received 30 to 60 minutes before breakfast to reduce the likelihood of diarrhea.

Modification of the Microbiota: Probiotics and Antibiotics

Probiotics are live bacteria that, when consumed in sufficient quantities, confer a health benefit to the host. Prebiotics are nutrients, usually carbohydrates, that encourage the growth of probiotic bacteria. Synbiotics are combinations of prebiotics and probiotics. Postbiotics consist of extracts from dead or lysed bacteria. The most robust data have evaluated the role of probiotics for IBS. In a recent meta-analysis including 35 randomized clinical trials, probiotics as a group improved global IBS symptoms (relative risk, 0.79; 95% CI, 0.70-0.89; number needed to treat, 7; 95% CI, 4-12.5), abdominal pain, bloating, and flatulence.[59] However, given the differences in probiotic preparations evaluated, data derived from grouping or directly comparing trials should be interpreted with caution.[82] Higher-quality studies have tended to demonstrate less of a treatment effect. Thus, the current literature does not allow recommendations regarding specific probiotic preparations for IBS.

Rifaximin is a poorly absorbed, broad-spectrum antibiotic that has been evaluated in IBS patients. A recent meta-analysis that included 5 randomized clinical trials that enrolled predominantly nonconstipated IBS patients demonstrated therapeutic gains of 9% to 10% for global symptoms (odds ratio, 1.57; 95% CI, 1.22-2.01) and bloating (odds ratio, 1.55; 95% CI, 1.23-1.96).[83] The 2 phase 3 trials in nonconstipated IBS patients used rifaximin 550 mg 3 times daily for 14 days. Clinical experience suggests that many rifaximin responders will eventually develop recurrent IBS symptoms. Recently released data from a large re-treatment trial suggest that second and third courses yield efficacy similar to that of the first course of rifaximin.[84] The role of other antibiotics in IBS treatment remains unknown, although antimicrobial resistance with repeated courses of systemically absorbed antibiotics may be a concern.

Centrally Acting Interventions

Antidepressants

Because of their effects on pain perception, mood, and motility, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. The efficacy of tricyclic antidepressants, selective serotonin-reuptake inhibitors, and, to a lesser extent, selective norepinephrine-reuptake inhibitors has been evaluated in IBS patients.[85] A meta-analysis identified 17 randomized controlled trials that enrolled 1084 IBS patients who were treated with antidepressants or placebo.[85] Collectively, antidepressants were effective for abdominal pain, with a relative risk of remaining symptomatic of 0.62 (95% CI, 0.43-0.88) and a number needed to treat of 4 (95% CI, 3-6). A subgroup analysis reported a number needed to treat of 4 for both tricyclic antidepressants and selective serotonin-reuptake inhibitors. Adverse events occurred more often in patients receiving an antidepressant (number needed to harm, 9; 95% CI, 5-111). Tricyclic antidepressants can cause dose-dependent constipation, dry mouth and eyes, drowsiness, weight gain, and QT-interval prolongation. Selective serotonin-reuptake inhibitors can cause sexual dysfunction, agitation, nausea, drowsiness, and diarrhea. Although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, there are few data addressing their efficacy for IBS.[86]

The adverse event profiles of different antidepressants can be leveraged to address different IBS subtypes.[87] For example, because tricyclic antidepressants can cause constipation, they may be best suited to IBS-D patients, whereas the prokinetic effects of se-

lective serotonin-reuptake inhibitors might make them a better choice for IBS-C patients. Similarly, tricyclic antidepressants might be a better choice for patients with insomnia, anorexia, or weight loss. On the other hand, selective serotonin-reuptake inhibitors might be a better choice for patients with significant anxiety. When a tricyclic antidepressant is selected to treat IBS, low doses (10-25 mg) should be started at bedtime and gradually titrated upward according to symptom response and tolerability. Selective serotonin-reuptake inhibitors are typically started at the lower range of standard dosing.

Psychological Therapies

Psychological therapies provide an alternative or adjunctive therapy for IBS patients. In a recent meta-analysis, 32 separate trials of highly variable quality, involving more than 2000 patients, evaluated 10 different "psychological therapies,"[85] which were more effective than control therapies, with a number needed to treat of 4 (95% CI, 3-5). In a subgroup analysis, similar numbers needed to treat were reported for cognitive behavioral therapy, hypnotherapy, multicomponent psychotherapy, and dynamic psychotherapy but not other techniques. Despite these encouraging results, variable third-party reimbursement, a lack of clinicians, and poor patient and clinician acceptance have limited widespread adoption of these therapies in clinical practice. Access to behavioral therapy may improve with the development of book-, Internet-, or application-based behavioral programs.[88,89]

Complementary and Alternative Medicine

Despite the paucity of evidence, many IBS patients use complementary and alternative therapies.[90] A meta-analysis of 5 studies demonstrated that acupuncture was no better than sham acupuncture in improving symptoms or quality of life in IBS patients.[91] Studies evaluating Chinese herbal remedies for IBS have yielded mixed results.[90] A clear understanding of the active ingredients and a lack of standardization are significant challenges facing clinicians with an interest in herbal therapies.

Bottom-Line Clinical Messages

1. IBS is a common, symptom-based illness that is defined by the presence of abdominal pain or cramping in association with constipation, diarrhea, or both.
2. The diagnosis of IBS can be confidently established with the use of symptom-based criteria, the exclusion of concerning features, and the judicious use of diagnostic testing.
3. Concerning features that should prompt a more detailed evaluation include new onset of symptoms after age 50 years; unexplained weight loss; a family history of organic gastrointestinal diseases such as colon cancer, inflammatory bowel diseases, or celiac disease; gastrointestinal blood loss; and unexplained iron-deficiency anemia.
4. Successful management of patients with IBS begins with a trusting, positive, patient-physician relationship.
5. A holistic approach that embraces lifestyle changes, dietary interventions, medications, or behavioral strategies offers the greatest likelihood of sustained treatment benefit.

Conclusions

IBS remains an enigmatic cause of significant distress, morbidity, and disability. For the foreseeable future, the diagnosis of IBS will rely on the identification of characteristic symptoms and the exclusion of organic disease mimics. As science advances, it is hoped that the confident diagnosis of IBS will be aided by novel biomarkers that can either rule out specific organic diseases or rule in IBS. An improved understanding of the pathophysiology of IBS will also pave the way for novel nonpharmacologic and pharmacologic therapies. For now, it is important for physicians to understand the role of dietary, lifestyle, and behavioral modification either with or without medical treatments for IBS.

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Study concept and design: All authors.
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REVIEW

INTESTINAL RESEARCH

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Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place

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Irritable bowel syndrome (IBS), a common gastrointestinal disorder involving the gut-brain axis, and inflammatory bowel disease (IBD), a chronic relapsing inflammatory disorder, are both increasing in incidence and prevalence in Asia. Both have significant overlap in terms of symptoms, pathophysiology, and treatment, suggesting the possibility of IBS and IBD being a single disease entity albeit at opposite ends of the spectrum. We examined the similarities and differences in IBS and IBD, and offer new thoughts and approaches to the disease paradigm. **(Intest Res 2016;14:297-304)**

Key Words: Irritable bowel syndrome; Inflammatory bowel disease; Gut-brain axis; IBS-IBD overlap syndrome

INTRODUCTION

Irritable bowel syndrome (IBS) and IBD are two common chronic gastrointestinal (GI) disorders with unknown etiology and mechanisms. As our understanding improves, what were initially thought of as two separate and distinct GI disorders seem to have more in common, particularly at the extreme spectrum of both disorders–the prodromal phase of IBD and the late phase of IBS. This is augmented by the overlap of symptoms as well as the presence of colitis, raising the question of whether IBS and IBD are essentially on the same timeline–an evolution of the same disease.

DILEMMA OF IBS-IBD

IBS is characterized by a disordered gut-brain axis, but can develop following an enteric infection, and is associated with persistent immune activation that is a feature of IBD. Similarly, IBD, which encompasses CD and UC, is characterized by chronic relapsing inflammation and immune activation; however, recent evidence also points to altered gut microbiota and disturbed psychology, which are features of IBS, being important, both in the development and maintenance of disease.

The considerable overlap of symptoms and colitis raises the questions of whether IBS is a prodromal or mild subset of IBD, or whether IBD is pathologically related to the cause of IBS, or do they even represent the same pathophysiological spectrum of a disease. These claims are supported by the association and prevalence of IBS coexisting with IBD, especially in CD, with 39% pooled prevalence and OR of 4.89, even in remission.[1]

Indeed, there are a few studies correlating an increased risk of IBD among those with initial IBS symptoms.[2-4]

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EPIDEMIOLOGY OF IBS AND IBD—BOTH ON THE RISE IN ASIA

The incidence of CD in the world ranges from 5.0 to 10.7 per 100,000 person-years, while the incidence of UC ranges from 6.3 to 24.3 per 100,000 person-years. The marked variations are due to geographical localities, with Asia tending to show the lowest incidence rate, as compared to predominantly UC in Europe, and CD in North America.[5] Even in Asia, with its large geographical area, there is variation in the annual incidence rate from 0.1 to 6.3 per 100,000 population for UC and 0.04 to 5.0 per 100,000 population for CD.[5]

Gender differences were reportedly equal in large population-based studies, although some contested a higher male preponderance for IBD in Asia.[5,6] The highest incidence ages of diagnosis were recorded in the second to fourth decades, therefore implicating the most productive age group, with socioeconomic impact in terms of hours off work and impaired productivity.

IBS in Asia shows a prevalence rate of 2.9% to 15.6%, with no predilection for the traditionally female gender.[7-9] The prevalence rate is highly dependent on the utilization of Manning or Rome-based criteria, and to a lesser extent on the geographical distribution. Age distribution still involves younger individuals in their early 20's, comparable to Western studies.

However, for both IBS and IBD, the prevalence and annual incidence has shown a consistently increasing trend in Asia; which is in keeping with a worldwide trend.

Several studies from Asia spanning from 1986 to 2006 had shown increasing prevalence of IBD, ranging from 1.3 to 7.6 in the 1990's to 6.3 to 30.9 per 100,000 in the new millennium.[10-14] In contrast, IBS is more variable, but the general trend has been on the increase, especially in affluent cities such as Singapore and Tokyo, while some reports indicate a common syndrome affecting both rural and urban populations.[15-18]

SIMILARITIES OF IBS AND IBD

Apart from similarities in symptoms and signs, there are several other pathophysiological similarities between IBD and IBS. These can be broadly categorized into four main components, including the brain-gut axis, genetic factors, microbiota, and the epithelial barrier, among others.

1. Brain-Gut Axis

It is a well-known fact that both IBD and more particularly IBS are predisposed to psychological comorbidities, with a cause and effect relationship. There is a bidirectional interaction between the central nervous system and the enteric nervous system, which in turn modulates the gut function.

There is evidence that depression and anxiety are more common in IBD patients, with the symptoms being more severe during active disease.[2] A large Swiss IBD Cohort Study involving 2,007 patients showed that although anxiety is more prevalent compared to depression in IBD patients, depression has a more significant negative effect on IBD activity.[19] Depression in itself predisposes to increased inflammation in response to stress, by releasing a higher amount of pro-inflammatory cytokines such as interleukin 6 (IL-6), compared to normal controls, as proven in human studies and animal models.[20,21] Interestingly, a bidirectional effect has also been shown, in which the IBD course is also worse in patients who are depressed.[22-24]

In IBS, it has been reported that 50% to 90% of patients have or had at some point one or more common psychiatric condition, including major depressive disorder, generalized anxiety disorder, social phobia, somatization disorder, or posttraumatic stress disorder.[2,25] Our own limited data suggest that these psychological comorbidities in IBS are often nonserious.[9] The limbic system is believed to be responsible by causing a surge in adrenocorticotrophic hormone and cortisol, and mediators such as IL-6 and IL-8 initiate a response in the enteric nervous system, resulting in symptoms of abdominal pain and diarrhea, which are typical of IBS.[20,26] A more prominent activation of the dorsolateral prefrontal cortex area, which controls emotional and autonomic responses, has been shown to be increased in IBS patients, compared to control patients.[27]

2. Genetic Factors

The Tumor Necrosis Factor (Ligand)-Superfamily Member 15, also known as the TNF-SF15 gene, is known to be associated with CD and also primary biliary cirrhosis. The expression of this protein subsequently acts as an autocrine factor inducing apoptosis, and also inhibits endothelial cell proliferation, resulting in inflammation.

Several studies from the USA, Sweden, and more recently the UK have also noted the association of TNF-SF15 polymorphism with increased risk of IBS.[28,29] This suggests a possible common pathway for both IBD and IBS through

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immune activation in both of these diseases.

Familial occurrence is common in both diseases, which highlights the possibility of shared genetic transmission. TNF-SF15 polymorphism may pave the way for identification of a precursor or trigger, whereas multi-gene analysis, such as the von Stein et al.[30] seven gene model, may be utilized to differentiate between IBS and IBD.

3. Microbiota

Dysbiosis (abnormal gut microbiota) has been linked with several diseases that include IBD and IBS. A recent study evaluating a dysbiosis index algorithm detected dysbiosis in 70% of treatment-naïve IBD patients and 73% of IBS patients, in comparison with only 16% of healthy subjects.[31]

Alterations in gut microbiota have been observed in IBS patients,[32,33] and are also seen in post-infectious IBS, which in turn is postulated to be a trigger for IBD.[33-36] Fluorescent *in-situ* hybridization studies have detected increased bacterial presence in the mucus layer of IBD and IBS patients. Commensal organisms in IBD and IBS patients are also inherently different when compared to healthy subjects.[34] Dysbiosis involving *Faecalibacterium prausnitzii* was noted to occur in a CD population in Europe, strengthening the argument for alterations of the intestinal microbiota as a cause of IBD.[37,38]

4. Impaired Epithelial Barrier

Increased gut permeability, which therefore increases susceptibility to injurious agents, has been suggested to precede clinical CD.[39] Stress exacerbates IBD, and has been shown to cause an increase in activation of gut mast cells, which subsequently increases gut permeability.[34,40]

Similarly in IBS, elevation in miRNA-29a has been noted. This plays a role in down-regulating glutamine synthetase, which causes increased gut permeability,[41] in a manner similar to IBD-related increases in permeability and subsequent injury.

Increased intestinal permeability due to changes at the cellular levels has been attributed to changes in transient receptor potential vanilloid receptor 1, protein zonulin 1, and α-catenin, and has indeed been implicated in both IBS and also IBD presenting with IBS symptoms.[18,42,43]

Bacterial gastroenteritis as opposed to viral gastroenteritis also predisposes to greater permeability disturbances, and is associated with increased postinfectious IBS.

This common endpoint of increased gut permeability is currently the subject of intense studies worldwide.

DIFFERENCES BETWEEN IBS AND IBD

Notable differences were also seen between IBD and IBS, although there are arguments that these could be considered similarities. These include the following:

1. Fecal Calprotectin

The advent of fecal calprotectin has revolutionized non-invasive testing in IBD. High calprotectin levels are almost always due to ongoing inflammation related to chronic IBD. Keohane et al.[44] found that IBD in remission with associated IBS exhibited greater fecal calprotectin levels than IBD in remission alone. This suggests that despite IBD being in remission, occult inflammation continues in the presence of IBS. In contrast, IBS is likely to have normal to low levels of calprotectin unless it is associated with a low degree of inflammation, as in postinfectious IBS.[45]

It has been proposed that a level below 40 μg/g is an indicator of no inflammation, whereas a level above 100 μg/g indicates significant inflammation, suggesting IBD. However, at the in-between level of 40 to 100 μg/g, it is uncertain whether this indicates a low level of IBD or IBS, or pre-IBD IBS.[46] In comparison to other biomarkers, including high sensitivity CRP, lactoferrin, tumor necrosis factor (TNF)-α, nitric oxide, and intraepithelial lymphocytes, fecal calprotectin has helped to identify active IBD patients, but not such that it has proved to be a good positive or negative predictor, as evident by being normal in IBS.[44,47,48] These other biomarkers, however, may be more useful as part of a diagnostic workup in combination with calprotectin.[49]

2. Degree of Inflammation

In IBD, mucosal inflammation is usually ongoing and slow to resolve, even in clinically asymptomatic patients. IBD in remission still exhibits a higher level of TNF-α and intraepithelial lymphocytes compared to IBS patients.[50] In contrast, IBS patients tend to exhibit low grade, variable, or even absent mucosal inflammation.[2]

3. Symptoms versus Inflammation Mismatch

Inherently, IBD is an organic disease, as evidenced by mucosal inflammation, whereas IBS lies more in the spectrum of a functional disorder, with no evidence of organic disease. IBS symptoms are nonspecific, and may precede diagnosis of both IBS and IBD by many years. Lack of mucosal inflam-

mation results in a mismatch compared to the severity of the reported symptoms.

In IBD, mucosal inflammation is characteristic, but the symptoms do not necessarily correlate with endoscopic findings.[51]

4. Visceral Hypersensitivity

The gut viscera are controlled by a complex, incompletely understood interaction between the enteric nervous system, the vagal and spinal primary afferents, and both small and large myelinated and unmyelinated fibers that control motility and peristalsis. The interaction of neuroimmune and intestinal epithelial cells may prove to be a protective barrier in health but has also been implicated as the likely cause of GI pathology. In addition, there are persistent increases in mast cells, vasoactive intestinal peptide, and substance P, among many other receptors, which again either maintains or is a causative agent of GI disease.

As proven by persistent pain despite minimal inflammation and the response to centrally-acting agents, visceral hypersensitivity is the likely explanation for the symptoms and brain responses in IBS.

However, in IBD, the hallmark of the disease is mucosal inflammatory change that correlates with disease severity, and is the target of healing treatment. Visceral hypersensitivity is more apparent in IBD patients in remission, further strengthening the argument for IBS as a pre-IBD state.

IBS-IBD DISEASE PARADIGMS

There is growing evidence that IBS or IBS-like symptoms are a prodrome before the formal diagnosis of IBD. It has also been documented that IBS symptoms occur in IBD patients in remission, particularly in cases of CD.

Over the years, several disease progression paradigms have been proposed (Fig. 1). Initially, after an episode of contaminated municipal water supply, it was proven that postinfectious IBS predates the formal diagnosis of IBS.[52] In 2012, Porter et al.[3] added to that work with the suggestion that post-infectious IBS is followed by IBS, and subsequently followed by active IBD. Berrill et al.[53] suggested that IBS is an early part of a disease spectrum that subsequently leads to IBD, and progresses towards "subclinical IBD," in which case, mucosal healing might not be the endpoint in therapy. Stanisic and Quigley[51] instead proposed "irritable IBD" as the unifying model of IBS symptoms in IBD in remission.

Our proposal that IBS and IBD comprise a single disease paradigm is not new, although variation exists as to what happens in-between the two conditions. Moreover, IBS is a disorder with a very broad spectrum, and immune activation has been found in only a fraction of cases. Thus, the association of IBS with IBD may be confined to this fraction of IBS. Indeed, further research is needed to support this idea.[3,18,54,55]

The initial or prodromal insult is enteric infection, resulting in postinfectious IBS, which is followed by a period of IBS-like symptoms without obvious colonic inflammation. We further propose an "early or pre-IBD" period at which there is a low level or grade of colonic inflammation occurring in IBS. This then leads to active IBD, followed by subclinical IBD with ongoing low-grade inflammation, although it is possible that irritable IBD occurs when the inflammation burns out.

This low-grade inflammation during the early pre-IBD period is suggested by studies showing that fecal calprotectin remains positive in one-third of IBS patients; this indicates that inflammation, along with further insults such as infections or stress, may inadvertently trigger IBD, followed by the extreme end of the spectrum, which is the proposed subclinical IBD (Fig. 1). Other studies showed that microscopic inflammation was found in up to 14.9% of cases in diarrhea-predominant IBS, supporting the claim of low-level ongoing inflammation prior to the diagnosis of IBD.[56] Indeed, patients

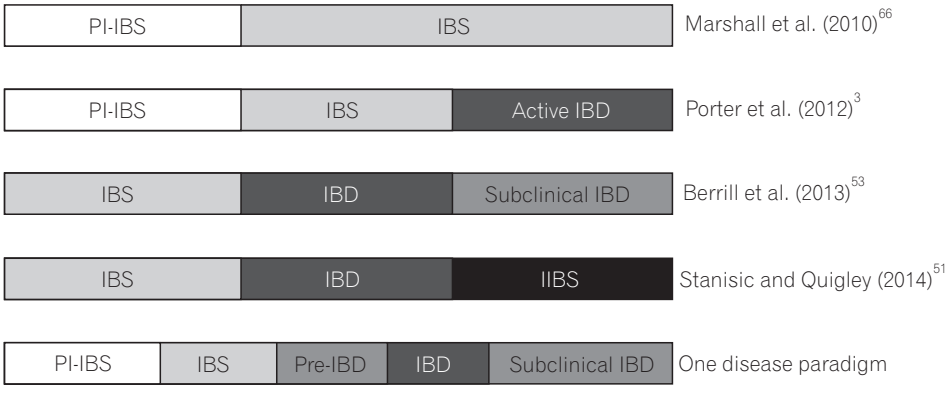

Fig. 1. Disease paradigms in IBS-IBD. Existing paradigms and our proposed one disease paradigm are shown here. These paradigms illustrate the evolution of concepts in IBS-IBD overlap syndrome. PI-IBS, postinflammatory IBS; IIBS, irritable IBS.

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with IBS are 15 times more likely to develop IBD compared to those with no IBS-like symptoms.[3]

The question is what may have caused the ongoing low-grade inflammation in the early or pre-IBD period? We believe that altered gut-brain axis and disturbed psychology associated with IBS can perpetuate and sustain the low-grade inflammation. Likewise, new triggers including new enteric infection in the form of small intestinal bacterial overgrowth (SIBO) or intestinal dysbiosis, that is often unsuspected in IBS or IBD, may have sustained the low-grade inflammation. Bloating is a common symptom present in both disorders, and SIBO is a cause of bloating that can be excluded easily through hydrogen breath testing.[57,58]

WHAT TO OFFER THESE PATIENTS?

The main challenge has always been to make a definitive diagnosis, but overlap between IBS and IBD can pose a problem. A colonoscopy with mucosal histopathological studies and/or Rome questionnaires may not be adequate to separate the two. Management consideration is shown in Fig. 2.

With fecal calprotectin (or other stool markers, e.g., lactoferrin), it is potentially easier to distinguish between IBD, IBS, or the proposed early or pre-IBD condition with its low-grade inflammation. This can further be of use as a risk-stratifying method to ensure these patients are followed up, thereby preventing or controlling active IBD.

Regulation of the gut microbiota as a potential trigger of IBS and IBD is also important. This therefore necessitates testing for SIBO or intestinal dysbiosis, and future strategies including the use of prebiotics, probiotics, or synbiotics are needed.

Often neglected but proven is the bidirectional relationship of anxiety and depression or other altered psychology states in IBD or IBS. Therefore, it is essential to have a holistic approach and to address such concerns in not only cases of active disease but for those in remission as well.[59-62]

FUTURE RESEARCH

Current research into IBS-IBD similarities has so far only scratched the surface. Further gene studies including NOD2 and IBD1-5 among others should be conducted to complement current information gleaned from the TNF-SF15 information we currently have.

Emerging gut microbiota research should be able to influence the management of IBS and IBD with utilization of pre/probiotics and perhaps vaccination strategies.

Gut-brain axis studies involving hypnosis and psychotherapy are beginning to show promising results, prompting a more inclusive view and stressing the importance of a multidisciplinary approach. Several studies are currently underway to assess the effect of IBS drugs such as tricyclics, and IBD drugs such as mesalamine, when used interchangeably to treat the opposite disorders. In several studies completed so far, although the above drugs had no major impact in IBS patients, there were improvements in some subtypes of IBS, suggesting that these drugs may be useful in patients at a certain threshold or timeline in their evolution of the IBS-IBD paradigm.[63-65]

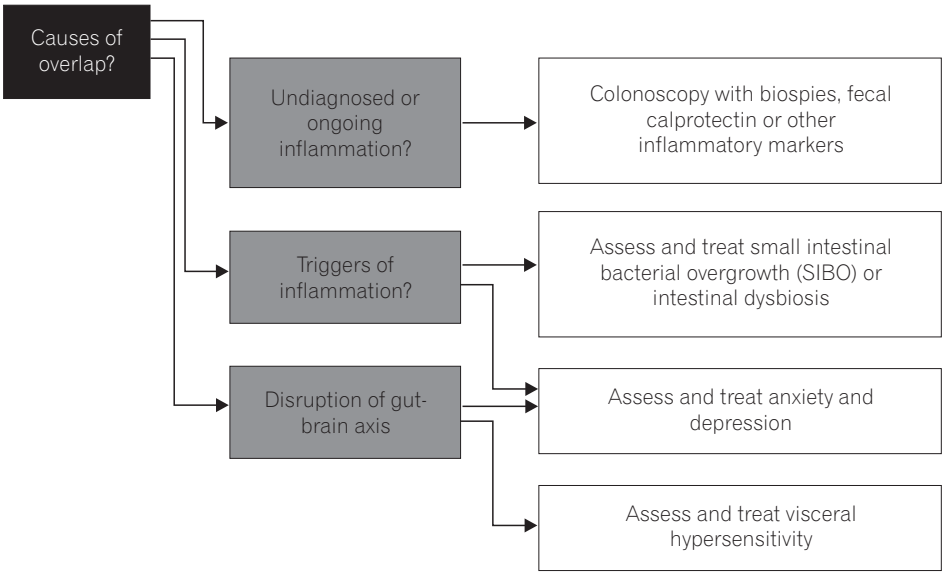

Fig. 2. Management consideration in IBS-IBD overlap. When considering progression or overlap of IBS-IBD, it is important to exclude undiagnosed or ongoing inflammation, and thus the need for biomarkers including fecal calprotectin (or others, either existing or in development) and pathological assessment. Triggers for ongoing inflammation are also sought especially occult infection and psychological dysfunction which are often subtle and not noticed. It is also important to assess and treat other disorders of the gut-brain axis (including visceral hypersensitivity).

CONCLUSIONS

Previously disputed, the idea of IBS and IBD being intimately interlinked seems to be gathering pace, backed by a litany of evidence and research developments. The disease paradigm may have to be altered to consider both IBS and IBD as belonging on the same timeline, but with differing presentation and outlook, allowing a more comprehensive management plan.

Ultimately, further research and studies into these particular areas may inadvertently lead to prevention strategies for IBS, thereby negating the subsequent consequences of IBD.

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Abbreviations:

5-HT	5-hydroxytryptamine
CBT	cognitive behavioural therapy
CI	confidence interval
CRC	colorectal cancer
cGMP	Cyclic GMP
EMA	European Medicines Agency
FDA	Food and Drug Administration

FODMAPs	fermentable oligo-, di-, and mono-saccharides and polyols
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhoea
IBS-M	irritable bowel syndrome with mixed stool pattern
IBS-U	irritable bowel syndrome unclassified
MC	microscopic colitis
OR	odds ratio
PI-IBS	post-infection IBS
RCT	randomised controlled trial
RR	relative risk
SeHCAT	23-seleno-25-homotaurocholic acid
SSRI	selective serotonin reuptake inhibitor
SIBO	small intestinal bacterial overgrowth
TCA	tricyclic antidepressant

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder whose symptoms include abdominal pain associated with a change in stool form or frequency. The condition affects between 5% and 10% of otherwise healthy individuals in the community at any one point in time and, in most people, runs a relapsing and remitting course. The best described risk factor is acute enteric infection, but IBS is also more common in people with psychological co-morbidity, and in young adult females. The pathophysiology of IBS remains incompletely understood, but it is well established that there is disordered communication between the gut and the brain, leading to motility disturbances, visceral hypersensitivity, and altered central nervous system processing. Other less reproducible mechanisms may include genetic associations, alterations in gastrointestinal microbiota, and disturbances in mucosal and immune function. In most people the diagnosis can be made based on the clinical history, with limited, judicious, use of investigations, unless alarm symptoms such as weight loss or rectal bleeding are present, or there is a family history of inflammatory bowel disease or coeliac disease. Once the diagnosis is made, an empathetic approach is key, and can improve quality of life and symptoms, and reduce health care expenditure. The mainstays of treatment include patient education about the condition, dietary changes, soluble fibre, and antispasmodic drugs. Other treatments tend to be reserved for those with more severe symptoms; these include central neuromodulators, intestinal secretagogues, drugs acting on 5-hydroxytryptamine or opioid receptors, or minimally absorbed antibiotics (all of which are selected according to predominant bowel habit), and psychological therapies. The increased understanding of the pathophysiology of IBS in the last 10 years has led to a healthy pipeline of novel drugs in development.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that has a substantial impact on quality of life and social functioning. [1,2] The pathophysiology of IBS is only partially understood. [3] It affects between and 5% and 10% of the general population, [4] and is characterised by recurrent abdominal pain in association with abnormal stool form or frequency. [5] Treatment aims to improve both abdominal pain and bowel habit, but often is targeted towards the most troublesome symptom. First-line therapies include dietary changes, soluble fibre, and antispasmodic drugs; in patients with more severe symptoms, treatments include central neuromodulators, including low-dose tricyclic antidepressants (TCAs), intestinal secretagogues, drugs acting on opioid or 5-hydroxytryptamine (5-HT) receptors, antibiotics, and psychological therapies. [6] The annual direct and indirect costs related to IBS are estimated to be up to €8 billion in Europe, [7] ¥123 billion in China, [8] and in excess of $10 billion in the USA. [9]

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the medical literature using MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials during the last 10 years with the terms “irritable bowel syndrome”, “epidemiology”, “prevalence”, “incidence”, “aetiology”, “pathophysiology”, “diagnosis”, “investigation”, “management”, “therapy”, and “treatment” in order to identify pertinent articles. In addition, we searched clinicaltrials.gov for unpublished trials. We included only publications in English, and selected those articles whose findings were, in our view, of the greatest importance, favouring randomised controlled trials, meta-analyses, and network meta-analyses.

EPIDEMIOLOGY

The most recent symptom-based diagnostic criteria for IBS, the Rome IV criteria, were developed by consensus among experts in functional gastrointestinal disorders. The criteria consist of abdominal pain associated with an alteration in either stool form or frequency, occurring for at least 6 months. [5] Patients are subgrouped according to predominant stool pattern, using the Bristol stool form scale: [10] IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), IBS with mixed stool pattern (IBS-M), and IBS unclassified (IBS-U) (Table 1). Methodological limitations make it difficult to obtain reliable estimates of prevalence, [11] particularly because, in the absence of universally accepted biomarkers of disease, the diagnosis relies on self-reported symptom clusters. However, as organic gastrointestinal disease in the community is relatively rare, and a diagnosis of IBS is made based on the presence of typical symptoms, population-based epidemiological studies provide a close approximation of true prevalence, which is between 5% and 10% in most geographical regions (Figure 1). [4]

Various iterations of these symptom-based diagnostic criteria have resulted in differences in reported prevalence, but disease impact is substantial even in people felt to have IBS, but not meeting such criteria. [12] In addition, both symptom interpretation and reporting are influenced by cultural factors, and can vary among ethnic groups.[11] Prior to publication of the Rome IV criteria in 2016, [5] two systematic reviews examining global prevalence of IBS were conducted. [4,13] The first reported a pooled prevalence of 11.2% (95% confidence interval (CI) 9.8% to 12.8%), [13] ranging from 1.1% in Iran, using the Rome III criteria, to 45% in Pakistan using Rome II. The second review reported a global prevalence of 8.8% (95% CI 8.7% to 8.9%). [4] Prevalence varied widely, from 1.1% in France using the Rome II criteria, and Iran using Rome III, to 35.5% in Mexico using Rome II. [14] Thus,

despite commonly accepted prevalence ranges, variation in estimates between studies is large, partly due to methodological heterogeneity.

Findings from a Rome Foundation 33-nation cross-sectional survey, examining worldwide prevalence and burden of functional gastrointestinal disorders in over 73,000 individuals in 26 countries, were published in 2020. [15] Using Rome IV criteria, prevalence rates ranged between 2% and 6%, with a pooled prevalence of 4.1%. In countries where both Rome III and IV criteria were applied, pooled prevalence fell from 10.1% with Rome III to 3.8% for Rome IV. However, there remains a dearth of prevalence data from Africa, Eastern Europe, and the Middle East.

RISK FACTORS

In two systematic reviews, rates of IBS were significantly higher in females [4,13] and, when 14 studies were pooled, prevalence was lower in those aged ≥50 (odds ratio (OR) 0.75; 95% CI 0.62 to 0.92) compared with those aged <50 years. [13] There are no reliable data on IBS and socio-economic status. IBS is more common in patients with functional somatic syndromes, such as fibromyalgia and chronic fatigue. [16] Many other psychosocial, biological, and environmental factors are associated with IBS, and may influence symptom severity (Figure 2). However, it is unclear if these are genuine risk factors; most studies are cross-sectional, and lack the temporal element needed to determine cause and effect.

Perhaps the best-recognised risk factor for IBS, observed in approximately 10% of patients, [17] is prior acute enteric infection. This is termed post-infection IBS (PI-IBS), and can occur after bacterial, viral, or protozoal infection. [18] In one retrospective cohort study, even non-specific gastrointestinal infections, which comprised the vast majority of cases, were associated with an equally high risk of PI-IBS to culture-confirmed bacterial or viral infections. [19] A meta-analysis of 45 observational studies reported a four-fold increase in

odds of developing IBS in exposed individuals 12 months post-infection (OR 4.2; 95% CI 3.1 to 5.7). [18] Risk factors for development of PI-IBS included female sex, antibiotic exposure, psychological distress preceding the illness, and severity of infection. [18] Prognosis may be better than in those with a non-infectious cause although, in one longitudinal follow-up study, 15% of those with PI-IBS remained symptomatic 8 years later. [20]

PATHOPHYSIOLOGY

The biopsychosocial model to explain symptoms of abdominal pain and disordered bowel habit in IBS conceptualised a genetic predisposition, where adverse events in early life, psychological factors, or gastrointestinal infections then trigger alterations in the enteric nervous system, which controls gastrointestinal motor, sensory, mucosal barrier, and secretory responses (Figure 3). [21]

"Traditional" Mechanisms: The Brain-gut Axis, Stress, Visceral Hypersensitivity, and Altered Motility

In addition to the psychological component of IBS, [22] gut-brain communication is bidirectional. Prospective longitudinal studies demonstrate that a subset of patients experience gastrointestinal symptoms first, [23,24] and psychological distress later. Gastrointestinal infection and psychological disorders appear to be distinct risk factors, contributing additively to the development of both PI-IBS and the extra-intestinal symptoms frequently linked to IBS, such as chronic fatigue. [19]

Altered visceral sensation in IBS is characterised by central abnormalities in sensory, emotional arousal, and prefrontal cortical regions of the brain. Alterations in the descending pathways modulating sensation, and peripheral mechanisms are also involved in the pathogenesis of visceral pain. [25] On average, about 60% of patients exhibit increased

sensitivity of the gut to different physiological stimuli. [26,27] Disordered motility in IBS is manifested by abnormal colonic myoelectric activity, [28] repetitive contractions of the small intestine and colon, associated with abdominal pain, and alterations in gastrointestinal or colonic transit. [29,30] Accumulation of different mechanisms (psychological, sensory, and motor) increases both gastrointestinal and non-gastrointestinal symptom severity, as well as impairments in quality of life. [31,32]

The Gut Microenvironment

As many IBS patients report that their symptoms are associated with eating, or eliminating, certain foods, [33] it has been assumed that diet and, more recently, gastrointestinal microbiota are involved in pathophysiology.

Dietary FODMAPs and Disaccharide Maldigestion

Fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs) are present in high levels in some fruits, artificial sweeteners, legumes, and green vegetables, and are poorly absorbed in all individuals. They have fermentative and osmotic effects, which may contribute to symptoms in some patients. [34] Although randomised controlled trials (RCTs) have confirmed that dietary modification can affect IBS symptoms, so far, they have not confirmed symptom generation by a specific food. Patients with IBS exhibit comparable increases in small intestinal water content and colonic volume to FODMAPs to those seen in healthy individuals, but symptomatic responses are greater in IBS, supporting the role of visceral hypersensitivity. [35] Dietary disaccharide maldigestion may induce symptoms secondary to osmotic diarrhoea and gas production following fermentation of unabsorbed sugars, [36,37] due to disaccharidase deficiency, classically lactase or, as more recently

demonstrated in 4% of patients with IBS, [38,39] sucrase-isomaltase, which digests sucrose and starch.

The Microbiome

Although some studies demonstrate that patients with IBS have a different gastrointestinal microbiome, compared with healthy controls, [40,41] the role of the microbiota is still questioned, particularly because what constitutes a "healthy" microbiome remains unclear. A systematic review demonstrated few consistent findings in IBS (possibly because age, sex, race, diet, and antibiotic intake were not controlled for in included studies), and certainly no microbiome signature differentiating IBS subgroups. [42] Antibiotics change the intestinal microbiome, and have been associated with development of IBS. [43] Small intestinal bacterial overgrowth (SIBO), has also been implicated, [44] but its role is controversial due, in large part, to limitations of available diagnostic tests, such as glucose and lactulose breath tests [45] and culture of jejunal aspirates. [46]

Bile Acids

Up to 25% of patients who meet criteria for IBS-D have idiopathic bile acid diarrhoea, demonstrated by abnormal retention following 23-seleno-25-homotaurocholic acid (SeHCAT) scanning, [47] or total 48-hour faecal bile acid levels. [48] The latter correlated with stool number and form, and colonic transit, in one case series of patients. [49] Excess faecal bile acids in IBS-D appeared to be associated with dysbiosis, specifically a Clostridia-rich microbiota, in a case-control study. [50]

Barrier Function and Immune Activation

Acute gastrointestinal infections induce changes in intestinal permeability and the microbiome. [51] This may promote activation of immune cells, including T-lymphocytes and mast cells, in the gastrointestinal epithelium, [52] leading to cytokine release, which can modify neural control of gastrointestinal motor, sensory, and secretory functions. Pathophysiological alterations can last for years. For example, in PI-IBS neuronal signalling remained sensitised 2 years after the infection. [53] Other investigators have reported increased gastrointestinal permeability and elevated immune cell counts, even in patients with IBS without an infective aetiology. [54,55]

Genetics

Although research into the genetics of IBS lags behind other conditions, like inflammatory bowel disease (IBD), genome-wide association studies have provided associations with variants on chromosome 9 (9q31.2 locus) that are linked to the functions of diverse ion channels and autonomic dysfunction, [56] and mutations in the sucrase-isomaltase gene, [38,39] as previously discussed. In addition, approximately 2% of IBS patients carry missense mutations in *SCN5A*, [57] which alters the function of the voltage-gated mechanosensitive Na^+ channel $Na_v1.5$, and affects smooth muscle function and mechanical sensitivity. In twin studies, concordance of a diagnosis of IBS is commoner in monozygotic, compared with dizygotic twins; however, having a parent with IBS is a stronger predictor, suggesting that environmental factors such as learned illness behaviour are more important. [58]

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Although IBS is a multifactorial and heterogeneous disorder, there are some typical features. The condition is most common among females aged 20 to 40 years, [4,13] although in

some countries appears more prevalent in males. [59] It can occur at any age; [15] the average age of participants in clinical trials of novel drugs in IBS is around 45 years, illustrating the broad age range of patients. Coexistent mood problems and extra-intestinal symptoms, including back pain, gynaecological and bladder symptoms, headache, and fatigue are common, [60,61] as is overlap with other functional gastrointestinal disorders. [62] The presence of abdominal pain is essential to the definition of IBS. Accordingly, the differential diagnosis is broad, but other features help narrow this down. Firstly, as IBS is a chronic disorder, causes of acute abdominal pain are ruled out. Secondly, the pain is recurrent, but it is intermittent rather than continuous. Thirdly, pain is usually in the lower abdomen, although Asian patients may report upper abdominal pain. [63] Finally, and most critically, pain in IBS is associated with defaecation, and occurs at the time when the patient experiences alterations in stool frequency or consistency. [5] Although IBS is subgrouped according to predominant stool pattern, [5] this fluctuates in many patients. [64] Abdominal bloating is not a cardinal symptom but is very common, and supports the diagnosis, particularly if it is diurnal. It is often accompanied by visible abdominal distension. [65]

In order to understand the precise meaning of terms such as diarrhoea or constipation, as well as the impact of the disorder on social functioning and wellbeing, a thorough history is essential. The Bristol stool form scale is a useful tool to assess stool consistency in the clinic, and can be used to direct treatment, which is discussed later. A detailed history helps differentiate between IBS and other disorders characterised by abdominal pain in association with altered bowel habit, including coeliac disease, IBD, colorectal cancer (CRC), and microscopic colitis (MC). These are considered below.

INVESTIGATIONS

Although there is no universally accepted biomarker for IBS, exhaustive investigation to exclude an organic cause for the symptoms is discouraged, as this is expensive, and many patients are not reassured by such an approach. [66] Once a clinical diagnosis of IBS is made, it is unlikely to be revised, even during extended follow-up. [67] Guidelines recommend a "positive" diagnosis using symptom-based diagnostic criteria, such as the Rome criteria, and minimising investigations (Figure 4). [6] Although the Rome IV criteria have yet to be validated independently, in secondary care sensitivity of the Rome III criteria was 68.8%, specificity 79.5%, and positive and negative likelihood ratios 3.35 and 0.39, respectively. [68] The addition of other features from the clinical history, including absence of nocturnal stools, presence of anxiety, depression, or extra-intestinal symptoms, and a normal full blood count and C-reactive protein enhances the diagnostic performance of the Rome III criteria. [69]

There is little evidence to support a routine panel of blood tests, other than full blood count, C-reactive protein, and serological screening for coeliac disease, which has a prevalence of 1% in most Western countries, and is an important differential diagnosis. A meta-analysis demonstrated an almost three-fold higher odds of positive coeliac serology in patients with symptoms suggestive of IBS (OR 2.75; 95% CI 1.35 to 5.61), compared with healthy controls, irrespective of predominant stool pattern. [70]

Whether any further investigations are required in a patient with new onset symptoms depends, to some extent, on bowel habit, unless alarm symptoms or signs (Table 2) are present. [71] The latter are an indication for urgent colonoscopy. Colonoscopy should also be performed if the patient is aged ≥50 years and has not already had age-related CRC screening. In addition, unexplained rectal bleeding or iron-deficiency anaemia needs investigation, regardless of age. A family history of coeliac disease, IBD, or CRC is also relevant. In a patient with IBS-C, the diagnosis is secure, unless there are obstructive

symptoms (excessive straining, sense of incomplete rectal evacuation, or digitation of the anus to facilitate defaecation) or digital rectal examination suggests a defaecatory disorder, [72] which is the result of incoordination of the normal functions required for rectal evacuation. If present, anorectal manometry with balloon expulsion testing may be helpful, as the treatment of choice for these conditions is biofeedback, [73] rather than dietary or drug therapy.

In a patient with diarrhoea, there may be greater concern for a missed organic diagnosis. Faecal calprotectin, which is a cytosol protein released by neutrophils, can differentiate between IBS and IBD, [74,75] avoiding the need for colonoscopy, for which the yield is low. In a cross-sectional survey of almost 500 patients with IBS, only 0.4% of patients were found to have IBD at colonoscopy, 1.5% MC, and there were no cases of CRC. [76] MC is more common in females over the age of 45 years. There are other clues to MC as a cause of symptoms, rather than IBS, which should lead to consideration of colonoscopy to obtain colonic biopsies. These include the fact that the presence of abdominal pain is variable, duration of symptoms tends to be shorter, and patients often have coexistent autoimmune disease, report nocturnal diarrhoea and weight loss, or are taking drugs, such as a non-steroidal anti-inflammatory drug or a proton pump inhibitor. [77,78]

Bile acid diarrhoea is another important differential in patients presenting with IBS-D, as its estimated population prevalence is 1%. It can be diagnosed using SeHCAT scanning, a fasting serum 7α-hydroxy-4-cholesten-3-one, fibroblast growth factor-19, or 48-hour faecal bile acid excretion, [79] but these are not universally available. A therapeutic trial of a bile acid sequestrant as a surrogate diagnostic test is an alternative, although it is unclear what dose should be used, and problems with medication compliance may compromise its utility. [80]

The reported association between SIBO and IBS is contentious. [44] Investigations to exclude SIBO should only be considered in patients with clear risk factors, such as previous gastric or intestinal surgery, or known structural abnormalities, including jejunal

diverticulosis. Hydrogen breath tests may be falsely positive, as they are a marker for rapid transit. [45] Instead, culture of jejunal aspirates should be considered if SIBO is suspected. [81]

NATURAL HISTORY AND IMPACT

The typical course in IBS consists of fluctuating symptoms, in terms of bowel habit. [64] Incidence of new-onset IBS was approximately 1.5% to 2.5% per year, over 10 to 12 years, in three longitudinal studies. [82-84] However, prevalence remains stable, because the number of people developing new symptoms is matched by the number whose symptoms disappear or fluctuate to another functional gastrointestinal disorder. [83,84] IBS causes morbidity, but not mortality, [85] and affects quality of life [1] to the same degree as organic gastrointestinal disorders such as Crohn's disease. [86]

It also impacts work productivity, [1,2] social integration, and psychosocial factors, such as general and gut-related anxiety, depression, and somatisation. [60,87] Some of these associations are bidirectional, [23,24] so that psychosocial factors can exacerbate IBS symptoms, and the illness experience, and vice versa. One cross-sectional survey showed the impact on daily activity differs according to stool pattern; those with IBS-D avoided travel or leaving the house, due to concerns about toilet access, and those with IBS-C avoided sexual intercourse and reported difficulty concentrating. [88] Associations with severity include overlap with other functional gastrointestinal disorders, [62] and consulter status. [89] However, those who consult with symptoms also have poorer quality of life, increased rates of psychological symptoms, and reduced coping. [89] There is a direct correlation between number of overlapping functional gastrointestinal disorders, reduced quality of life, and increased health care utilisation and gastrointestinal surgery. [62] Patients are willing to accept a 1% median risk of sudden death in return for a 99% chance of cure of their symptoms with a hypothetical medication. [90]

MANAGEMENT

As no medical therapy is proven to alter the natural history of IBS, and the majority of RCTs are only conducted over a 12-week period meaning that their long-term efficacy is unknown, an empathetic approach is key. This can improve quality of life and symptoms, [91] reduce health care visits, and enhance adherence to treatment. [92,93] Management should commence with explanation of the disorder, its pathophysiology, and natural history. In fact, structured patient education about the condition led to a significantly greater improvement in symptoms, compared with written information, in one RCT. [94] Treatment is directed towards the predominant symptom, with a realistic discussion of the limitations of available therapies, in order to manage expectations, as most improve symptoms in only 25% to 30% of patients (Table 3), and have only been tested in referral populations. The final decision as to the choice of treatment should be the patient's, after they receive full information on available options in a dialogue with the doctor.

Lifestyle, Diet, and Probiotics

The effect of lifestyle changes in IBS has not been well studied; in a small RCT of physiotherapist-administered exercise, symptoms improved significantly, compared with a control arm with no changes to physical activity. [95] Traditionally, patients with IBS were told to increase dietary fibre intake. However, bran may exacerbate symptoms, [96] although ispaghula husk was more efficacious than placebo in a meta-analysis of seven RCTs (relative risk (RR) of remaining symptomatic 0.83; 95% CI 0.73 to 0.94). [97] Several RCTs demonstrate that FODMAP restriction leads to an improvement in IBS symptoms, compared with habitual diet. [98,99] However, other RCTs suggest that "traditional" dietary advice to eat small regular meals, avoid known trigger foods, and reduce alcohol and caffeine, is as effective as a low FODMAP diet. [100,101] Long-term FODMAP restriction may lead to

384 deleterious alterations in the microbiome. [102] FODMAPs should, therefore, be reintroduced to
385 tolerance after a limited period of restriction, but RCTs conducted to date only examine the
386 effect on symptoms during FODMAP elimination. There is little evidence to support benefit
387 of a gluten-free diet in IBS. [103] However, as wheat contains fructans, which is a FODMAP, it
388 incorporates elements of a low FODMAP diet; some patients may, therefore, adapt a low
389 FODMAP diet to one that instead avoids gluten. [104] There have been numerous RCTs of
390 probiotics in IBS but, although some trials show positive results, ability to make
391 recommendations as to which combination, species, or strain is effective is limited due to the
392 wide variety of products studied, and the conflicting results among individual trials. [105]
393
394 **First-line Medical Therapies**
395 Laxatives, antidiarrhoeals, and antispasmodics are all used first-line in IBS. Most
396 RCTs of these drugs are old, and are hampered by suboptimal methodology and
397 heterogeneous patient selection, meaning that efficacy according to predominant stool pattern
398 is uncertain. In addition, efficacy endpoints do not meet current recommendations from the
399 Food and Drug Administration (FDA) or European Medicines Agency (EMA). Although
400 osmotic and stimulant laxatives are efficacious in chronic constipation, [106] there is little
401 evidence for their use in IBS. A placebo-controlled trial of polyethylene glycol in 139
402 patients with IBS-C demonstrated an increased number of bowel movements, but no
403 improvement in abdominal pain. [107] Similarly, there are only a few small RCTs of
404 antidiarrhoeals, such as loperamide. [6] Nevertheless, some patients find laxatives or
405 antidiarrhoeals useful. Antispasmodic drugs were more efficacious than placebo in a meta-
406 analysis of 26 trials (RR of remaining symptomatic 0.65; 95% CI 0.56 to 0.76), although side
407 effects were more common (RR 1.60; 95% CI 1.15 to 2.21). [6] In terms of individual drugs,
408 otilonium, cimetropium, pinaverium, and hyoscine had the most evidence for efficacy;

availability is an issue in some countries. A 4-week RCT of pinaverium, recruiting 427 Chinese patients with IBS-D, and which used FDA-recommended endpoints, demonstrated a significant benefit of the drug over placebo for both abdominal pain and diarrhoea, [108] suggesting antispasmodics may be efficacious in IBS-D. Peppermint oil also appeared superior to placebo in a meta-analysis of seven RCTs (RR of remaining symptomatic 0.54; 95% CI 0.39 to 0.76), [6] although a subsequent placebo-controlled trial of small intestinal or ileocolonic-release formulations did not demonstrate efficacy for either FDA or EMA-recommended endpoints. [109]

Second-line Medical Therapies

Given the accepted role of the gut-brain axis in IBS, the use of antidepressant drugs and CNS targeted medications, or central neuromodulators, as a potential therapy is logical. There is some evidence for efficacy of TCAs; a meta-analysis of 12 RCTs reported a RR of remaining symptomatic of 0.65 (95% CI 0.55 to 0.77) compared with placebo, but trial quality was low and in most RCTs patients were not recruited according to predominant stool pattern. [110] Adverse events were more common (RR 1.56; 95% CI 1.23 to 1.98). TCAs have neuromodulatory properties and also slow gastrointestinal transit, [111] so may be best for patients with predominant pain and/or diarrhoea. Evidence for efficacy of selective serotonin reuptake inhibitors (SSRIs) in the same meta-analysis was less convincing. [110] A 12-week placebo-controlled trial of pregabalin in 85 patients failed to demonstrate adequate relief of symptoms, but there were significant improvements in global symptoms, pain, diarrhoea, and bloating. [112] All other second-line therapies are licensed and are used based on predominant stool pattern.

5-HT_4 receptor agonists accelerate gastrointestinal transit. Tegaserod was more efficacious than placebo in IBS-C, [113] but was withdrawn due to a small excess number of

cerebrovascular and cardiovascular ischaemic events. It was reintroduced in the USA in 2018 for female patients <65 years without existing cardiovascular disease. Prucalopride, another 5-HT_4 agonist, was superior to placebo in chronic constipation; [106] there are no RCTs in IBS-C. Intestinal secretagogues, such as lubiprostone, linaclotide, plecanatide, and tenapanor act on ion channels in enterocytes, leading to water efflux, thereby accelerating gastrointestinal transit and improving stool consistency. Placebo-controlled trials have demonstrated efficacy of these drugs in IBS-C; [114-117] there have been no head-to-head trials. A network meta-analysis of 15 RCTs demonstrated similar efficacy for all drugs, but linaclotide was ranked first for improvements in global symptoms, abdominal pain, and stool frequency; tenapanor ranked first for improvement in bloating. [118] Diarrhoea was the most common adverse event with all drugs except lubiprostone, which causes nausea in up to 20% of patients. [118]

Licensed therapies for IBS-D include the 5-HT_3 antagonists alosetron and ramosetron, a peripherally acting mixed opioid receptor agonist/antagonist eluxadoline, and the minimally absorbed antibiotic rifaximin. 5-HT_3 antagonists and eluxadoline slow gastrointestinal transit and reduce visceral hypersensitivity. [119] 5-HT_3 antagonists also alter rectal compliance. [120] Rifaximin has been tested on the basis that alterations in the gastrointestinal microbiota and SIBO may, in part, be responsible for symptoms in IBS; the exact mechanism of action remains uncertain. [121] Although all these drugs have demonstrated efficacy over placebo, [113,122-124] again there have been no head-to-head trials. A network meta-analysis of 18 RCTs demonstrated that 5-HT_3 receptor antagonists ranked first for improvement in global symptoms, abdominal pain, and stool consistency. [125] All drugs, except rifaximin, were more likely to cause constipation than placebo. A crossover placebo-controlled trial of ondansetron, another 5-HT_3 antagonist, in 120 patients with IBS-D demonstrated significant improvements in stool consistency and urgency, but not pain; [126] a large RCT is ongoing. [127]

Figure 5 outlines the spectrum of medications available for pain, constipation, and diarrhoea in IBS, as well as drugs in development. Overall, there is a plethora of choices for diarrhoea or constipation, but still an unmet clinical need for relief of pain.

Psychological Therapies

Similar to central neuromodulators, psychological therapies may exert not only central effects on mood, but also peripheral effects on pain perception, visceral hypersensitivity, and gastrointestinal motility. [128,129] A meta-analysis of 36 RCTs demonstrated that cognitive behavioural therapy (CBT), gut-directed hypnotherapy, relaxation therapy, multi-component psychological therapy, and dynamic psychotherapy were all more effective than a control intervention. [110] Some have evidence for efficacy out to 12 months of follow-up. [130] These may be intensive, in terms of hours of therapist contact, but subsequent RCTs demonstrate that minimal contact CBT, CBT via the telephone, and group gut-directed hypnotherapy are also effective, even for patients whose symptoms are refractory to medical therapy. [131-133] Whether earlier intervention with psychological therapies can change the natural history of IBS, or whether augmentative therapy with a psychological therapy and a central neuromodulator has additive benefit, is unclear.

FUTURE DIRECTIONS AND CONTROVERSIES

Reasons for the difference in prevalence of IBS across different countries, remain uncertain, and prevalence data from certain regions are lacking. Our understanding of the epidemiology is likely to increase as the Rome Foundation global cross-sectional survey database of 73,076 participants is mined further. [15] Despite considerable efforts, a biomarker for IBS remains elusive. A validation study of antibodies to bacterial toxins and host cell adhesion proteins performed only modestly in distinguishing IBS from health. [134] A case-

control study reported distinct faecal and urinary metabolomic profiles in those with IBS, [135] which might allow the development of microbe-based treatments. The efficacy of probiotics and faecal microbiota transplantation is inconsistent, [105,136] although a RCT of faecal microbiota transplantation using a single, healthy, well-characterised donor demonstrated efficacy. [137] However, more than 50% of patients in this trial continued to have moderate to severe symptoms. With the discovery of actionable biomarkers to identify the mechanisms underlying symptoms the hope is that, in the future, IBS therapy will move away from drugs targeting the predominant symptom, or symptoms, towards one where patients are stratified based on underlying pathophysiology, using these biomarkers, in order to facilitate individualised treatment. [138]

Other pharmacological therapies are in development (Figure 5). Drugs that reduce uptake of sodium ions from the lumen, via transporters expressed in the intestine, result in water retention in the lumen and looser stools. These include mizagliflozin, a sodium-glucose cotransporter-1 inhibitor, and DRAinh-A250, an inhibitor of the solute carrier 26A3. In a phase 2 placebo-controlled trial of mizagliflozin in patients with chronic constipation, response rates were significantly higher with 5mg and 10mg doses, and the medication appeared safe, [139] albeit after only 1 week of treatment. When administered intraluminally, DRAinh-A250 blocked fluid absorption in mouse colonic loops and reversed loperamide-induced constipation; [140] there are no human studies to date.

Bile acids are physiological laxatives, and are implicated in the pathophysiology of IBS. [48] Inhibition of the ileal bile acid transporter by elobixibat accelerated colonic transit in patients with constipation, [141] and a trial in Japan demonstrated that a 10mg dose was efficacious in patients with constipation, including IBS-C. [142] Although the drug is licensed in Japan, adverse events occurred in 30% of patients, particularly diarrhoea and abdominal pain, and this was only a 2-week trial.

Novel analgesic approaches include further refinements of existing secretagogues. Cyclic GMP (cGMP) production in enterocytes is stimulated by some of these drugs, such as linaclotide. When transported into the extracellular space at the basolateral membrane, [143] cGMP leads to decreased conduction of submucosal afferent nociceptive neurons, attenuating visceral pain. [144] A preliminary RCT of targeted colonic delivery of linaclotide in patients with IBS-C demonstrated pain relief, without effects on constipation, [145] suggesting that cGMP release from enterocytes reduces the function of peripheral visceral afferents.

When conventional opioids bind to μ-opioid receptors, they induce analgesia through activation of G protein-mediated pathways, but they also activate β-arrestin, which inhibits gastrointestinal motility and depresses central functions, such as cognition and respiration. New biased μ-opioid receptor ligands activate the G protein pathway exclusively, leading to analgesia with reduced gastrointestinal dysfunction. [146] Oliceridine is a biased μ-opioid receptor ligand with comparable analgesic effects to morphine although there are, as yet, no human studies in visceral pain. [147] The cannabinoid type-2 receptor agonist, olorinab, has the potential to alter immune function, as well as sensation, given expression of cannabinoid type-2 receptors in the brain, peripheral nervous system, and gastrointestinal tract. In an open-label trial in patients with quiescent Crohn's disease, it reduced abdominal pain and improved bowel movements. [148] Clinical trials are being conducted in IBS. [149] The histamine-$_1$ receptor antagonist ebastine appears to attenuate visceral hypersensitivity *in vitro* [150] and, in a RCT of 45 patients, led to significant improvements in both global symptoms and abdominal pain compared with placebo; [150] a larger trial is in progress. [151]

In summary, the greater understanding of pathophysiological mechanisms in IBS has ushered in the development of novel treatment strategies to manage patients, particularly the abdominal pain component of IBS, for which central neuromodulators or psychological therapies are currently the main approaches. The diverse molecular mechanisms to which

drugs in development are targeted augurs for substantial impact in the management of IBS in the foreseeable future. Nevertheless, a strong doctor-patient relationship with attention to the clinical history, an appreciation of the impact of symptoms on the patient's life, together with an explanation of the condition and its natural history, and shared decision-making, remain key to effective management.

Contributors

ACF, ADS, MC, and MC did the literature search, wrote the manuscript, and drafted the figures. ACF and MC revised the initial manuscript. All authors critically revised subsequent versions of the manuscript and approved the final version of the manuscript.

Declaration of Interests

ACF has no conflicts of interest. ADS has no conflicts of interest. MC has acted as a consultant to Allergan outside the submitted work. MC reports grant from Allergan, grant from Novartis, grant from Takeda, and other from Allergan, Ironwood, Arena, Takeda (consulting with fees going to employer, Mayo Clinic), outside the submitted work.

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FIGURE LEGENDS.

Figure 1. Global Prevalence of Irritable Bowel Syndrome According to the Rome III Criteria*.

***Note, the prevalence data reported here are taken from studies using the Rome III criteria for IBS, summarised in references 4, 13, and 15.**

Figure 2. Factors Affecting Symptom Severity in Irritable Bowel Syndrome.

Figure 3. Pathophysiological Mechanisms Involved in Irritable Bowel Syndrome.

***Genome-wide association studies have demonstrated associations with variants of chromosome 9 (reference 56), and mutations in the sucrase-isomaltase gene (references 37 and 38), and studies have shown approximately 2% of IBS patients carry mutations in *SCN5A* (reference 57), which alters the function of the voltage-gated mechanosensitive Na^+ channel $Na_v1.5$.**

†See references 17 to 20.

±Gastrointestinal symptoms include abdominal pain, abnormal stool form and/or frequency, and bloating (reference 5); non-gastrointestinal symptoms include back pain, gynaecological and bladder symptoms, headache, and fatigue (reference 60).

Figure 4. Suggested Diagnostic Algorithm for Patients with Suspected Irritable Bowel Syndrome.

***Abdominal pain, related to defaecation, associated with change in stool form or stool frequency (reference 5).**

†Full blood count and C-reactive protein/erythrocyte sedimentation rate

±See Table 2.

§Including family history of inflammatory bowel disease, coeliac disease, or colorectal cancer, or features suggestive of microscopic colitis (female, age ≥50 years; co-existent autoimmune disease; proton pump inhibitor or non-steroidal anti-inflammatory drug

use; duration of diarrhoea < 12 months; weight loss; or nocturnal diarrhoea (references 77 and 78)).

‡Consider measuring SeHCAT retention, serum 7α-hydroxy-4-cholesten-3-one, serum fibroblast growth factor-19, or 48-hour faecal bile acid excretion, where available, or a trial of a bile acid sequestrant, to exclude bile acid diarrhoea.

****If the initial faecal calprotectin level is within the abnormal range the suspicion for inflammatory bowel disease is high, proceed to colonoscopy (reference 74); if the initial faecal calprotectin level is indeterminate according to local laboratory values, repeat the test off non-steroidal anti-inflammatory drugs and refer for colonoscopy if the repeat test remains indeterminate or is within the abnormal range.**

††If features suggestive of a defaecatory disorder, including obstructive symptoms (such as a feeling of incomplete evacuation or the need to digitate during defaecation) or paradoxical anal contraction on straining during digital rectal examination, are present consider anorectal manometry with balloon expulsion testing.

Figure 5. Current and Emerging Treatment Options for Irritable Bowel Syndrome.

Table 1. The Rome IV Criteria for Irritable Bowel Syndrome*.

Rome IV IBS Diagnostic Criteria			
1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months and associated with two or more or the following: a. Related to defaecation; b. Associated with a change in frequency of stool; c. Associated with a change in stool form. **AND** **2.** Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis			
IBS-C	**IBS-D**	**IBS-M**	**IBS-U**
≥25% of bowel movements of Bristol stool form types 1 or 2, and <25% of Bristol stool form types 6 or 7.	≥25% of bowel movements of Bristol stool form types 6 or 7, and <25% of Bristol stool form types 1 or 2.	≥25% of bowel movements of Bristol stool form types 1 or 2, and ≥25% of bowel movements of Bristol stool form types 6 or 7.	Patients who meet criteria for IBS, but who do not fall into one of the other three subgroups according to Bristol stool form type.

***Adapted from reference 5.**

Table 2. Lower Gastrointestinal Alarm Symptoms and Signs (Based on the UK's NICE Guidance*).

Definite Referral Criteria
• Aged ≥40 years with unexplained weight loss and abdominal pain. • Aged ≥50 years with unexplained rectal bleeding. • Aged ≥60 years with change in bowel habit, a positive faecal occult blood test, or iron deficiency anaemia.

***Adapted from reference 71.** Regardless of age, adults with unexplained rectal bleeding or iron-deficiency anaemia (especially if accompanied by abdominal pain, change in bowel habit, or weight loss), or an abdominal or rectal mass, need investigation to exclude other gastrointestinal disorders, including cancer.

Table 3. Summary of Evidence for Efficacy of Treatment Approaches for Irritable Bowel Syndrome*.

Therapy	Specific Intervention†	IBS Subgroup Studied	Efficacy	Quality of Data	Adverse Events	Limitations of Data
Diet, lifestyle, and probiotics	Soluble fibre (e.g. ispaghula 20 - 30g/day)	No specific IBS subgroup recruited	Effective	Moderate	Total adverse events no more common with soluble fibre in three RCTs	Only one RCT at low risk of bias; only a small number of patients in existing RCTs
	Low FODMAP diet	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events rarely reported	All RCTs at high risk of bias; heterogeneity between study designs; imprecision in estimate of effect; impact of FODMAP reintroduction not studied within the design
	Exercise	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events not reported	Only two RCTs, which were at high risk of bias; inconsistent effects on symptoms
	Probiotics	No specific IBS subgroup recruited	May be effective	Very low	Total adverse events no more common with probiotics in a meta-analysis of 36 RCTs	Heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual probiotic, meaning that it is difficult to know which species or strain is effective
First-line therapies	Peppermint oil (200mg three times daily)	No specific IBS subgroup recruited	Effective	Low	Total adverse events no more common with peppermint oil in a meta-analysis of six RCTs	Only two RCTs at low risk of bias; heterogeneity between studies; trials used very specific formulations so data cannot be extrapolated to other available products; heartburn may be an issue
	Laxatives (e.g. polyethylene glycol 13.8g once daily and titrated)	Patients with IBS-C	Unclear efficacy	Low	Rates of abdominal pain numerically higher with polyethylene glycol in one RCT	Only two RCTs; both RCTs unclear risk of bias; effect on abdominal pain unclear
	Antidiarrhoeals (e.g. loperamide 4mg as required)	Patients with IBS-D and IBS-M	Unclear efficacy	Very low	Total adverse events no more common with antidiarrhoeals in two RCTs	Only two RCTs; both RCTs unclear risk of bias; not all patients met criteria for IBS; no significant effect on IBS symptoms when data pooled; constipation may be an issue

	Antispasmodics (e.g. cimetropium 50mg three times daily, hyoscine 10-20 mg three times daily, otilonium20-40mg three times daily, or pinaverium 50mg three times daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	May be effective	Very low	Total adverse events significantly more common with antispasmodics in a meta-analysis of 26 RCTs, particularly dry mouth, dizziness, and blurred vision	Only two RCTs at low risk of bias; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each individual antispasmodic
Second-line therapies	5-HT_4 agonists (e.g. tegaserod 6mg twice daily)	IBS-C	Effective	High	Diarrhoea significantly more common with tegaserod in a meta-analysis of six RCTs	Concerns regarding small excess of cardiovascular and cerebrovascular events led to withdrawal of tegaserod, reintroduced in 2018 but only for specific patients; no RCTs of prucalopride
	Linaclotide (290mcg once daily)	IBS-C	Effective	High	Diarrhoea significantly more common with linaclotide in a meta-analysis of three RCTs	None
	5-HT_3 antagonists (e.g. alosetron 0.5-1mg twice daily, ramosetron 2.5-5mcg once daily, or ondansetron 4mg once daily and titrated)	IBS-D and IBS-M	Effective	High	Constipation significantly more common with alosetron in a meta-analysis of three RCTs	All RCTs of ramosetron conducted in Japan; serious adverse events with alosetron included ischaemic colitis and severe constipation leading to restricted use; ramosetron is safer, although constipation is still more common with active therapy
	TCAs (e.g. amitriptyline 10-30mg at night or desipramine 50mg at night)	No specific IBS subgroup selected, other than one RCT in patients with IBS-D	Effective	Moderate	Total adverse events significantly more common with TCAs in a meta-analysis of six RCTs, particularly dry mouth and drowsiness	Only three RCTs at low risk of bias; possible publication bias; some atypical trials included
	Lubiprostone (8mcg twice daily)	IBS-C	Effective	Moderate	Nausea significantly more common with lubiprostone in a meta-analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	Plecanatide (3-6mg once daily)	IBS-C	Effective	Moderate	Diarrhoea significantly more common with plecanatide in a meta-analysis of two RCTs	Only a modest benefit over placebo in published RCTs

	Tenapanor (50mg twice daily)	IBS-C	Effective	Moderate	Rates of diarrhoea numerically higher with tenapanor	Awaiting publication of all phase 3 trial data
	Eluxadoline (100mg twice daily)	IBS-D	Effective	Moderate	Rates of constipation, nausea, and vomiting numerically higher with eluxadoline in a pooled analysis of two RCTs	Heterogeneity between studies; only a modest benefit over placebo in published RCTs; no benefit over placebo in terms of abdominal pain; serious adverse events include acute pancreatitis and sphincter of Oddi spasm
	Rifaximin (550mg three times daily)	IBS-D and IBS-M	Effective	Moderate	Total adverse events no more common with rifaximin in a pooled analysis of three RCTs	Only a modest benefit over placebo in published RCTs
	SSRIs (e.g. fluoxetine 20mg once daily)	No specific IBS subgroup selected, other than one RCT in patients with IBS-C	May be effective	Low	Total adverse events no more common with SSRIs	Only one RCT at low risk of bias; heterogeneity between studies
	Pregabalin (225mg twice daily)	No specific IBS subgroup recruited	May be effective	Low	Total adverse events numerically higher with pregabalin, particularly blurred vision, dizziness, and altered sensation	Only one single-centre RCT although global symptoms, abdominal pain, diarrhoea, and bloating improved significantly
Psychological therapies	CBT or gut-directed hypnotherapy	No specific IBS subgroup recruited	Effective	Very low	Adverse events not reported in individual RCTs, precluding their assessment in a meta-analysis of 36 RCTs	All RCTs at high risk of bias due to the nature of the interventions studied; heterogeneity between studies; possible publication bias; only a small number of RCTs assessing each intervention; time consuming due to need for therapist contact; limited availability in some countries

***Data adapted from reference 6.**

†Most drugs should be trialled for 3 months, with their efficacy then reviewed, with the exception of rifaximin, which is a 2-week treatment course. A low FODMAP diet should not be maintained long-term; the restriction phase in RCTs to date has been a maximum of 3 to 4 weeks.

Irritable bowel syndrome

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Abstract | Irritable bowel syndrome (IBS) is a functional gastrointestinal disease with a high population prevalence. The disorder can be debilitating in some patients, whereas others may have mild or moderate symptoms. The most important single risk factors are female sex, younger age and preceding gastrointestinal infections. Clinical symptoms of IBS include abdominal pain or discomfort, stool irregularities and bloating, as well as other somatic, visceral and psychiatric comorbidities. Currently, the diagnosis of IBS is based on symptoms and the exclusion of other organic diseases, and therapy includes drug treatment of the predominant symptoms, nutrition and psychotherapy. Although the underlying pathogenesis is far from understood, aetiological factors include increased epithelial hyperpermeability, dysbiosis, inflammation, visceral hypersensitivity, epigenetics and genetics, and altered brain–gut interactions. IBS considerably affects quality of life and imposes a profound burden on patients, physicians and the health-care system. The past decade has seen remarkable progress in our understanding of functional bowel disorders such as IBS that will be summarized in this Primer.

Irritable bowel syndrome (IBS) is a functional bowel disorder (that is, not associated with structural or biochemical abnormalities that are detectable with the current routine diagnostic tools) characterized by abdominal pain or discomfort, stool irregularities and bloating (BOX 1). Symptoms can be debilitating in many individuals, but may be mild or moderate in other patients. In addition, IBS is often associated with other somatic comorbidities (for example, pain syndromes, overactive bladder and migraine), psychiatric conditions (including depression and anxiety) and visceral sensitivity. The population prevalence of IBS is high (~11%) and the condition has considerable consequences for quality of life (QOL) that are comparable to other chronic diseases, such as diabetes mellitus and hepatitis. IBS is diagnosed based on symptoms, and a distinction is made between the following subtypes of IBS: IBS with pain or discomfort and predominant constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (IBS-U) (FIG. 1). Moreover, other diseases (including other functional gastrointestinal diseases, such as functional dyspepsia and gastroesophageal reflux disease) that may cause the typical IBS symptoms should be excluded. Although a substantial proportion of patients will experience spontaneous remission over time, there is currently no treatment that cures IBS; relief of symptoms is the most that can be achieved.

IBS is a multifactorial disease. Hence, the underlying pathogenesis is considered complex and the precise molecular pathophysiology is far from understood. Several functional alterations have been described, such as altered visceral sensitivity, functional brain alterations, bowel motility and secretory dysfunctions, and somatic and psychiatric comorbidities. Furthermore, gastrointestinal abnormalities — such as immune activation, gut dysbiosis (microbial imbalance), impaired mucosal functions, nerve sensitization, post-infectious plasticity, altered expression and release of mucosal and immune mediators, and altered gene expression profiles — have been associated with IBS. However, a coherent link between particular pathologies and IBS symptoms is yet to be established.

Moreover, results from studies assessing the contribution of most of the proposed pathological factors are inconsistent and the particular aetiology is often not related to particular gut symptoms. For example, some studies have found evidence for gut micro-inflammation in IBS, whereas others could not confirm this finding, despite similar gastrointestinal symptoms. Such discrepancies, which also apply to the other biomarker candidates (not only to inflammation), strongly suggest the existence of IBS subpopulations, which, despite the similarity in gut symptoms, can be defined and distinguished by their pathophysiology and in-depth

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assessments of clinical and molecular biomarker clusters. The same heterogeneity is evident with respect to clinical diagnosis and management. Indeed, medical treatment, nutritional intervention and psychotherapy lack consistent and homogeneous efficacy, but can be effective in some subgroups.

This Primer summarizes recent progress in our understanding of IBS prevalence, comorbidities, QOL and the putative roles of inflammation, genetics, the intestinal microbiota and the brain–gut axis in IBS pathogenesis. Furthermore, we will discuss the current diagnostic approach and highlight the therapeutic options in IBS, including drugs, nutrition and psychotherapy.

Epidemiology

Global prevalence and incidence

Prevalence rates of IBS vary between 1.1% and 45%, based on population studies from countries worldwide (FIG. 2; Supplementary information S1 (table)), with a pooled global prevalence of 11.2% (95% CI: 9.8–12.8)[1]. Prevalence rates of 5–10% are reported for most European countries, the United States and China[1]. Population statistics for IBS in most African and many Asian countries are unavailable, which might point to the inability to differentiate between infectious diarrhoea and IBS in tropical countries, especially in those nations with poor health-care systems or limited patient access to medical care, or to less attention of the health-care system for functional disorders, once an acute infection has been excluded[2].

Gathering subtype-specific prevalence information is complex. IBS subtypes overlap considerably in terms of symptoms, and patients vary over time in terms of their predominant symptoms, and thus switch subtype[3]. The few population studies that have differentiated between IBS subtypes suggest that, in countries with a total IBS prevalence of ~10%, IBS-C and IBS-D each account for one-third of the affected population[4]. Incidence rates of IBS (that is, the annual occurrence of new cases) are not reported for most countries, but a few long-term surveys (≥10 years) in the United States allow for an estimation of the annual incidence in the range of 1–2%[5]. At the same time, disappearance rates of 2% have been reported[6], indicating spontaneous disease remission.

Association between IBS and other disorders

Not only do IBS subtypes overlap[6] but population-based studies also report a substantial overlap of ≥20% with other functional gastrointestinal disorders of the upper and lower gastrointestinal system: functional dyspepsia, heartburn, gastroesophageal reflux disease and nausea on the one hand[7], and diarrhoea, incontinence, pelvic floor dyssynergia and constipation on the other hand[8]. An overlap of IBS with inflammatory bowel diseases (IBDs; including Crohn disease and ulcerative colitis) during remission phases has been proposed[9] but is not mutually agreed on[10].

Other IBS-associated disorders (FIG. 3) include functional non-gastrointestinal syndromes, such as urological chronic pelvic pain syndrome (this term includes interstitial cystitis and chronic prostatitis), vulvodynia, overactive bladder, prostatic pain syndrome, premenstrual syndrome, sexual (including erectile) dysfunction, chronic pelvic pain, fibromyalgia syndrome, chronic fatigue syndrome, migraine, eating disorders, nutritional intolerances and others[11]. All of these syndromes considerably overlap with IBS in population studies to a degree that is often beyond what is expected based on the prevalence rates of the individual diseases. Given that many of these conditions are only diagnosed in specialized centres, it has been questioned as to whether some of these conditions — for example, IBS and chronic pelvic pain — are one and the same disease[12].

In addition, most epidemiological studies note the presence of psychiatric comorbidities (such as anxiety, depression, somatization or neuroticism) not only for IBS but also for these IBS-associated diseases. Again, the rates are above the expected levels for IBS and the population prevalence of these symptoms[13]. Thus, the entire disease entity (IBS, functional gastrointestinal disorders and other functional non-gastrointestinal disorders) has been included in the term 'somatic symptom disorder'

Box 1 | **IBS definition and subtypes: Rome III criteria**

Diagnostic criteria* for irritable bowel syndrome (IBS) include recurrent abdominal pain or discomfort‡ at least 3 days per month in the past 3 months associated with two or more of the following:

- Improvement with defaecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in the form (appearance) of stool

*Criteria fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis.
‡Discomfort means an uncomfortable sensation not described as pain. In pathophysiological research and clinical trials, a pain or discomfort frequency of at least 2 days per week during screening evaluation for subject eligibility. Adapted with permission from REF. 119, American Gastroenterology Association.

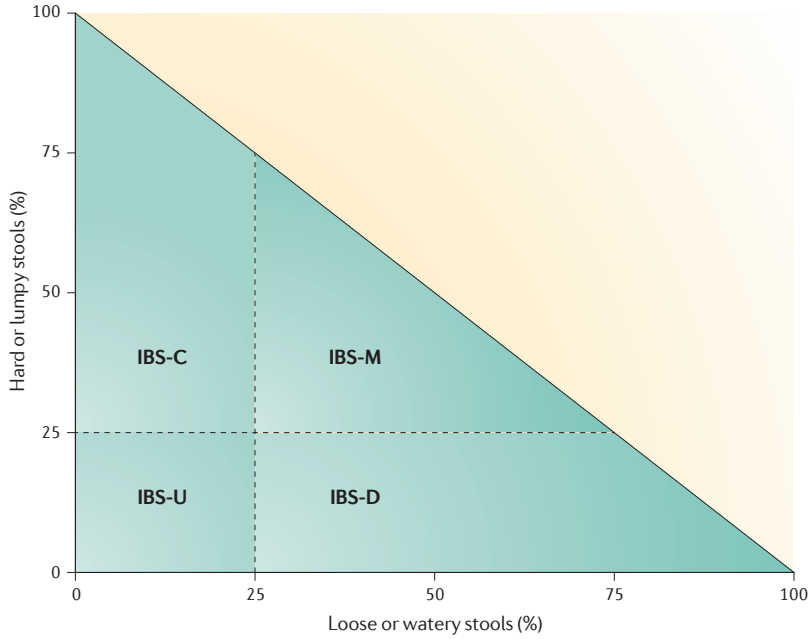

Figure 1 | **IBS subtypes according to the Rome III criteria.** A two-dimensional graph of the four possible irritable bowel syndrome (IBS) subtypes according to bowel form at a particular point in time, and the percentage of time this bowel form has to be present to meet the criteria for IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), mixed-type IBS (IBS-M) and unsubtyped IBS (IBS-U). Adapted with permission from REF. 119, American Gastroenterology Association.

in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5)[14] and in psychiatric or psychosomatic clinical management[15]. Patients with IBS who were treated by psychiatrists frequently did not receive adequate attention with respect to their gastrointestinal symptoms before the release of DSM-5.

Risk factors for IBS

The best-documented risk factor for IBS is female sex, which is associated with an odds ratio of 1.67 (95% CI: 1.53–1.82) across many population-based studies[16], with explanations varying between sex-different health care, consultation behaviour and biological functions (for example, hormonal regulation of gut functions). The incidence of IBS decreases with advancing age (>50 years)[1], but is similar in children and adolescents compared with adults and does not necessarily transmit from childhood to adulthood[17]. However, family aggregation has been reported[18] that is driven by genetics[19] as well as by social learning[20]. BOX 2 lists the personal, disease, psychosocial and social factors that have been found to be associated with increased risk of IBS, although some of these factors have only been identified in individual studies[21] or have been found to vary between countries and settings.

Post-infectious IBS

Several studies have shown an association between IBS and preceding gastrointestinal infections of bacterial, viral or other origin[22,23]. The pooled odds ratio is 7.3 (95% CI: 4.7–11.1) for the development of IBS after infectious gastroenteritis[24], with a median prevalence of ~10%[22]. This association seems to differ with respect to epidemic infectious events that affect many people at the same time and individual infections, such as travellers' diarrhoea. That is, prevalence data are reported to be higher (15–30%) in epidemic events[22] and lower (5–10%) following travellers' diarrhoea[23]; these differences are presumably due to different reporting biases in these populations. Thus, a median prevalence of 10% might better reflect the true prevalence of post-infectious IBS than the extreme values reported in individual studies. Risk factors for the development of post-infectious IBS are female sex, younger age, the severity of the initial infection and premorbid psychological conditions[22–24]. Based on symptoms alone, post-infectious IBS cannot be distinguished from IBS without an infectious origin, but inflammatory biomarkers may. The most valid distinction may be a sudden onset that is well remembered by the patient and is associated with fever, bloody stools and a positive laboratory stool test for an infective agent.

Mechanisms/pathophysiology

Although the aetiology of IBS remains largely undetermined, our understanding of the potential mechanisms involved in gut dysfunction, visceral sensation and symptom generation is rapidly advancing. Growing evidence suggests that, in IBS, the epithelial barrier, gut microbiota, food antigens and bile acids elicit abnormal responses in the key regulators of sensorimotor functions, including the hypothalamus–pituitary–adrenal (HPA) axis, the immune system, the brain–gut axis and the enteric nervous system (ENS) (FIG. 4). Accordingly, these factors might have a role as potential biomarkers of disease (BOX 3). In addition to these putative biomarkers, psychological factors ('psychomarkers') such as depression and anxiety, which are known to respond to abdominal symptoms (bottom-up), and psychosocial factors ('stress') that influence physiological (intestinal) functions, such as motility and visceral sensitivity (top-down), have been acknowledged and will be discussed in more detail.

The epithelial barrier

The epithelial gut lining represents an enormous surface that is in constant contact with the environment and with billions of bacteria that constantly challenge the intestinal immune system. Increased intestinal permeability is considered an early event in IBS that leads to low-grade immune cell infiltration of the gut mucosa[25]. Indeed, increased epithelial permeability has been primarily described in post-infectious IBS in general and in IBS-D in particular, although some reports have also shown that IBS-C and IBS-M might also involve an increase in epithelial permeability[25]. Evidence for the presence of this remodelling in IBS has been provided by electron microscopy, which has detected enlarged spaces between epithelial cells and cytoskeletal condensation in gut biopsies of patients with IBS-D[26]. In addition, Ussing chamber experiments, which measure epithelial membrane properties on colonic mucosal biopsies, have shown excessive passage of macromolecules from the luminal to the basolateral side of gut tissue

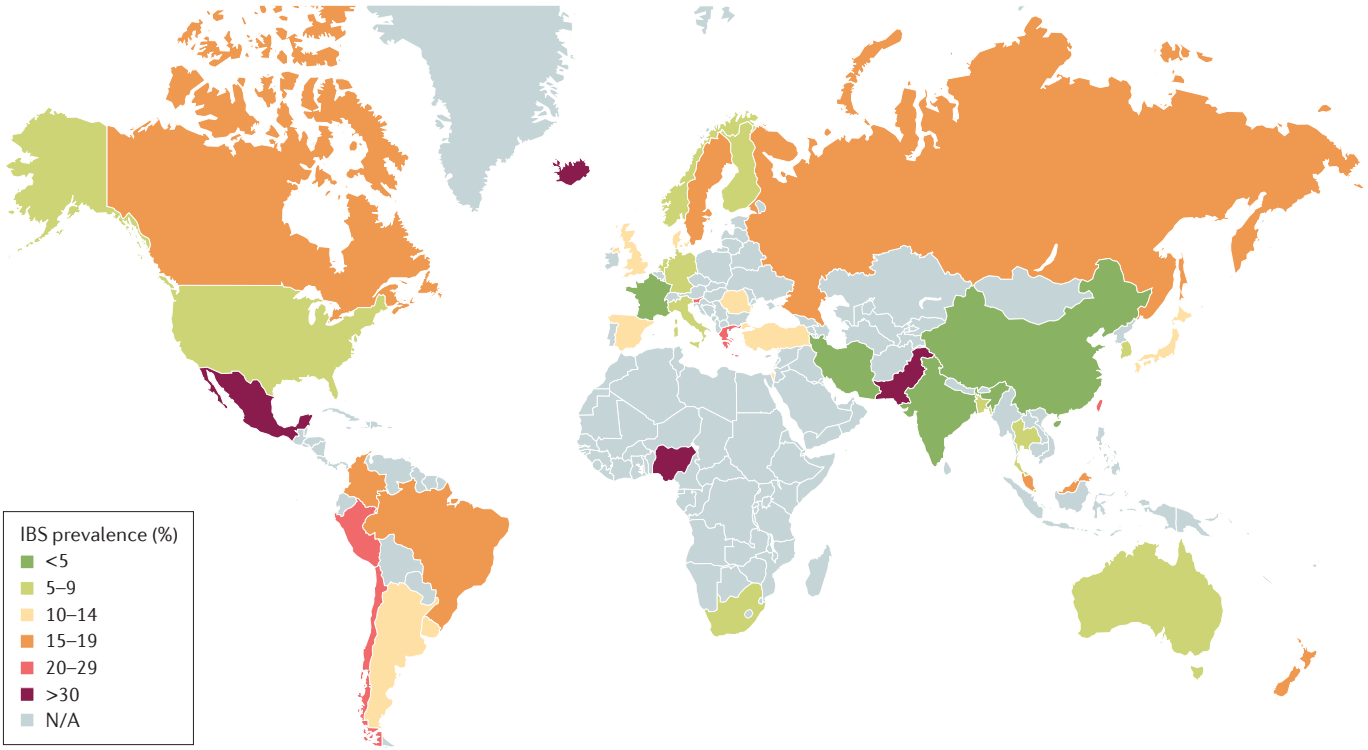

Figure 2 | **IBS prevalence in population studies around the world.** Pooled prevalence data per country are colour-coded. Data from REF. 1 are supplemented by studies from another nine countries (see Supplementary information S1 (table)). IBS, irritable bowel syndrome; N/A, not applicable.

in biopsies obtained from patients with IBS compared with asymptomatic controls, hence providing the functional correlate for the described structural epithelial barrier defects[27].

Morphological and functional changes in intestinal permeability are related to abnormal gene and protein expression of tight junction proteins, including a reduction in the expression of occludin and zonula occludens protein 1 (REFS 25,28). These findings have recently been corroborated by genetic and epigenetic findings in tight junction proteins claudin 1, claudin 2 and cingulin, as outlined below. Tight junction changes are probably the result of both bacterial-mediated and proteasome-mediated degradation triggered by low-grade inflammation[29]. Accordingly, inflammatory mediators including eicosanoids, histamine and proteases increase intestinal permeability. This may involve the participation of ENS neurons, which may amplify these effects[27,30].

Increased intestinal permeability has been linked to diarrhoea and pain severity[26], suggesting that this mechanism might have a role in symptom generation in IBS. Although the exact causes underlying the 'leaky' gut barrier in IBS remain elusive, it has been postulated that numerous factors could be involved, including genetics, epigenetics, dysbiosis and food allergies[25]. Confocal laser endomicroscopy of the duodenal mucosa of patients with IBS after challenge with food to which the patients reported intolerance showed epithelial breaks and increased intervillous spaces, indicative of increased intestinal permeability. These studies suggest a causative effect of food in the increased epithelial permeability in IBS[31].

Bile acids

A subset of patients with features compatible with IBS-D present with increased levels of total faecal bile acids caused by increased excretion and synthesis of serum C4 (7α-hydroxy-4-cholesten-3-one; a surrogate for bile acid synthesis), which in turn influences bowel habit by accelerating colonic transit and inducing diarrhoea and visceral hypersensitivity in IBS[32–34]. Of note, genes involved in bile acid metabolism and function have been reported to be associated with colonic transit in IBS-D, as outlined below.

Immune response

It has been argued that the immune system participates in the pathophysiology of IBS based on the clinical observation that infectious gastroenteritis is a strong risk factor for the development of IBS[24]. Additional clinical support comes from the evidence that about one-third of patients with IBD in remission experience IBS-like symptoms[35]. These inferential data have been subsequently enriched by quantitative immunohistochemistry data showing increased infiltration of T cells and mast cells in the mucosa of the small and large intestine of some patients with IBS[36].

Two randomized controlled trials (RCTs)[37,38] in patients with IBS demonstrated that the anti-inflammatory agent mesalazine was not superior to placebo in alleviating IBS symptoms, although both studies clearly indicated that subgroups, particularly patients with post-infectious IBS, had sustained symptomatic responses. Thus, these studies confirm the hypothesis that immune activation has a considerable role in some patients with IBS.

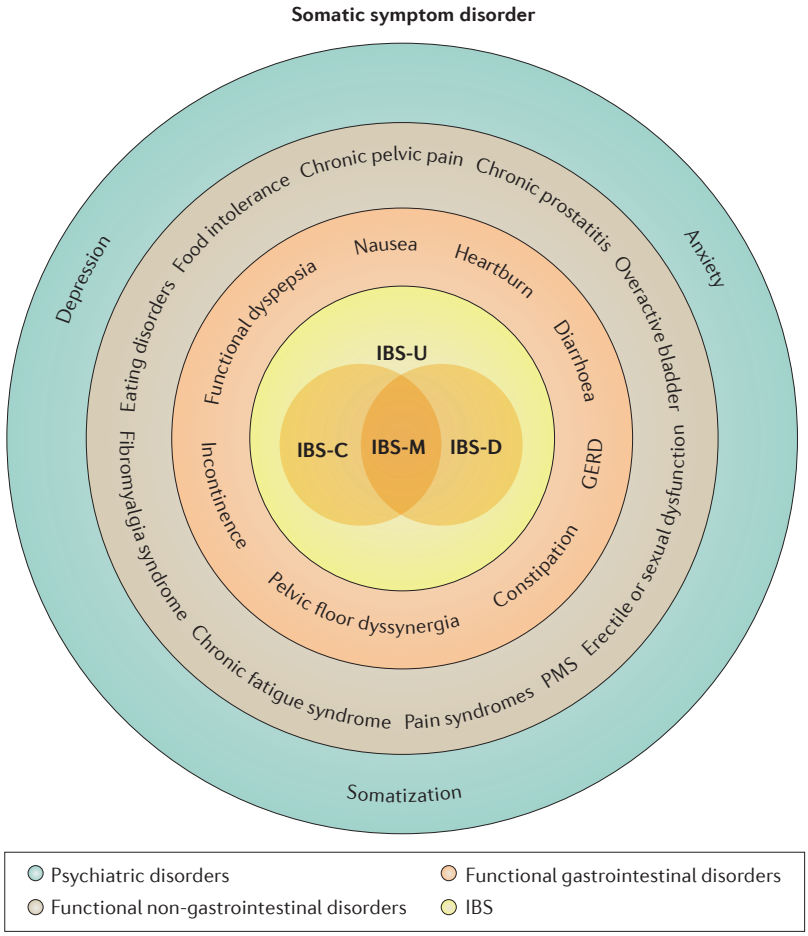

Figure 3 | **IBS-associated comorbidities.** A model of irritable bowel syndrome (IBS) and its associations with other clinical, intestinal, extra-intestinal and psychiatric conditions. For each of the listed disorders, overlap with IBS symptoms has been reported in the literature[11]. The different components should be viewed as layers of complexity: the IBS subtypes are part of the group of functional bowel disorders, these are part of all kinds of functional disorders and these again are part of a 'layer' of psychiatric disorders. GERD, gastroesophageal reflux disease; IBS-C, IBS with constipation; IBS-D, IBS with diarrhoea; IBS-M, mixed-type IBS; IBS-U, unsubtyped IBS; PMS, premenstrual syndrome.

Although mucosal immunocyte numbers are not always increased in IBS, there is strong functional and molecular evidence of an increased state of activation of immune cells in about half of patients with IBS[36]. Data from several studies point to the importance of mast cells as key components of inducing and maintaining low-grade immune activation in IBS[36]. For instance, higher proportions of mast cells were found in a degranulating state in colonic biopsies from patients with IBS than in control samples, suggesting that increased activation of mast cells is involved in the condition[39]. In addition, biopsy supernatants from patients with IBS contained higher amounts of mast cell mediators, including proteases and histamine[36] as well as polyunsaturated fatty acid metabolites[40], than controls. Mucosal immune activation is coupled with altered gene expression of several components of the host mucosal immune response to microbial pathogens (see below), suggesting that the microbiota might contribute to the observed immune activation[36].

Neuroimmune interactions

Mucosal mediators isolated from biopsy samples from patients with IBS have been extensively studied to identify their effect on bowel physiology and sensory perception in isolated tissues or laboratory animals[41]. Compared with controls, mucosal mediators from patients with IBS evoked higher activation of visceral and somatic pain pathways when applied to intestinal preparations isolated from rodents[42,43]. Mast cells and enteroendocrine cells have been suggested to participate in this abnormal neural signalling, as indicated by the activation of human ENS neurons via mast cell-derived histamine, enteroendocrine cell-derived serotonin (also known as 5-hydroxytryptamine (5-HT)) and protease-dependent mechanisms[30,42] (FIG. 5). Although most of the proteases are secreted by mast cells, some of the serine and cysteine proteases that are present at a higher level in the mucosa or stool of patients with IBS than controls might be of other, probably pancreatic or bacterial, origin. In line with these findings, serine proteases in faecal supernatants from individuals with IBS-D evoked colonic hypersensitivity to distension[44]. By contrast, faecal cysteine protease activity was augmented in some patients with IBS-C compared with controls and increased protease activity correlated with abdominal pain and impaired epithelial permeability[45]. Further work showed the implication of serine proteases that act on protease-activated nociceptors located on intestinal nerves conveying pain stimuli to the brain[43]. Importantly, mucosal mediators from patients with IBS and visceral hypersensitivity — but not from normosensitive patients with IBS — acutely activated spinal nociceptors when given to animal models[46]. In the same model, chronic exposure to soluble mediators from patients with IBS-D was shown to sensitize nociceptive neurons[47], implying that chronicity is associated with long-lasting plasticity alterations.

Attention has been directed to agonists of the transient receptor potential cation channels (TRPs), which have been implicated in the pathogenesis of sensory hyperalgesia. Colon tissue samples from patients with IBS have increased levels of specific polyunsaturated fatty acids, which stimulate sensory neurons from mice via the activation of TRP subfamily V member 4 (TRPV4) and generate visceral hypersensitivity[40]. The importance of those visceral afferents that express TRPs in IBS symptomatology is underscored by the finding that peripheral blood mononuclear cell (PBMC) supernatants from patients with IBS-D cause mechanical hypersensitivity of visceral afferents via tumour necrosis factor (TNF) and TRPA1; this was not observed if control supernatants were used[48].

Recent data support the concept that the chronic release of factors with known effects on nerves in the intestinal milieu might not only have functional effects but could also affect the ENS and sensory fibres in a structural manner. For example, immunohistochemistry showed a 57.7% and 56.1% increase in mucosal neurons and neuronal outgrowth, respectively, in patients with IBS compared with healthy controls[49]. Indeed,

the intestinal mucosa of patients with IBS contains increased levels of nerve growth factor (NGF), primarily in mucosal mast cells. Experimentally, the effect of NGF was demonstrated in primary cell cultures of the rat myenteric plexus and the neuroblastoma cell line SH-SY5Y, which showed an increase in neurite growth, and protein and mRNA expression of growth-associated protein 43 (GAP43; also known as neuromodulin) — a key neuronal growth protein — following exposure to supernatant obtained from mucosal biopsies of patients with IBS[49].

Box 2 | **Risk factors for IBS**

Personal factors
- Sex (female)
- Age (>50 years)
- Birth cohort*
- Breast feeding (<6 months)*
- Herbivore pet in childhood*
- Birth weight (low)*
- Body mass index (low)*

Psychological factors
- Illness behaviour
- Low quality of life
- Acute psychological stress
- Stressful life events
- Sexual or physical abuse history
- Anxiety, depression or somatization
- Intimate partner violence*
- Addictive behaviour*

Somatic issues
- Gastrointestinal infection
- Somatic symptoms (pains, for example, joint pain and migraine)
- Endometriosis
- Abdominal obesity
- Diverticular disease (left side)
- Antibiotic use
- Abdominal surgery
- Spicy food consumption*
- Sleep problems*
- Low exercise level*

Social conditions
- Socioeconomic status (childhood)
- Family history of substance abuse
- Family history of mental illness
- Working conditions (insufficient autonomy)*
- Shift work*
- Marital status (never married)*
- Number of family members (with more members increasing the risk)*
- Childhood war exposure*

Less well-established factors are marked (*) and are based on single studies (for example, REF. 21), whereas all others have been shown in more than one study.

Microbiota

The gastrointestinal microbiota is a diverse and numerous ecosystem that inhabits the entire gastrointestinal tract and has a systemic influence on our health. Owing to its enormous complexity and high interindividual variability, the microbiota is still in large part undefined regarding the scope of its contribution to human physiology and tolerable compositional variations under which normal functions are preserved[50]. The evidence for an involvement of altered gut microbiota composition in IBS pathophysiology has been accumulating (BOX 4), but the aetiological role remains uncertain. The most prominent markers of IBS are derived from uncultured bacteria. Two groups of uncultured Clostridiales are significantly depleted in IBS[51,52], and bacteria related to *Ruminococcus torques* (a species belonging to the Lachnospiraceae) are profoundly enriched in patients with IBS[51,53,54] and levels positively correlate with bowel symptoms[51,52,55]. In addition, increased Firmicutes to Bacteroidetes ratios have been observed at the phylum level, at least in a subset of patients[51] (for a recent review see REF. 56). Given the provided evidence, the dysbiosis of microbiota in IBS has been acknowledged by the Rome Foundation Working Team[57] as a plausible contributing factor to the disorder. Experiments with animal models have shown that colonization of germ-free animals with microbiota from patients with IBS can induce visceral hypersensitivity[58], impair intestinal permeability and alter gastrointestinal transit time[59] — indicating the importance and the possible aetiological role of the microbiota in IBS.

Although diet changes have an effect on the abundance of particular microbial groups, the microbiotic signature (in terms of present species) is very stable[60]. To observe a profound effect, the dietary change has to be dramatic (for example, vegans switching to high-fat and high-protein diets[61]). Dietary interventions (such as low dietary content of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs; BOX 5), or the addition of sweeteners (fructo-oligosaccharides) or fibre (psyllium)) can improve symptoms of some but not all patients with IBS. Future studies should evaluate the relevance of these microbial groups for IBS and could contribute to a better understanding of the role of the microbiota in the pathophysiology of IBS that is currently acknowledged for the following contexts.

Fermentation of non-digestible foods. An important role of the microbiota is degradation of non-digestible dietary components[62]. It is generally accepted that fermentation of carbohydrates is desirable because of the beneficial effects of the main fermentation products — short-chain fatty acids (SCFAs) — including energy supply to gastrointestinal epithelial cells, a decrease in inflammation and improvement in gut barrier function[63]. However, in patients with IBS, the presence of the resistant carbohydrates FODMAPs can provoke IBS symptoms[64]. This might be a result of overproduction or underproduction of relevant metabolites owing to the disturbed microbiotic balance, for example,

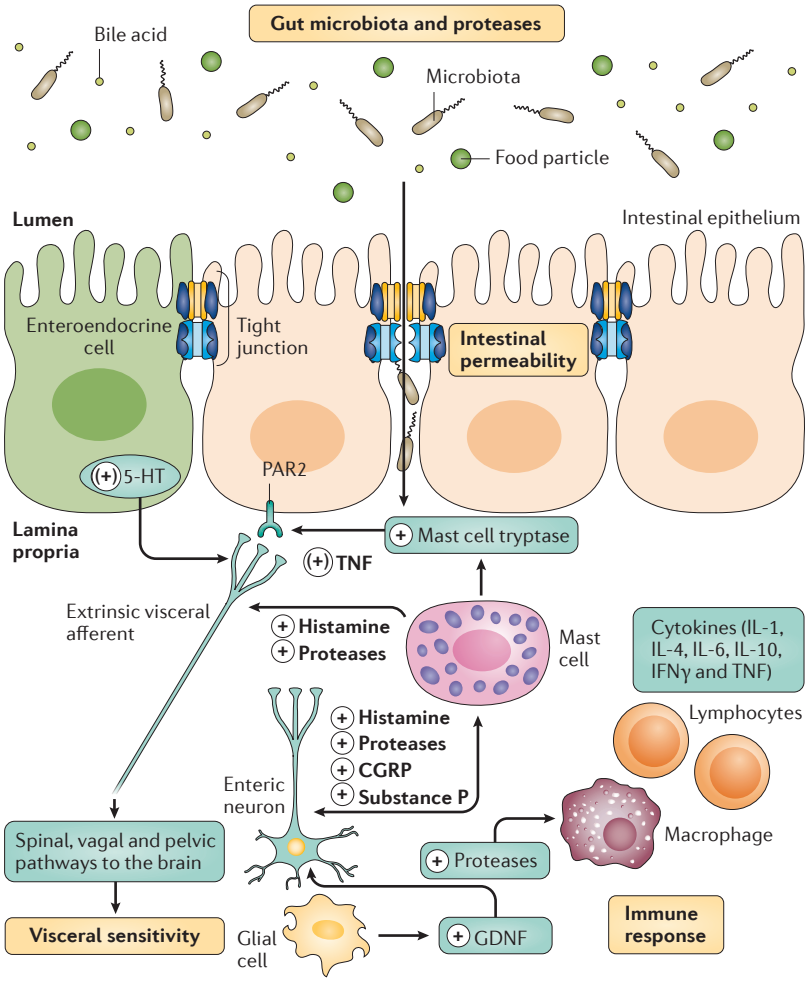

Figure 4 | **Overview of the pathophysiology of IBS.** Although the aetiology of irritable bowel syndrome (IBS) has not yet been completely elucidated, various factors have a role, including composition of the gut microbiota, intestinal permeability, immune cell reactivity and sensitivity of the enteric nervous system, the brain–gut axis (spinal, vagal or pelvic pathways) or the brain. The figure highlights those mediators that are probably involved in IBS pathology. The plus symbols indicate whether a mediator activates or inhibits its target cell; those in parentheses denote actions established in animal models and those without parentheses are effects demonstrated in humans (human tissue). 5-HT, 5-hydroxytryptamine (also known as serotonin); CGRP, calcitonin gene-related peptide; GDNF, glial cell-derived neurotrophic factor; IL, interleukin; PAR2, proteinase-activated receptor 2; TNF, tumour necrosis factor.

due to an increased abundance of gas-producing and decreased abundance of gas-utilizing microorganisms. The quantity and composition of SCFAs in the gut differs between patients with IBS and healthy controls, although the available data are not always in agreement[65,66]. Moreover, the production of microbial SCFAs stimulates regulatory T cell differentiation and affects the balance between pro-inflammatory and anti-inflammatory mechanisms[67], suggesting that inadequate levels of SCFAs could provoke low-grade intestinal inflammation as observed in patients with IBS[68,69]. Finally, studies of microbiota show that the abundance of several SCFA-producing bacteria — including *Roseburia*, *Blautia* and *Veillonella*[70] — is significantly increased compared with the levels of these bacteria in healthy controls, providing a potential mechanistic basis for the development of IBS symptoms.

Other carbohydrate-utilizing gastrointestinal bacteria — namely, *Dorea* spp. — show significant increases in abundance in patients with IBS[51]; these are the main gas-producing bacteria in the human gastrointestinal tract[71]. The overproduction of gas is associated with IBS[72] and this phenomenon could underlie flatulence and abdominal pain. The excessive production of gas can also cause faster colonic transit in patients with IBS-D, as the colons of these patients are more sensitive to increased intestinal volume than healthy controls[73]. Intestinal gases are efficiently removed by methanogenic archaea[74], which seem to be depleted in patients with IBS[51,52] and are negatively correlated with the presence of loose stools[52]. However, a significant increase in the abundance of this microbial group is characteristic of patients with slow transit and constipation[75], whereas the degree of the methanogenic activity could be correlated with the severity of constipation in those with IBS-C[76].

Another potential pathway for microbiotic involvement in IBS is protein degradation. The luminal contents of patients with IBS contain increased levels of proteases[30], which could be due to the increased secretion of endogenous and microbial proteases in response to protein-rich nutrition (typical of western diets), but could also be due to insufficient endogenous protease degradation by the disturbed gastrointestinal microbial community[77]. Serine protease inhibitors are produced by many bacteria, including bifidobacteria[78], and their activity could prevent the excessive proteolytic activity of intestinal content in IBS. The depletion of bifidobacteria has been noted in both faecal and mucosal samples of patients with IBS[51,79], suggesting an important role for this bacterial genera in IBS. The fermentation of proteins generates numerous health-compromising substances[80]. Among these, hydrogen sulfide is a relevant toxin that impairs epithelial metabolism[81] and can be further converted to tetrathionate, which stimulates the growth of tetrathionate-utilizing pathogens from Gammaproteobacteria[82,83]. The abundance of several Gammaproteobacteria significantly correlates with bowel symptoms in patients with IBS[51,52], and also with the levels of the inflammatory markers interleukin 6 (IL-6) and IL-8 (REF. 51) that are typically increased in IBS[54].

Microbiota and 5-HT. 5-HT is an important metabolite that, among other functions, regulates gastrointestinal motility; disturbed levels of 5-HT seem to be relevant for IBS pathology[84]. As much as 90% of 5-HT is produced in enteroendocrine cells present in the gastrointestinal tract, and it has been recently shown that intestinal bacteria are needed for the stimulation of 5-HT synthesis. Attempts to identify microorganisms that are capable of 5-HT synthesis have shown that, in contrast to *Bacteroides* spp. and altered Schaedler flora (a community of eight bacterial strains), only specific spore-forming commensal bacteria have this feature. The majority of these spore-forming bacteria belong

Box 3 | **Structural and functional biomarker candidates in IBS***

Altered motility and stool behaviour
- Altered colonic transit time
- Impaired bile acid transport‡

Mucosal permeability
- Reduced epithelial resistance§
- Reduced expression of ZO1§

Immune imbalance
- Increased numbers of intraepithelial $CD3^+$ lymphocytes§
- Increased mucosal cell density and reactivity§
- Increased nerve mast cell association in the lamia propria region§
- Increased levels of T_H2 cytokines in the blood‖
- *TNFSF15* and *TNF* polymorphisms§,‖
- Increased levels of the pattern recognition receptors TLR2 and TLR4§
- Increased levels of anti-flagellin autoantibodies‖
- Increased levels of histamine and proteases in biopsy supernatants§
- Increased production of IL-1β and TNF by PBMCs‖
- Increased levels of β-defensin 2 antimicrobial peptide‡

Neural plasticity
- Increased nerve fibre density in the epithelium and lamina propria§
- Mostly visceral hypersensitivity, but ≤40% of patients are normosensitive or hyposensitive
- Mucosal biopsy supernatants activate the enteric nervous system independent of stool behaviour or visceral sensitivity§
- Mucosal biopsy supernatants activate sensory fibres and dorsal root ganglion neurons (mostly hypersensitive IBS)
- PBMC supernatants evoke mechanical hypersensitivity involving cytokines and TRPA1

Serotonin metabolism and signalling
- Increased plasma levels of serotonin in IBS-D‖
- Increased enterochromaffin cell density§
- Altered *SERT* expression and polymorphism§
- Serotonin receptor and transporter polymorphisms§

Others
- Increased levels of cysteine and serine proteases‡
- Increased levels of mucosal PARM1§
- Increased levels of BDNF and NGF§
- Increased levels of rectal PYY and somatostatin cell count§
- Altered microbiota diversity and composition‡

BDNF, brain-derived neurotrophic factor; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhoea; IL-1β, interleukin 1β; NGF, nerve growth factor; PARM1, prostate androgen-regulated mucin-like protein 1; PBMC, peripheral blood mononuclear cell; PPY, peptide YY; *SERT*, serotonin reuptake transporter; T_H2, T helper 2; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFSF15, TNF superfamily member 15; TRPA1, transient receptor potential cation channel subfamily A member 1; ZO1, zonula occludens 1. *Based on data available in REF. 244. ‡In stool. §Intestinal biopsy. ‖In blood.

to the Clostridales class within the Firmicutes phylum. Two recent comprehensive studies[51,85] revealed an increase of the Firmicutes phylum members on the account of the Bacteroidetes members in IBS. Given that the Clostridiales class within the Firmicutes phylum are the most diverse and the most abundant group of the microbiota[70], it is not clear if the observed feature of the IBS microbiota is associated with 5-HT-mediated pathophysiology, but this possible link should certainly be further investigated.

Brain and behaviour

IBS is narrowly defined by recurrent abdominal pain and discomfort associated with altered bowel habits in the absence of an organic origin and/or explanation of symptoms. However, given that IBS is nearly always associated with increased anxiety and patients often show comorbidities with other chronic pain and psychiatric conditions, a more widespread dysregulation of the nervous and immune systems is probably implicated[86].

The brain, the gut and its microbiota and the immune system show reciprocal associations in health and disease. On the one hand, the brain, via the autonomic nervous system and the HPA axis, can influence intestinal motility and fluid secretion[87], intestinal epithelial permeability[25,88,89], immune function[90] and gut microbial composition[91], all of which have been reported to be dysregulated in IBS. On the other hand, several of these peripheral alterations can influence brain structure and function either developmentally or in response to acute perturbations, setting up circular regulatory loops between the gut and the brain[92].

In addition to its role in the bidirectional communications with the gut, the brain plays an essential part in assessing the salience of received or expected interoceptive (sensory) information[93], determining how much of this information is amplified or tuned down, to what degree it is modulated by affect[94] and how much of this interoceptive information from the gut is consciously perceived (visceral sensitivity). One of the best-studied behavioural aspects of IBS-related central processing of gut-related information involves a coping strategy referred to as catastrophizing, a term that refers to a bias towards prediction of a high likelihood of worst outcomes[95]. This measure strongly correlates with the severity of pain symptoms and is a primary treatment target in cognitive–behavioural therapy.

Multimodal brain imaging has made it possible to identify differences in functional (evoked and resting state) and structural (grey matter and white matter tracts) aspects of specific brain networks that provide a neurobiological substrate for previously observed affective and cognitive features of IBS (reviewed in REFS 92,96) (FIG. 6). These networks include the salience, attention, sensorimotor and emotional arousal networks. Profound sex-related differences in these networks have also been identified in both healthy individuals and patients with IBS (reviewed in REF. 96). Cross-sectional correlations of brain networks with several clinical and non-brain biological parameters show a relationship between some of these brain signatures with IBS symptom severity and duration, a history of early adverse life events[93], gut metabolite and microbial composition[97], gene expression profiles in PBMCs[98] and gene polymorphisms[99]. On the basis of these neurobiological findings, a comprehensive IBS pathophysiological model can be formulated (FIG. 6), which includes alterations in the appraisal of and selective attention to interoceptive signals (salience and attentional network), central sensory processing of interoceptive information (sensorimotor network) and engagement of emotional arousal associated with experience and expectation of

gut sensations. This disease model not only identifies neurobiological correlates of well-characterized clinical and behavioural features of IBS but also provides a plausible explanation for the common coexistence of IBS with other chronic pain conditions and with increased trait anxiety.

Although these findings have identified disease-relevant brain alterations in patients with IBS, mechanistic and longitudinal studies are required to determine the causality between these factors. For example, are central sensorimotor alterations a consequence of increased signals from the gut, are they the consequence of dorsal horn sensitization by increased descending pain-facilitating signals or are they a genetically determined trait that predisposes individuals to IBS and might be present in asymptomatic relatives[100]? The correlation of gut microbial signatures and PBMC expression profiles with structural alterations in the

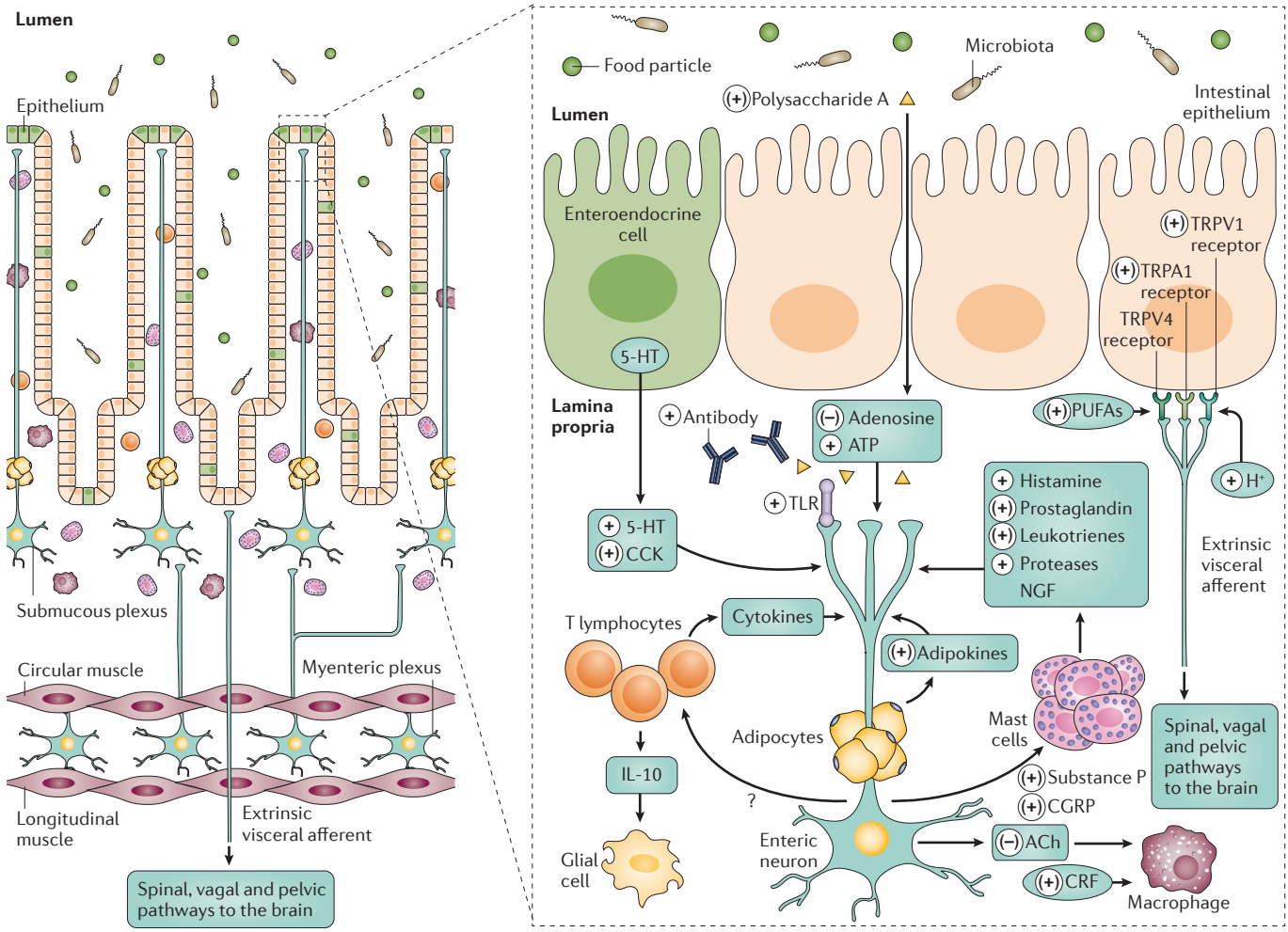

Figure 5 | **Neuroimmune interactions in the gut.** An intimate anatomical and functional association between enteric neurons, terminals from extrinsic nerves and cells of the enteric immune system is the basis for neuroimmune interactions in the gut wall. Functional signalling between nerves and immune cells mostly happens in the epithelial and submucosal layers where there is a high density of immune cells — in particular, T lymphocytes, mast cells and macrophages. The neuroimmune interactions are bidirectional. Enteric neurons, extrinsic nerves and glial cells respond to cytokines and mast cell mediators. Some patients with irritable bowel syndrome (IBS) have circulating autoantibodies against neuronal structures and antibodies that are generated as a response to antigen exposure from the lumen. Neurons can respond directly to antibodies through direct activation of channels or receptors. They also respond to antigens through pathways involving neuronal Toll-like receptor 3 (TLR3), TLR4 and TLR7. Direct signalling between microbiota and the host involves activation of neurons through polysaccharide A. These direct effects of luminal factors are very likely to be outnumbered by signalling between epithelial (in particular, enteroendocrine cells), immune and nerve cells. Neurons also express receptors for adenosine and ATP; both molecules are released in the gut wall under inflammatory or stress conditions. Reciprocally, nerves release factors that affect epithelial or immune cells. The best-documented effect is the activation of mast cells through the release of calcitonin gene-related peptide (CGRP) from extrinsic visceral afferents or enteric neurons. Conversely, acetylcholine (ACh) inhibits the activation of macrophages. Neurogenic inflammation, which is sometimes observed in animal models, is probably caused by the release of CGRP and substance P from extrinsic fibres followed by permeabilization of blood vessels. In addition, adipocytes in the lamina propria nestle against nerve fibres, and release of their pro-inflammatory mediators modulates nerve activity. The plus and minus symbols indicate whether a mediator activates or inhibits its target cell; those in parentheses denote actions established in animal models and those without parentheses are effects demonstrated in humans (human tissue). 5-HT, 5-hydroxytryptamine (also known as serotonin); CCK, cholecystokinin; CRF, corticotropin-releasing factor; IL-10, interleukin 10; NGF, nerve growth factor; PUFA, polyunsaturated fatty acid; TRP, transient receptor potential cation channel.

Box 4 | **Dysbiosis in IBS**

Microbiota species increased in IBS

- Enterobacteriaceae
- *Veillonella*
- *Streptococcus**
- *Dorea*
- *Blautia*
- *Roseburia*
- *Ruminococcus*
- *Methanobrevibacter*‡

Microbiota species decreased in IBS

- *Bifidobacterium*
- *Collinsella*
- *Streptococcus*‡
- *Faecalibacterium*
- Christensenellaceae
- Clostridiales
- Uncultured
- *Methanobrevibacter*§

IBS, irritable bowel syndrome. *IBS with diarrhoea. ‡IBS with constipation. §Mixed-type IBS.

sensorimotor network suggests a possible role of these peripheral factors in influencing the brain. Similarly, are the altered salience and attention network alterations a secondary response to the chronically increased perception of visceral signals or are they a primary abnormality that is responsible for the generation of aberrant endogenous pain modulation, as well as emotional and autonomic nervous system responses? Future studies will need to address the question of whether these brain signatures differ between subgroups of patients with IBS, such as male and female patients, patients with a history of early adversity, patients with different durations of symptoms and patients with post-infectious IBS.

Genetic and epigenetic data

The latest genetic and epigenetic findings support current models of IBS pathogenesis that suggest disturbed intestinal barrier function, immune response and neuronal signal transduction[101] (FIG. 6). The data even point towards potential diagnostic biomarkers or therapeutic options (BOX 3). For example, silencing the microRNA-29 (*mir-29*) family or amplifying *mir-199a* expression might have important therapeutic implications for selected patients with IBS and symptoms caused by increased intestinal permeability or hypersensitivity[102,103].

Genetic data. Genetic studies to date range from family and twin studies to candidate gene approaches and, more recently, genome-wide association studies (GWAS). Regardless of enlarged sample sizes, increased statistical power and meta-analyses, genetic variants associated with IBS are still scarce and/or have not been replicated in independent cohorts. A recent paper summarizes all currently available genetic data that have been replicated[101].

Polymorphisms or variants in several genes have been found to be associated with IBS. Genes encoding proteins involved in homeostasis of epithelial barrier function, such as cadherin 1 (*CDH1*) and cell division cycle 42 (*CDC42*), the immune system, such as *IL6, IL10, TNF* and TNF superfamily member 15 (*TNFSF15*; encoding cytokines and neuronal signal transduction) and others (such as neurexophilin 1 (*NXPH1*) and sodium voltage-gated channel α-subunit 5 (*SCN5A*)) have been replicated in several studies[101]. In 2014, a small pilot study reported an association between IBS and a locus on chromosome 10 (containing the protocadherin 15 (*PCDH15*) gene) in a discovery sample from Australia that could not be replicated in additional cohorts from Sweden and the United States[104]. Mutations in the following genes encoding proteins involved in the serotonergic system have also been shown to be associated with IBS: solute carrier family 6 member 4 (*SLC6A4*; also known as 5-HTTLPR or SERT), 5-HT receptor 3A (*HTR3A*), *HTR3E* and *HTR4* (REF. 101). A polymorphism in *SLC6A4* has been found to be associated with altered brain responses, visualized through functional brain imaging following visceral pain stimuli in patients with IBS[105]. Furthermore, a functional polymorphism in *HTR3A* could be associated with altered amygdala responsiveness, anxiety and increased symptom score in IBS[106]. These findings underline the effect of polymorphic serotonergic and other genes in modulating gut-derived brain response in areas that process visceral perception and integrate autonomic control, salience and somatosensory and emotional central networks (FIG. 6).

Variants of genes encoding proteins that are involved in bile acid synthesis regulation (the Klotho-β (*KLB*) gene, the fibroblast growth factor receptor 4 (*FGFR4*) gene and the G protein-coupled bile acid receptor 1 (*GPBAR1*) gene) are associated with accelerated colonic transit in patients with IBS-D[107,108]. These variants also correlate with the colonic transit response to chenodeoxycholic acid (a bile acid used to treat constipation) in IBS-C[109] and to colesevelam (a bile acid sequestrant used to treat diarrhoea) in patients with IBS-D[110,111].

Finally, a locus at 7p22.1 in which the genes KDEL endoplasmic reticulum protein retention receptor 2 (*KDELR2*) and GRID2-interacting protein (*GRID2IP*) localize was significantly associated with IBS risk in the index GWAS (a large twin discovery sample from Sweden) and all replication cohorts in Europe, the United States and Australia[112]. However, the underlying molecular cause for this association finding has not been elucidated.

Epigenetic data. Even less insight into the role of epigenetics in IBS pathology is available compared to the genetic implications. To date, only a few miRNA studies have been performed. These studies reported on the differential expression profiles of miR-29a, miR-29b, miR-103, miR-16, miR-125b and miR-199a in the intestinal mucosa of patients with IBS-D. Upregulation of miR-29a and miR-29b was reported to accompany downregulation of the target genes encoding glutamine synthetase (*GLUL*)[102], claudin 1 (*CLDN1*) and

NF-κB-repressing factor (*NKRF*); *CLDN1* and *NKRF* correlated with increased gut permeability[103]. In addition, decreased expression of miR-103, miR-16 and miR-125b correlated with the upregulation of the target genes encoding the tight junction proteins claudin 2 (*CLDN2*) and cingulin (*CGN*)[113]. In turn, a diminished miR-199 level correlated with an upregulation of *TRPV1* and increased visceral sensitivity[114]. Moreover, variants residing in miRNA target regions of the 5-HT receptor genes *HTR3E* and *HTR4B* — namely, c.*76G>A and c.*61T>C — were found to be associated with IBS-D. Both variants were reported to impair miRNA regulation and to lead to disturbed expression regulation of miR-510 and miR-16, respectively[115,116]. One pilot study further indicated increased levels of circulating miR-150 and miR-342-3p in the blood of patients with IBS[117]. Of note, miR-150 has been described to be associated with IBD and pain, whereas miR-342-3p has been predicted to target genes that are relevant for pain signalling, colonic motility and smooth muscle function[118].

Diagnosis, screening and prevention

The diagnosis of IBS relies on the patient fulfilling diagnostic criteria for IBS[119] in conjunction with normal results on a limited number of additional tests and investigations used to rule out other diagnoses with reasonable certainty (FIG. 7). Although a substantial proportion of clinicians[120] prefer a process of thorough exclusion of other diseases, the current recommendation is to base diagnosis on symptoms[119]. There is currently no valid biomarker for IBS[121]. The choice of the tests or investigations deemed necessary to rule out other conditions varies depending on the clinical situation and the symptom profile of the patient. In the majority of cases with a typical clinical history compatible with IBS, only a limited number of laboratory tests are recommended without any need to perform invasive investigations. Screening for IBS risk and for prevention of IBS development is currently not applicable, given the heterogeneity of the disease and the multiplicity of putative pathophysiological mechanisms.

Box 5 | FODMAPs and a low FODMAP diet*

FODMAPs stands for fermentable oligosaccharides (fructans present in wheat, rye, onion and garlic chicory; and galactans present in legumes and beans), disaccharides (lactose present in milk and milk products), monosaccharides (fructose present in artificial sweeteners) and polyols (sugar alcohols present in apples, pears, stone fruit, cauliflower, mushrooms and sweeteners). A low FODMAP diet may include reasonable amounts of:

- Vegetables: bamboo shoots, cucumber, carrot, corn, aubergine (eggplant), lettuce, leafy greens, pumpkin, potato, squash, yam, tomato and courgette (zucchini), among others
- Fruits: banana, cantaloupe, grapes, grapefruit, kiwifruit, kumquat, lemon, lime, mandarin, orange, passion fruit, pawpaw, pineapple, rhubarb and tangerine, among others
- Protein: beef, chicken, canned tuna, egg, egg whites, fish, lamb, pork, shellfish, turkey, cold cuts, nuts and seeds, among others
- Dairy and non-dairy alternatives: lactose-free milk, cream cheese, hard cheeses (cheddar, parmesan and Swiss), mozzarella and sherbet (almond milk, rice milk and rice-milk ice-cream), among others
- Grains: wheat-free grains or wheat-free flours and products made with these (for example, bagels, breads, crackers, noodles, pancakes, pastas, pretzels and waffles), corn flakes, cream of rice, grits, oats, quinoa and rice, among others
- Beverages: water, coffee and tea, and low FODMAP fruit or vegetable juices, among others

*See REFS 171,174.

Diagnostic criteria

As individual symptoms have poor sensitivity and specificity to diagnose IBS, diagnostic criteria incorporating a combination of symptoms have been developed, similar to the DSM system within psychiatry. The first attempt was the so-called Manning criteria, published in 1978 (REF. 122). In this publication, several symptoms were shown to be more common in patients with IBS than in patients with another organic gastrointestinal disease. By combining these symptoms, IBS could be discriminated from other organic gastrointestinal diseases. The experience from the Manning criteria was then used to develop the Rome Foundation criteria, with three different versions over the past 15 years (Rome I, II and III); the latest criteria, the Rome III criteria, was published in 2006 (REFS 119,123,124). The updated Rome IV criteria are expected in May 2016. The sensitivity and specificity of the Rome criteria have been found to be 69–96% and 72–85%, respectively, in different studies, but a problem with these studies is how to define the gold standard for an IBS diagnosis[121].

The common feature in all of these diagnostic criteria is abdominal pain and/or discomfort associated with abnormal bowel habit (diarrhoea (loose and frequent stools), constipation (hard and infrequent stools) or alternating constipation and diarrhoea). All of these criteria require a certain duration and frequency of the symptoms to fulfil the diagnostic criteria for IBS; that is, the symptoms should be chronic and recurring. Thus, the practical clinical use of the diagnostic criteria for IBS involves demonstrating through the clinical history the presence of a combination of these symptoms for ≥3 days per month in the past 3 months, with symptom onset ≥6 months before the diagnosis (Rome III criteria). However, it should be noted that patients with some organic gastrointestinal disease also meet these diagnostic criteria[125] and, as such, the sensitivity and specificity of these criteria is suboptimal to distinguish the different disease entities[125,126].

Clinical features

Besides the symptoms included in the diagnostic criteria, there are other clinical features that support a diagnosis of IBS, even though none of them is mandatory for an IBS diagnosis. One recent study found that variations in stool consistency and frequency or an unpredictable bowel pattern ('irregularly irregular') could be used to discriminate IBS-D adequately from organic gastrointestinal disease[127]. Moreover, abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week), excessive straining during defaecation, urgency (having to rush to the toilet), feelings of incomplete evacuation and mucus with bowel movements support an IBS diagnosis, but are nonspecific[124].

The same is true for postprandial worsening or exacerbation of symptoms, which is common in IBS[128], but is also observed in other gastrointestinal diseases. The presence of other functional gastrointestinal diagnoses (such as functional dyspepsia)[129], as well as reporting numerous functional non-gastrointestinal symptoms and syndromes (such as chronic fatigue, fibromyalgia, uro-gynaecological symptoms, muscle and joint pain and sleep disturbances)[11,130] and psychological comorbidity (such as anxiety and depression)[131], are all common and support an IBS diagnosis.

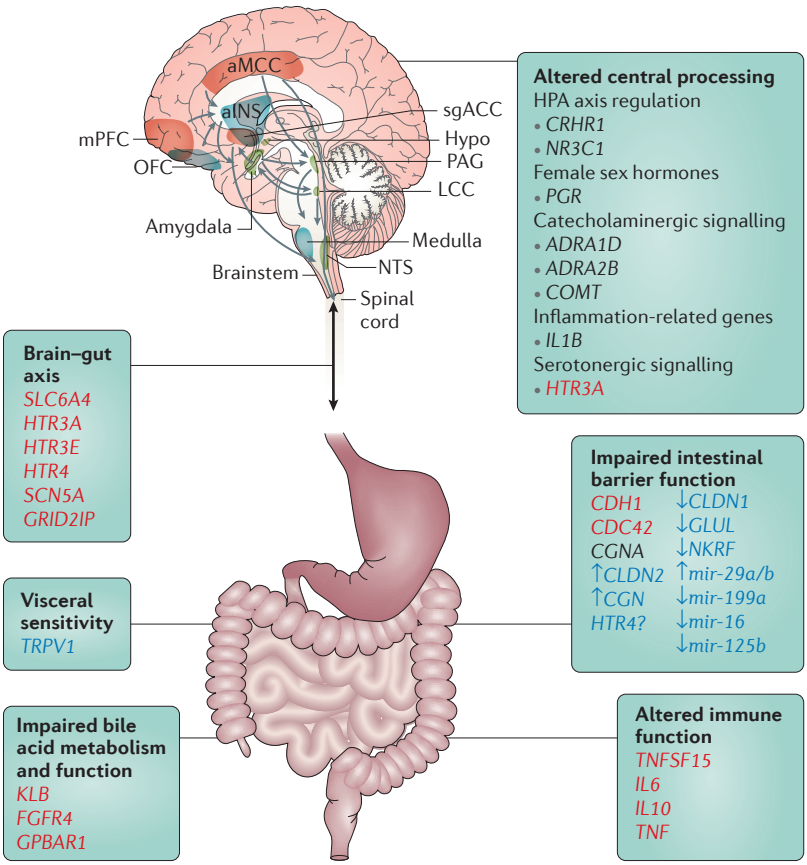

Figure 6 | **Summary of the genetic findings associated with different pathophysiological mechanisms underlying IBS.** Irritable bowel syndrome (IBS)-related pathways that are potential pharmacogenetic targets are marked in red when based on genetic findings and in blue when based on epigenetic findings; those in black are currently not seen as potential pharmacogenetic targets[101]. Various pathways might be affected in specific subgroups of patients with IBS: epithelial barrier (permeability), immune function, impaired bile acid metabolism and function, neuronal processing and signal transduction via spinal afferents from the periphery to the central nervous system in addition to the bidirectional crosstalk via the brain–gut axis, presumably contributing to psychological conditions such as anxiety, depression and somatization. Brain networks that have been associated with structural and functional alteration in IBS are depicted. *ADRA*, adrenoceptor-α; aINS, anterior insula; aMCC, anterior midcingulate cortex; *CDC42*, cell division cycle 42; *CDH1*, cadherin 1; *CGN*, cingulin; *CLDN*, claudin; *COMT*, catechol-*O*-methyltransferase; *CRHR1*, corticotropin-releasing hormone receptor 1; *FGFR4*, fibroblast growth factor receptor 4; *GLUL*, glutamate-ammonia ligase (also known as glutamine synthetase); *GPBAR1*, G protein-coupled bile acid receptor 1; *GRID2IP*, GRID2-interacting protein; HPA, hypothalamus–pituitary–adrenal; *HTR*, 5-hydroxytryptamine receptor; hypo, hypothalamus; *IL*, interleukin; *KLB*, Klotho-β; LCC, locus coeruleus complex; *mir*, microRNA; mPFC, medial prefrontal cortex; *NKRF*, nuclear factor-κB-repressing factor; *NR3C1*, nuclear receptor subfamily 3 group C member 1; NTS, solitary nucleus; OFC, orbitofrontal cortex; PAG, periaqueductal grey; *PGR*, progesterone receptor; *SCN5A*, sodium voltage-gated channel α-subunit 5; sgACC, subgenual anterior cingulate cortex; *SLC6A4*, solute carrier family 6 member 4; *TNF*, tumour necrosis factor; *TNFSF15*, TNF superfamily member 15; *TRPV1*, transient receptor potential cation channel subfamily V member 1.

Physical examination

A physical examination should be part of the evaluation to reassure patients and also to help exclude another organic cause of the symptoms. Admittedly, an abdominal examination, which is part of the routine examination, rarely discloses a specific diagnosis (that is, abdominal tenderness is present in various diseases), but the absence of objective findings on a physical examination has been found to support a diagnosis of IBS[132]. A digital rectal examination is an important part of the physical examination and a useful tool to identify patients with dyssynergic defaecation, which is important to exclude in patients with constipation[133,134] as well as to exclude rectal cancer. Perianal inspection should also be part of the examination to rule out perianal fistulas and other relevant anal pathology.

Laboratory tests

From the existing literature, it is not obvious which laboratory test to recommend in the diagnostic work-up of patients with IBS symptoms. Only serological tests for coeliac disease seem to be more likely to be abnormal in patients with symptoms compatible with IBS than in the general population[135], even though a large multicentre trial failed to confirm this[136]. However, few studies have systematically evaluated the usefulness of laboratory tests in patients with potential IBS. A recent systematic review demonstrated that C-reactive protein (CRP) levels of ≤0.5 mg per dl or faecal calprotectin levels of ≤40 μg per g essentially exclude IBD in patients with IBS symptoms[137]. On the basis of the existing literature, it seems reasonable to perform a complete blood count and CRP measurement, as these are inexpensive and can be used to reassure the health-care provider and the patient. A thyroid profile can be included if the clinical suspicion of thyroid disease is high, a serological test for coeliac disease can be recommended in patients with non-constipated IBS and — if there is suspicion of an inflammatory process — a faecal calprotectin measurement can be added. Stool analyses to detect gastrointestinal infections can be considered if diarrhoea is predominant and difficult to treat, especially in regions where infectious diarrhoea is common[138]. As stated previously, there is currently no valid diagnostic biomarker, even though preliminary data have suggested that certain biomarkers or biomarker assays (BOX 3) for clinical use might prove to be valid following further scientific investigation[139,140].

Alarm features

Alarm features for IBS are symptoms that should raise the clinical concern of another gastrointestinal disease rather than IBS. Whether the use of alarm features (BOX 6) improves the performance of diagnostic criteria for IBS is not totally clear[125,141]. However, from a clinical point of view, it seems reasonable to use these to select patients for further diagnostic testing, even though these may be

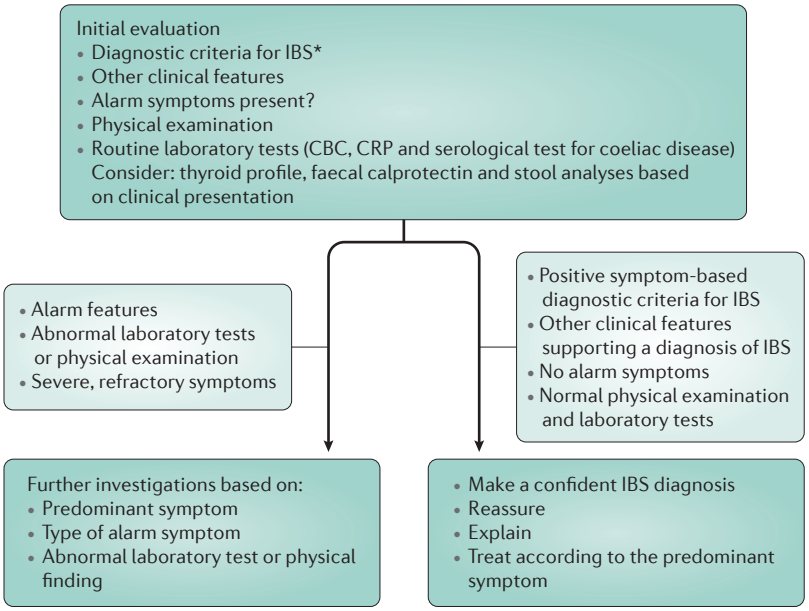

Figure 7 | **A diagnostic algorithm for patients with IBS.** This diagram gives a schematic overview of the sequential approach to irritable bowel syndrome (IBS) diagnosis[144]. CBC, complete blood count; CRP, C-reactive protein. Figure from REF. 144, Nature Publishing Group.

present in a substantial proportion of patients without indicating a serious underlying condition in the gastrointestinal tract[142]. Alarm symptoms can necessitate further investigations to rule out another gastrointestinal disease before an IBS diagnosis can be recommended. Moreover, the predominance of diarrhoea, especially when watery and frequent, should alert the clinician to consider alternative diagnoses[143].

Invasive investigations

In the majority of patients with symptoms compatible with IBS and normal routine laboratory tests but without alarm features[144], no additional invasive investigations are needed and, importantly, performing investigations does not seem to improve patient satisfaction or QOL[145,146].

Colonoscopy should be performed when alarm features prompt an investigation and when there is suspicion of an inflammatory condition in the gastrointestinal tract based on history or laboratory parameters (increased CRP or faecal calprotectin levels)[137], or based on the indications for colorectal cancer screening in countries with population screening programmes[147,148].

When the patient complains of watery diarrhoea as the predominant symptom, a colonoscopy with biopsies should also be considered to rule out microscopic colitis, especially in women >50 years of age[143,149]. Moreover, bile acid-induced diarrhoea has recently been found to be a very important differential diagnosis in patients with IBS symptoms with frequent, loose stools[32,33], and a diagnostic test should be considered (75-homocholic acid taurine (^{75}SeHCAT) test or serum C4 levels)[150]. Unfortunately, these tests are not available in all centres, therefore a therapeutic trial with a bile acid-binding agent is often used as an indirect, but far from perfect, assessment of bile acid-induced diarrhoea.

Carbohydrate malabsorption is another differential diagnosis in patients with IBS-D[151–153], and lactose or fructose hydrogen breath tests can be considered[154,155], but a trial period with dietary exclusion of the suspected carbohydrate for several weeks is often used instead.

If coeliac disease is suspected, based on a positive serological test or the clinical history, an upper gastrointestinal endoscopy with duodenal biopsies should be performed. Small intestinal bacterial overgrowth has been proposed to be common in IBS, but its prevalence and clinical importance is uncertain, therefore routine clinical testing for this cannot be advocated[156,157], especially as valid tests with adequate sensitivity and specificity are lacking.

Management

Only a fraction of patients with IBS-like symptoms (~50%) seek medical care[158]. Most of these patients will initially consult primary care physicians for their symptoms, and the factors that drive this consultation are symptom severity, especially pain, the occurrence of alarm symptoms (BOX 6) and concerns that symptoms might indicate an underlying severe disease — for example, cancer[159]. Therefore, in many cases, gastrointestinal specialist care is needed to exclude diseases that can mimic IBS symptoms — for example, by endoscopy. Once a positive diagnosis of IBS has been established, clinical management can be carried out as well by primary care physicians and at substantially lower costs[160].

Management of IBS involves an integrated approach, including the establishment of an effective patient–provider relationship, education, reassurance, dietary alterations, pharmacotherapy and behavioural and psychological treatment[161]. Owing to the fact that ~50–70% of patients with IBS report additional somatic and psychological symptoms when they are asked[161,162], a stepped-care approach including aspects of cognitive and interpersonal therapy is most appropriate[15]. The initial treatment strategy should be based on predominant symptoms and includes antispasmodics for abdominal pain, antidiarrhoeals for IBS-D and laxatives for IBS-C, whereas nutritional interventions and psychotherapy can be used in all subtypes.

Nutrition

Food ingestion is one of the most commonly reported factors that results in the exacerbation of symptoms among patients with IBS[163,164]. Postprandial symptoms per se and fear of their occurrence (anticipatory anxiety) contribute profoundly to reduced QOL in IBS[128]. Up until recently, food-related symptoms had received scant attention from clinical scientists, leaving patients to find their own way through the plethora of usually non-validated and untested diagnostic tests and dietary regimens, which could result in clinically relevant nutritional deficits[165].

It has become evident that food intolerance (a physiological reaction to food allergens that is not associated with an immune response), and not classical IgE-mediated food allergy (which involves activation of the

Box 6 | **Alarm features for IBS**

- Unintended weight loss (>10% in 3 months)
- Presence of blood in the stools not caused by haemorrhoids or anal fissures
- Symptoms that awaken the patient in the night
- Fever in association with the bowel symptoms
- Family history of colorectal cancer, inflammatory bowel disease or coeliac disease
- New onset of irritable bowel syndrome (IBS) symptoms after 50 years of age

immune system), is the major mechanism responsible for symptomatic responses to certain foods[165]. This is not to say that immune responses to food or food components are irrelevant for IBS. For example, one study demonstrated that exposure of the small intestine to certain food antigens led to subtle ultrastructural changes in the duodenal mucosa of patients with IBS, but not in controls[31]. Another study also reported local immune responses to gluten among a group of non-coeliac patients with IBS[166]. Taken together, these observations leave the door open to the possibility that at least some patients with IBS may mount an, as yet to be defined, immunological response to certain dietary components, a response that seems to be confined to the mucosal immune system.

How does one explain food-related symptoms in IBS? Given the primacy of food ingestion as a stimulus to most gastrointestinal functions, postprandial pain and rectal urgency in IBS could simply reflect an exaggeration of a normal physiological phenomenon. Exaggerated motor responses to food and, especially to lipids, have also been demonstrated in the small intestine in IBS[167]. Furthermore, tryptophan, the 5-HT precursor, and related compounds present in some foods could modulate psychological comorbidities and gastrointestinal symptoms in IBS[168]. Food-related symptoms could also be mediated through interactions between our diet, the products of digestion and the gut microbiota. Products of bacterial metabolism, such as deconjugated bile salts, SCFAs and gases, could exert potent effects on colonic physiology and thereby induce symptoms.

Although patients with IBS readily incriminate specific food items as those that are especially likely to precipitate symptoms, only 11–27% of those are correctly identified when confirmed in formal, blinded food challenge studies[169]. The limitations of dietary surveys and the poor reproducibility of reported food intolerances notwithstanding, some food items are reported as being more problematic: wheat, fruit and vegetables[170]. Current enthusiasm for diets low in FODMAPs is consistent with these observations.

Fibre and fibre-based supplements accelerate colon transit, increase stool bulk and facilitate its passage, resulting in an increase in stool frequency. These effects translate into clinically meaningful benefits for people with chronic constipation and IBS-C. Indeed, fibre and products based on synthetic fibre-like substances became a cornerstone in the management of IBS. However, RCTs found that not all patients gained relief and some even complained of exacerbation of their symptoms (including pain, bloating and distension). Recent meta-analyses and systematic reviews have shed some light on this issue by showing that fibres are heterogeneous and the consumption of soluble fibres such as psyllium, calcium polycarbophil and ispaghula bring symptomatic benefits, whereas insoluble fibres, represented by bran, are ineffective in patients with IBS[169].

Interest in the use of low FODMAP diets (BOX 5) in patients with IBS is increasing. RCTs have confirmed some beneficial effects of low FODMAP diets on IBS symptoms[171], but they were not superior to conventional dietary advice when directly compared[172]. There are some limitations; studies to date have been small and, as has been the case with many studies of dietary interventions in IBS, suffer from some methodological limitations[173]. Furthermore, low FODMAP diets are complex, may require supervision by a qualified dietician and involve the elimination of many food items commonly regarded as components of a 'healthy' diet. Some initial investigations suggest that the low FODMAP diet may suppress the growth of bacterial species commonly regarded as important components of healthy microbiota, such as bifidobacteria[174]. Included in the FODMAP category are some molecules, such as lactose, fructose and sorbitol; some patients with IBS may benefit from the removal of one of these substances alone[175]. Predicting responders is difficult, as commonly used challenge tests, such as the lactose or fructose breath hydrogen test, do not seem to be of value[175,176].

The concept of 'non-coeliac gluten sensitivity' has been advanced to explain instances of IBS-type symptoms that develop in individuals who do not satisfy diagnostic criteria for the diagnosis of coeliac disease (that is, positive serology and appropriate changes in small intestinal morphology)[177]. This remains an unsettled and contentious issue with some studies reporting that, when tested in a blinded manner, gluten did induce the usual IBS symptoms in some patients with IBS[178]. Others argue that gluten contributes little to IBS symptomatology, but that fructans (FODMAPs contained in wheat), and not gluten, are the culprits of wheat-related problems. Results of clinical trials assessing the role of gluten exposure in IBS pathology have therefore, not surprisingly, yielded mixed results[179,180]. Although gluten-free diets are currently enjoying considerable popularity among patients with IBS and the population at large in the United States, the rationale for gluten exclusion in IBS has yet to be firmly established.

Patients with IBS commonly consume any one or combinations of a wide variety of dietary supplements ranging from vitamins to 'digestive enzymes', antioxidants and essential oils. Few, if any, of these have been subjected to rigorous study. Prebiotics (non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon) and probiotics (live microbial food ingredients that alter the microflora and confer health benefit) have also been used for decades in IBS in the absence of supportive data. Prebiotics and probiotics are now subjected to more-rigorous studies, as they might

contribute to altered microbiota in IBS[181,182]. Although these studies must be interpreted with care, a recent meta-analysis does suggest efficacy for probiotics (as a category) in IBS[183]. However, high-quality RCTs remain few in number and available data provide scant information to assist the consumer in choosing a particular product to alleviate symptoms[184] or to make a recommendation on prebiotics or synbiotics (a combination of a prebiotic and a probiotic) in IBS[185].

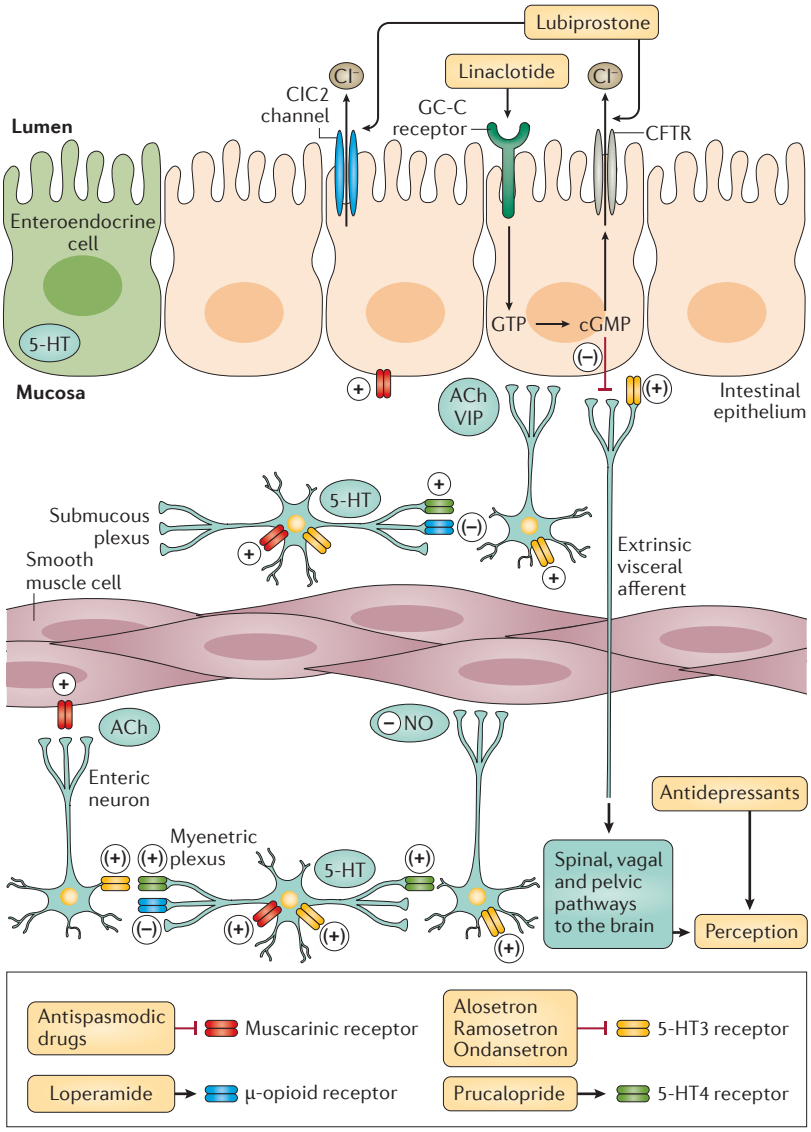

Figure 8 | **Mechanisms of action of different drugs used for the treatment of IBS.** Drugs currently used for the treatment of irritable bowel syndrome (IBS) (orange boxes) target nerve activity, epithelial functions or the contractile state of the smooth muscle layers. Several drugs act by enhancing the activity of chloride channels to increase fluid secretion into the intestinal lumen as a consequence. Other mechanisms of action include modulation of visceral sensitivity at a central or peripheral level. Finally, drugs act to modulate signal transduction at the neuromuscular junction or alter motility by direct myogenic actions. The plus and minus symbols indicate whether a mediator activates or inhibits its target cell; those in parentheses denote actions established in animal models and those without parentheses are effects demonstrated in humans (human tissue). 5-HT, 5-hydroxytryptamine (also known as serotonin); ACh, acetylcholine; CFTR, cystic fibrosis transmembrane conductance regulator; ClC2, chloride channel protein 2; GC-C, guanylyl cyclase C; VIP, vasoactive intestinal peptide.

Drug therapy

Broadly speaking, the current therapeutic armamentarium in IBS aims to alter predominant problematic bowel habits and/or visceral pain. However, an emerging area is manipulation of the gastrointestinal microbiota.

Antispasmodic drugs. Pain in IBS is mediated through central and peripheral mechanisms, and is in part the result of smooth muscle spasms. The mode of action of antispasmodic drugs is probably their ability to antagonize the binding of acetylcholine to the muscarinic receptor at the neuromuscular junction, with smooth muscle relaxation as a consequence[186]. Some studies have demonstrated a beneficial effect of otilonium bromide and hyoscine over placebo, with a number needed to treat (NNT) of four patients[187]. An adverse effect of anti-muscarinic agents is constipation because of their strong inhibition of intraluminal fluid secretion[186]. Accordingly, these drugs are best used in patients without constipation and should be taken 20 minutes before meals to ease postprandial symptoms. Peppermint oil, which also inhibits smooth muscle contraction albeit by calcium channel blockade, is beneficial in reducing IBS symptoms[188]. A recent RCT in patients with IBS-D and IBS-M demonstrated that a novel formulation of peppermint oil, designed to cause a sustained release within the small bowel, was superior to placebo in causing a reduction in total symptoms[189].

Low-dose antidepressants. Antidepressants, such as tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs), are recommended by existing guidelines for the treatment of pain in patients who are refractory to antispasmodics and dietary alterations[190]. However, these drugs are not licensed anywhere in the world for the treatment of patients with IBS, and their use is off-label. Given the lack of licensed indication, the rationale for using such drugs should be discussed in detail with patients. The exact analgesic mechanism of action of low-dose antidepressants is incompletely understood but is considered to be both peripheral, via alterations of histaminergic and/or cholinergic transmission within the gastrointestinal tract, and central, via modulation of both ascending visceral sensory afferents and central transmission[191]. SSRIs are generally well tolerated. Adverse effects such as constipation, dry mouth, drowsiness and fatigue are reported with TCAs. TCAs may be particularly effective for treating pain in patients with IBS-D, but are less suitable for patients who have IBS-C.

Laxatives and motility accelerants. In those with constipation, simple laxatives such as senna and docusate are often effective in managing symptoms. However, the use of lactulose is not recommended as it is often poorly tolerated by patients with IBS because of worsening of bloating and discomfort. Linaclotide, a minimally absorbed guanylyl cyclase C agonist peptide (FIG. 8), can be used as second-line therapy after laxatives have failed in patients with IBS-C and symptoms

have lasted for >1 year. Linaclotide has a dual action through increasing intraluminal fluid secretion thereby giving its laxation effect but also an analgesic effect via modulation of colonic nociceptors[192], and its effects caused reduced abdominal pain, bloating and bowel symptoms in two well-designed Phase III RCTs[193,194]. Lubiprostone, a minimally absorbed, locally active, bicyclic fatty acid derivative of prostaglandin E1, activates type 2 chloride channels on the enterocyctic apical membrane, thereby stimulating fluid secretion. Lubiprostone has been shown to improve global intestinal symptoms in IBS-C[195]. 5-HT4 receptor agonists (such as prucalopride), which promote gut motility through the activation of the serotoninergic pathways, have been shown to be effective in increasing complete spontaneous bowel movements in patients with chronic constipation[196].

Antidiarrhoeals. The μ-opioid receptor agonist loperamide is frequently used as a first-line agent in IBS-D and improves diarrhoea by inducing peristalsis, which prolongs the gastrointestinal transit time. As loperamide does not cross the blood–brain barrier, central adverse effects are limited. Its main benefit is reducing stool frequency and defaecation urgency, and improving the consistency of the stool[197]. Eluxadoline, a mixed μ-opioid receptor agonist and δ-opioid receptor antagonist, has been evaluated in a Phase III RCT, although safety concerns have been expressed concerning the excess rates of pancreatitis[198].

5-HT3 receptor antagonists, such as alosetron, ramosetron and ondansetron, are effective in the management of IBS-D symptoms. The mechanism of action of 5-HT3 receptor antagonists is complex and incompletely understood, but is considered to proceed through inhibition of the ascending excitatory component of the peristaltic reflex and of the high amplitude propagating contractions within the gastrointestinal tract[199]. However, a central effect of 5-HT3 receptor antagonists on pain cannot be excluded[200]. Safety concerns, with respect to ischaemic colitis, have been confined to alosetron, which subsequently led to restrictions in its prescription[201]. Consequently, other 5-HT3 receptor antagonists have been investigated, with ondansetron[202] and ramosetron demonstrating efficacy in RCTs[203].

Manipulation of the microbiota. Given the burgeoning evidence of the role of the microbiota in IBS, both antibiotics and probiotics have been evaluated. The non-absorbable antibiotic, rifaximin, has been demonstrated to cause a reduction in symptoms, with a NNT of approximately 11 patients, although it is not clear whether repeated courses of treatment are needed[204]. The mechanisms by which rifaximin exerts its positive effects on IBS symptoms are incompletely understood and may include modulation of the gut microbiota, but also direct effects on local micro-inflammation. Rifaximin is approved for use in the United States, but has not yet received regulatory approval in Europe. Probiotics can reduce pain and symptom severity, although recent meta-analyses have highlighted that inconsistencies in study design render definitive recommendations problematic[183,184,205]; again, it is unclear whether probiotics act on IBS symptoms through direct modulation of the microbiota, indirect via the gut immune system or otherwise.

Others. A proportion of patients use herbal supplements either as single herbs or in combination. Four weeks of treatment with iberogast, which is a mixture of nine plant extracts, improved abdominal pain and QOL in a double-blind RCT of 208 patients with all types of IBS[206]. Although the mechanism of action is poorly understood, it is probably multifaceted via acetylcholine, 5-HT and opioid receptors in the gastrointestinal tract[207]. Although herbal remedies represent a promising intervention, further rigorously designed larger RCTs in the subtypes of IBS are needed.

Psychotherapy

The biopsychosocial model of IBS suggests that abdominal symptoms secondarily influence anxiety and depression (bottom-up) and psychosocial factors influence physiological factors, such as motor function, sensory threshold and stress reactivity of the gut (top-down)[208].

Treatment concepts that target these psychosocial factors of patients with IBS should be based on evidence-based models that take the following three components into account: altered peripheral regulation of gut function, altered brain–gut signalling and reducing psychological distress, including general hypervigilance and a general mindset of catastrophizing[209]. Such models might be helpful as a basis of patient education and a target for effective treatments. To further improve treatment programmes, we have to learn more about IBS-specific interactions and the role of stress and visceral sensitivity for clearer evidence on which group of patients might benefit from which treatment approach. In addition, it should be noted that patients with IBS often experience additional functional symptoms, pointing to the complexity of the condition[15].

The effect of IBS symptoms on patients' feelings of shame, fearfulness and embarrassment is well established; patients report being poorly understood by their physicians, as well as by their family members and friends[210]. Patients who experience a positive therapeutic physician–patient relationship have fewer IBS-related follow-up visits[211].

International treatment guidelines for IBS have advocated for a graded treatment approach[212,213]. The National Institute of Health and Care Excellence (NICE) guidelines advise that patients whose symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS) should be considered for referral to cognitive–behavioural therapy (CBT), hypnotherapy (gut-directed hypnosis) or other psychological therapy, such as psychodynamic (interpersonal) therapy and mindfulness-based therapy[190].

BOX 7 describes the four major psychological-based therapies for patients with IBS. Several meta-analyses have been performed in the field of psychological and behavioural therapies (including studies in stress reduction and relaxation) that took 45 RCTs into account with a total of 3,325 patients with IBS of all subtypes (TABLE 1). Overall, the NNT for psychological therapies is four patients (95% CI: 3–5) and, therefore, better than the majority of drugs[214]. In a stepped-care approach (beginning with the least intensive or invasive treatment and stepping up or down depending on the needs of the patients), a psychology-based self-aid (educational) approach has been shown recently in a meta-analysis as an effective treatment option for all subtypes of IBS[250]. Compared with control treatments, a medium effect size was demonstrated on decreased symptom severity and a large effect size on increased patient's QOL.

The best evidence is available for CBT. Although CBT is not routinely available in primary care, it can be accessed in some local hospitals and health-care systems. There are medium-to-large significant pooled effect sizes for an improvement of IBS symptoms using CBT with a medium significant pooled effect size for QOL and a small-to-medium pooled effect size for psychological comorbid symptoms. The NNT for CBT is only three patients, with a limited variance between the RCTs. Nevertheless, to date there is no evidence of a superiority of CBT compared with other psychological treatments in IBS.

Box 7 | **Evidence-based psychological treatments**

Cognitive–behavioural therapy

Cognitive–behavioural therapy (CBT) is based on the assumption that irritable bowel syndrome (IBS) symptoms are a response to stressful life events, maladaptive behaviour and an inappropriate attribution of symptoms. CBT aims to modify these behaviours and thoughts through education, which consists of the explanation of IBS symptoms and the CBT model, and by identification of the psychological factors that are interacting with their physical symptoms. On the basis of these findings, patients and therapists work together to identify the potential associations between IBS symptoms and their thoughts, emotions and actions. Finally, behavioural therapy (for example, stress management) is applied[245].

Psychodynamic (interpersonal) therapy

Psychodynamic (interpersonal) therapy (PIT) aims to obtain insights into symptom development as a consequence of interpersonal conflicts or difficulties in relationships with key people. Patients are encouraged to discuss their symptoms in depth, emotional factors are explored and links between symptoms and emotional factors are identified[246].

Gut-directed hypnosis

In gut-directed hypnosis (GDH), as opposed to standard hypnotherapy, suggestions are made on how to control and normalize gastrointestinal function and metaphors are used to bring about improvement. GDH differs from other forms of psychological treatment in which therapy is provided to patients in a conscious state. After information on the effects of hypnosis is given, participants are provided with a compact disk (created by hypnotherapists) for practicing at home on a daily basis[247].

Mindfulness-based therapy

Mindfulness-based therapy (MBT) for IBS has been adapted from the mindfulness-based stress reduction programme. The basic course emphasizes the relevance of mindfulness in coping with IBS-related symptoms and perceptions. With a range of behavioural and cognitive techniques, MBT promotes sensory versus emotional processing of interoceptive signals and counteracts catastrophizing as a maladaptive cognitive coping style[215].

Validation of psychodynamic (interpersonal) therapy, gut-directed hypnosis and mindfulness-based therapy (BOX 7) has only been done in a very limited number of tertiary treatment centres and the generalization of these treatment approaches is limited. Finally, mindfulness-based therapy for IBS shows some promising initial results, particularly in the subgroup of female patients with IBS[215]. Very limited data on multicomponent therapies and on the combination of antidepressants and psychological treatments are available[169]. Overall, there is a lack of reports of adverse effects of psychological and behavioural treatment approaches and treatment resistance in patients with IBS. Psychological therapies have also regularly not distinguished between IBS subtypes and, thus, might have missed differential indications and advantages and disadvantages.

Quality of life

In the field of medicine, general QOL and disease-specific QOL are distinguished. General QOL is a measure of the entire health perception of a person. Representative general QOL can be assessed using the Medical Outcome Study 36-item Short-Form Health Survey (SF-36)[216] or the EuroQOL survey[217]. SF-36 is the most popular instrument that can evaluate physical functioning, physical role, bodily pain, general health perceptions, vitality, social functioning, emotional role and mental health[216]. Disease-specific QOL is a measure of life disturbance that is specifically caused by the disease[218,219].

QOL in patients with IBS is greatly disturbed. Patients with IBS showed impaired general QOL with lower values on all SF-36 subscales except physical functioning than healthy controls in one study[220], whereas lower values on the SF-36 subscales in patients with IBS (except physical functioning, physical role and emotional role) than in healthy controls were observed in another study[221]. All subscales of SF-36, except the physical functioning and physical role domains, were lower in patients with IBS than in healthy controls regardless of culture[222]. The degree of disturbance of general QOL in patients with IBS has been shown to be worse in several subcategories than in those with gastroesophageal reflux disease, diabetes mellitus or severe chronic kidney disease[220]. Finally, a study has shown that patients with IBS had more disturbed general QOL in physical role, bodily pain, general health perceptions and social functioning than non-consulters with IBS (individuals who do not seek treatment)[221].

QOL seems to be the same among IBS subtypes. However, disease-specific QOL, as measured with the IBS-QOL in patients with IBS-D or IBS-M, was worse than in patients with IBS-C in one study[222]. In this study, increased food avoidance in patients with IBS-D and IBS-M may have been responsible for the lower QOL[222], but there are controversial reports[218].

In severe IBS, both gastrointestinal symptoms and psychiatric comorbidity independently contribute to disturbed QOL[223] (FIG. 9). Another study revealed that the QOL of patients with IBS was more influenced by the extraintestinal symptoms — such as tiring easily, low in energy, the feeling that there is something

seriously wrong with their body, feeling tense, feeling nervous, feeling hopeless, difficulty sleeping and low sexual interest — than by gastrointestinal symptoms[224]. The psychological and psychosocial dimensions of food ingestion might also have a role. Eating with family and friends is probably the most common form of social interaction worldwide. An inability to participate in such a fundamental component of social intercourse because of a fear of pain, urgency, diarrhoea or distension occurring during or immediately after a meal can be devastating and can result in social isolation[210].

Systematic reviews have clarified that improvement of IBS-related pain by treatment results in better QOL in patients with IBS[225]. The disease-specific IBS-QOL and IBS-QOL questionnaires can measure the efficacy of treatment, especially long-term therapies[226]. Although the SF-36 can also detect the efficacy of long-term treatment (>1 year), it is less sensitive than the IBS-QOL. Both measures struggle to detect drug or psychotherapy efficacy in the short term (<1 month)[226,227], but IBS-QOL is sensitive enough to detect efficacy for mid-term (3 months) treatment[203]. A therapeutic gain of ≥14 points in IBS-QOL denotes a clinically meaningful change. Even if primary end points based on cardinal symptoms of IBS are similar between treatments, a treatment resulting in better QOL may be preferred by patients over another treatment that does not improve QOL.

Outlook

The field of research into IBS has expanded considerably over the past decade with many new studies, in part driven by the development of new therapeutic agents. This trajectory seems likely to continue as patients with IBS account for a substantial proportion of all gastrointestinal consultations, and many questions in the field remain unanswered (BOX 8).

Patient stratification and biomarkers

Many classes of drugs have been evaluated by RCTs in IBS and these have often produced disappointingly small differences from placebo[187,214,228]. These small differences conceal the fact that some patients benefit from the drugs.

Table 1 | **Evidence-based psychological treatments for IBS**

Psychological treatment approach*	*n* of studies (*n* of participants)	Main findings	Comments
CBT[248]	18 RCTs (1,380)	• Symptom score: medium-to-large significant pooled effect size‡ (0.67) • QOL: medium significant pooled effect size (0.48) • Psychological distress (depression and anxiety): small-to-medium pooled effect size (0.21) • NNT for CBT was 3 (95% CI: 2–6)	• CBT was superior to waiting lists, basic support or medical treatment alone at the end of treatment but not superior to other psychological treatments
PIT[249]	2 RCTs (273)	Both studies compared PIT with 'supportive listening' applied by the same therapist. Compared with controls: • PIT significantly improved symptoms • PIT showed a large cost-effectiveness • PIT was widely acceptable • PIT significantly improved QOL • PIT significantly reduced costs • The calculated OR for benefit was 2.92 (95% CI: 1.76–4.83) • NNT for dynamic psychotherapy was 3.5 (95% CI: 2–25)	• PIT is less well standardized in terms of its performance (that is, duration, setting and phases)
GDH[247]	7 RCTs (452)	• 6 of 7 RCTs reported a significant reduction (all $P < 0.05$) in overall gastrointestinal symptoms compared with supportive therapy only • Response rates ranged between 24% and 73% • Efficacy was maintained long term in four of five studies • NNT was 4 (95% CI: 3–8)	• Very few professionals are trained for the specific implementation of GDH and therefore their services can be difficult to access • The mechanisms by which GDH exerts its effect are poorly understood
MBT[215]	2 RCTs (79)	• Women showed greater reductions of symptoms compared with a control group immediately after training (26.4% versus 6.2%; $P = 0.006$) and at 3 months follow-up (38.2% compared with 11.8%; $P = 0.001$) • Changes in QOL, distress and anxiety were not different between groups immediately after treatment • Significantly greater improvement in the MBT group than in the control group evident at 3 months follow-up • The beneficial effects persisted for ≥3 months	• In another RCT, the IBS symptom severity in the mindfulness-based stress reduction group was not retained at 6 months follow-up
Relaxation[214§]	6 RCTs (255)	• Overall, no benefit of relaxation training or therapy in IBS was detected in the RCTs	• The field of studies on relaxation techniques is diverse
GSHs[250]	10 RCTs (886)	• Compared with control conditions, a moderate effect size on symptom severity (0.72) and a large effect size on the increase of patients' QOL (0.84) was found	• GSHs might be an easily accessible and a cost-effective treatment alternative. However, there is a wide heterogeneity and variance in its performance

The NNT data are based on Ford *et al.*[214]. CBT, cognitive–behavioural therapy; GDH, gut-directed hypnosis; GSH, guided self-help intervention; IBS, irritable bowel syndrome; MBT, mindfulness-based therapy; NNT, number needed to treat; OR, odds ratio; PIT, psychodynamic (interpersonal) therapy; QOL, quality of life; RCT, randomized controlled trial. *See REF. 245. ‡Effect size (for example, Cohen's d): effect sizes of 0.2–0.5 are regarded as small, between 0.5 and 0.8 as moderate and >0.8 as large. §Methods and techniques applied are progressive muscle relaxation, biofeedback and transcendental or yoga meditations.

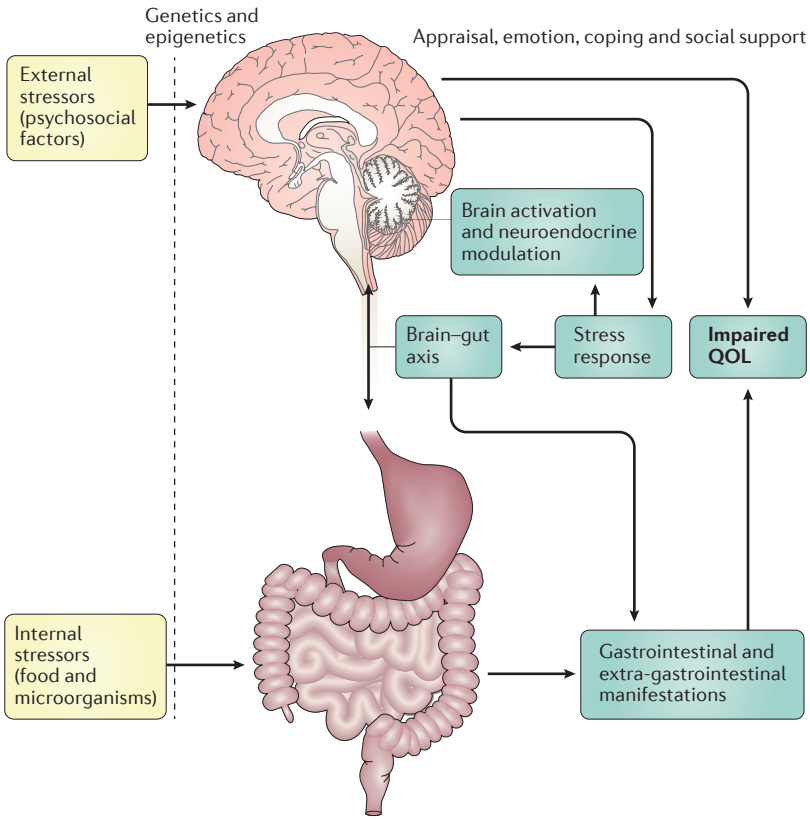

Figure 9 | **Concept of multifactorial quality-of-life effects in IBS.** The genome and epigenome partially determine ('filter') the response of an individual to external stressors (psychosocial factors) and internal stressors (ingested food or microbiota). These, together with social support, appraisal, emotion and coping behaviours against stressors, determine the stress response affecting the brain–gut interactions. This response might involve regional brain activation, changes in autonomic and neuroendocrine function, which might lead to many of the clinical manifestations observed in irritable bowel syndrome (IBS), including visceral hypersensitivity, alteration in gastrointestinal motility, increased mucosal permeability and low-grade inflammation. These gastrointestinal symptoms and other extra-intestinal manifestations (such as multiple somatic symptoms and psychiatric comorbidities) impair the quality of life (QOL) of patients with IBS.

Proper stratification of patients by relevant underlying disease mechanism has been an issue, therefore many trials use unselected patients with IBS, independent of the underlying disease mechanisms and clinical presentations. The use of 5-HT receptor-modulating drugs has taught the research community that restricting 5-HT3 receptor antagonists to patients without constipation improved their effectiveness with significant differences from placebo[229,230], owing to the fact that 5-HT3 receptor antagonists slow transit and aggravate constipation. However, RCTs rarely measure transit as a requirement for trial entry, which depends on symptoms recorded in daily symptom diaries. The use of more-objective biomarkers to select patients for RCTs would be expected to improve the effect size and reduce the number needed to test to show a significant difference from placebo.

The lack of reproducible, widely available biomarkers that reflect the targets of 'older' drugs has been a considerable limitation. Antispasmodics are a good example of such drugs that have fallen out of favour because we cannot reliably identify those with excessive motor activity who might be expected to respond. Future novel non-invasive motility assessments, such as MRI[231], capsule endoscopy[232] and the pressure-sensitive, temperature-sensitive and pH-sensitive SmartPill (Given Imaging Ltd, Yoqneam, Israel)[233] (which can measure intestinal contractions), hold the possibility of identifying such patients in the future.

Although individual genetic markers seem likely to be associated with only quite modest increases in risk for IBS, they might be important predictors of drug sensitivity in particular pathways. 5-HT3 receptor antagonists are good examples of drugs with a wide range of sensitivities such that effective doses for one patient can produce unacceptable constipation in another. This finding may be due to a combination of important functional polymorphisms in genes involved in 5-HT synthesis (tryptophan hydroxylase 1 (*TPH1*)), those involved in 5-HT reuptake via the 5-HT transporter (*SLC6A4*) and polymorphisms in the 5-HT3 receptor genes (which alter sensitivity). Several small studies have suggested significant differences in responder status to one 5-HT3 receptor antagonist, ramosetron, according to polymorphisms in *TPH1* (REF. 234) and to another 5-HT3 receptor antagonist, alosetron, according to polymorphisms in *SLC6A4* (REF. 235). However, these studies are underpowered and have not yet been reproduced[202]. By analogy with other complex disorders[236], the effect of any one individual polymorphism may be limited but combining polymorphisms that predict low 5-HT production with rapid uptake and low receptor sensitivity would be expected to be associated with higher odds ratios for success of 5-HT manipulation. Future studies should be powered to examine this notion such that the dose can be tailored to individual patients. Similarly, polymorphisms in the *FGF19*–*FGFR4* pathway, which controls bile acid synthesis[107,108], influence colonic transit and should be explored to see if different combinations alter sensitivity to bile acid sequestrants or bile acid transporter inhibitors.

Mode of action of food intolerances

Dietary restrictions such as low FODMAP diets (BOX 5) are another example in which implementation of an effective treatment is hampered by lack of biomarkers to predict response or reliably identify the key component (or components) of food that are responsible for symptoms. Although poorly absorbed fermentable carbohydrates can undoubtedly cause symptoms in some patients, visceral sensitivity is the key to why some individuals experience symptoms and some do not[237], at least in the case of lactose malabsorption. However, no trial of lactose exclusion in IBS has used measures of sensitivity to stratify patients. While rectal barostat tests to assess visceral sensitivity are difficult, although not impossible to standardize across centres, alternatives might be to use simple cutaneous pressure or thermal stimulation[238]. More remotely, somatization questionnaires concerning non-gastrointestinal symptoms such as headache, backache, dyspnoea and palpitations have been shown to correlate, albeit weakly, with rectal distension pressure thresholds for pain[239].

Box 8 | **Key questions to be addressed in future research**

Can we develop clinically applicable biomarkers to stratify patients to disease mechanisms, thereby reducing the number of patients needed to evaluate new therapeutic agents? Possible factors that should be taken into account are:

- Transit time
- Evidence of bile acid excess
- Immune activation
- Biopsy supernatant mediators that activate enteric neurons
- Mucosal serotonin availability

Can we assess the role of genetic markers in irritable bowel syndrome? Possible factors that should be taken into account are:

- Gene and environment interactions
- Biomarker discovery — for example, by genome-wide association studies
- Pharmacogenetics

Can we identify the mode of action of food intolerances to allow rational designs of diets? Possible tests are:

- Nutrient challenge meals
- MRI studies of intestinal volumes and gas or water content of the stool

Can we characterize the functional effects of changes in microbiota to improve efficacy of manipulation of the microbiota as a novel therapy? Possible studies are:

- Randomized controlled trials of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) intervention with assessment of changes in microbiota
- Effect of placebo-controlled diets on faecal or serum bacterial metabolites

The physical form of food is another key variable whose importance is yet to be defined. Many of the dietary components implicated in IBS symptoms are actually consumed as solids and hence delivered into the duodenum more slowly after trituration by antral contractions. The rapid entry of osmotically active poorly absorbed substrates — mainly in liquid form — such as lactose in a patient with lactose malabsorption[240,241] or mannitol in healthy volunteers[241] result in a rapid influx of water into the small intestine, which probably stimulates transit and rapid delivery into the colon. This leads to the virtually instantaneous generation of gas[242], mainly hydrogen, given that the microbiota are unable to fully metabolize the sudden excess of substrate. Furthermore, distension of the ascending colon generates propulsive colonic motility, which a sensitized individual may experience as cramps; a slower delivery in a solid matrix may be better tolerated. Future studies should define how the physical form of FODMAPs alters their tolerability, which would allow a less restrictive diet that may be easier to follow and, hence, more widely adopted than at present.

Functional effect of changes in microbiota

Many studies have found profound differences in the microbiota of selected patients with IBS, but the agreement on the involved species between studies is poor[57]. Given the very large number of different species that have overlapping metabolic capabilities and functional effects, focusing on function may be more helpful than just identifying the species present.

Analysis of urine and stool metabolites, including bile acids and endogenous tryptase, may provide simpler biomarkers of function that could predict responsiveness to microbiota manipulation. Thus, low levels of butyrate, a SCFA, might encourage the provision of prebiotics that favour butyrate-producing bacteria, such as *Eubacterium rectale* and *Roseburia cecicola*. Future studies should also take into account the important role of transit time and its variability. The challenge of rapid transit favours organisms with either enhanced growth capacity or those that adhere to the mucosa to deal with rapid flow within the colon[243], although, these results need to be replicated and studied in more detail to enable dissection of the extent to which differences in microbiota are the cause or the effect of rapid transit. Better insight might also enable the tailoring of diet to the existing microbiota in a patient, based on their metabolic capabilities and response to a substrate provided in the diet.

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Prior Stressor Exposure Sensitizes LPS-Induced Cytokine Production

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Exposure to stressors often alters the subsequent responsiveness of many systems. The present study tested whether prior exposure to inescapable tailshock (IS) alters the interleukin (IL)-1β, tumor necrosis factor (TNF)-α, or IL-6 response to an injection of bacterial endotoxin (lipopolysaccharide; LPS). Rats were exposed to IS or remained as home cage controls (HCC); 24 h later animals were injected i.p. with either 10 μg/kg LPS or equilvolume sterile saline. IS significantly increased plasma TNF-α, IL-1β, and pituitary, hypothalamus, hippocampus, cerebellum IL-1β 1 h, but not 2 h, after LPS, compared to controls. Additional animals were injected with LPS or saline 4, 10, or 21 days after exposure to IS and tail vein blood was collected and assayed for IL-1β. An enhanced plasma IL-1β response occurred 4 days after IS, but was gone by 10 days. These results suggest that exposure to IS sensitizes the innate immune response to LPS by resulting in either a larger or a more rapid induction of proinflammatory cytokines.

Key Words: stress; cytokine; interleukin-1; immune system; brain; sensitization

INTRODUCTION

Exposure to stressful events often results in long-lasting changes in the responsivity of a variety of systems. For example, repeated exposure to the same stressor (homotypic stress) often results in habituation of the hypothalamic–pituitary–adrenal (HPA) axis and brain stem catecholaminergic activity (Sakellaris & Vernikos-Danellis, 1975; Borrell, Torrellas, Guaza, & Borrell, 1980; Vernikos, Dallman, Bonner, Katzen, & Shinsake, 1982; Armario, Casterranos, & Balasch, 1984; Dobrakovova & Jurcovicova, 1984; Natelson et al., 1988; Pitman, Ottenweller, & Natelson, 1988; De Boer, Koopmans, Slangen, & Van der Gugten, 1990; Hauger, Lorang, Irwin, & Aguilera, 1990; Lachuer, Detton, Buda, & Tappaz, 1994). Conversely, exposure to a test stressor that is different (heterotypic stress) from that used during the initial repeated exposure results in sensitization of the HPA axis and brain stem catecholaminergic activity (Sakellaris & Vernikos-Danellis, 1975; Vernikos et al., 1982; Konarska, Stewart & McCarty, 1989; Lachuer et al., 1994). In addition, a single exposure to a stressor has been shown to sensitize central pathways involved in drug reward (Piazza & Le Moal, 1998), fear and anxiety (Agid, Kohn, & Lerer, 2000; Goenjian et al., 2000), and neuroendocrine responses (van Dijken et al., 1993; Schmidt, Binnekade, Janszen, & Tilders, 1996).

Stress-induced sensitization of neuronal pathways is of particular interest since it has been implicated in the pathogenesis of psychiatric disorders such as drug psycho-

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sis, panic, anxiety, posttraumatic stress, and depressive disorder (Shore, Tatum, & Vollmer, 1986; Engdahl, Dikel, Eberly, & Blank, 1997; Brown, Rush, & McEwen, 1999; Agid et al., 2000; Goenjian et al., 2000). It is thought that cross-sensitization may occur between stressors and other stimuli if they activate a common neuronal pathway. For example, this process has been implicated in drug addiction because stressors and drugs of abuse activate overlapping neural circuitry (Antelman, Eichler, Black, & Kocan, 1980; Leyton & Stewart, 1990), and has been argued to be the mechanism by which stressors enhance the rewarding properties of drugs (Piazza & Le Moal, 1998). Sensitization of the monoamine pathways is the most likely effect of stressors since they play a fundamental role in reward processes (Robinson & Berridge, 2000).

It has been suggested that stressors and activation of the immune system also lead to the stimulation of common neuronal pathways (Dunn & Welch, 1991; Dunn, Wang, & Ando, 1999). Activation of the innate or nonspecific immune system results in the production of proinflammatory cytokines such as interleukin-1 (IL-1β) and IL-6 by phagocytic cells (Janeway, Travers, Walport, & Capra, 1999). During infection these proinflammatory cytokines stimulate inflammation of the infected site by inducing local dilation of blood vessels, upregulation of intercellular adhesion molecules (iCAMs), recruitment of immune cells to the infected area, and stimulation of infiltrating immune cells (Janeway et al., 1999). All of these responses are critical for localization and elimination of the invading pathogen. In addition, proinflammatory cytokines signal the brain, leading to activation of regions involved in the neurally mediated components of host defense (Dunn, 1993; Brady, Lynn, Herkenham, & Gottesfeld, 1994). This aspect of host defense has been called the ''sickness response'' (Kent, Bluthe, Kelley, & Dantzer, 1992a) and includes fever, increased NREM sleep, reductions in food and water intake, reduced exploration, reduced social behavior, hyperalgesia, HPA activation, and increased sympathetic nervous system activity (see Maier, Watkins, & Fleshner, 1994, for review). Together, these changes reduce the capacity of pathogens to replicate while simultaneously maximizing the host's ability to recover from the precipitating insult (Blalock, 1984; Roberts, 1991). Interestingly, brain-derived cytokines are induced in response to the peripheral cytokine signal (Laye, Parnet, Goujon, & Dantzer, 1994; Quan, Sundar, & Weiss, 1994) and these brain-derived cytokines are involved in mediating sickness responses (Krueger, Walter, Dinarello, Wolff, & Chedid, 1984; Sapolsky, Rivier, Yamamoto, Plotsky, & Valer, 1987; Hart, 1988; Dantzer & Kelley, 1989; Dascombe, Rothwell, Sagay, & Stock, 1989; Kluger, 1991; Kent et al., 1992b; Kent, Rodriguez, Kelley, & Dantzer, 1994; Maier, Watkings, & Nance, 2001). Thus, sickness responses can be blocked by intracerebral administration of the IL-1 receptor antagonist (IL-1ra), and induced by intracerebral injection of IL-1β (Rothwell & Luheshi, 1994; Schobitz, De Kloet, & Holsboer, 1994).

Classically, it has been thought that the release of proinflammatory cytokines and the expression of ''sickness behaviors'' only occur when the immune system is activated by a pathogen. There is now evidence that exposure to a novel environment, restraint, foot shock, tail shock, or simple exposure to conditioned stimuli that were present during foot shock increase circulating levels of IL-6 (LeMay, Vander, & Kluger, 1990a; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). Moreover, stressors such as inescapable tail shock (IS) increase brain levels of IL-1β (Nguyen et

al., 1998) and induce sickness responses such as fever and increases in acute phase proteins (Deak et al., 1997). Consistent with the idea that these sickness responses to IS are mediated by brain IL-1β, the responses can be blocked by intracerebroventricular (icv) administration of alpha-melanocyte-stimulating hormone, a functional IL-1 receptor antagonist (Milligan et al., 1999). Data such as these have led to the suggestion that activation of the acute phase response in reaction to stress may represent an anticipatory defensive immune response (Deak et al., 1997).

While it has been known that stress exacerbates inflammatory diseases such as psoriasis, asthma, and arthritis (Mei-Tal, Meyerowitz, & Engel, 1970; Thomason, Brantley, Jones, Dyer, & Morris, 1992), which are known to result from the activation of cells involved in innate immunity, little is known about the enhancing effects of stress on actual innate immune function. Deak, Nguyen, Fleshner, Watkins, and Maier, (1999) have shown that IS facilitates recovery from subcutaneous bacterial challenge and Dhabhar and McEwen (1996) have found restraint to enhance skin delayed-type hypersensitivity responses. In addition, Zhu et al. (1995) have shown that 5 days of cold water stress enhances proinflammatory cytokine production from *in vitro* stimulated peritoneal macrophages. However, no study has examined the effects of an acute session of stress on *in vivo* proinflammatory cytokine production following immune challenge. This is an important issue, as these cytokines are critical in mounting innate immune responses and in signaling the brain that infection has occurred.

In the present experiments we investigated whether exposure to an acute session of IS 1, 4, 10, or 21 days before administration of bacterial cell wall (lipopolysaccharide; LPS) would alter the cytokine response to LPS. Plasma IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), along with IL-1β levels in various brain regions were measured 1 and 2 h following ip administration of 10 μg/kg LPS from rats exposed to IS 24 h prior, while only plasma IL-1β was measured from rats exposed to IS 4, 10, or 21 days prior to LPS challenge.

MATERIALS AND METHODS

Subjects. Adult male Sprague Dawley rats (275–325 g; Harlan Sprague Dawley, Inc., Indianapolis, IN) were individually housed in suspended wire cages (24.5 × 19 × 17.5 cm) with food and water available ad libidum. Colony conditions were maintained at 22°C on a 12-h light, 12-h dark cycle (lights on, 0700–1900 h). Rats were given at least 2 weeks to habituate to the colonies before experimentation. Care and use of animals were in accordance with protocols approved by the University of Colorado Institutional Animal Care and Use Committee.

Stress protocol. Animals either remained in their home cages as controls (HCC) or were placed in Plexiglas tubes (23.4 cm long × 7 cm diameter) and exposed to 100 5-s, 1.6-mA inescapable tailshocks, with an average intertrial interval of 60 s. All stress procedures occurred between 0800 and 1000 h. After stressor termination, rats were returned to their home cages.

LPS administration. One, 4, 10, or 21 days after exposure to IS or serving as HCC, animals were injected ip with either 10 μg/kg LPS (*Escherichia coli* endotoxin 0111: B4, Sigma Lot No. 17H4041) or equal volume sterile, endotoxin-free saline (Abbott Laboratories, North Chicago, IL). Preliminary studies showed that this dose results in a submaximal cytokine and corticosterone response (unpublished results).

Plasma and tissue collection. In some experiments animals were decapitated 60 or 120 min after administration of LPS or saline. Trunk blood was collected for later measurement of cytokines and endotoxin. Tubes were stored on ice and immediately spun in a refrigerated centrifuge. Plasma was aliquoted and stored at 20°C until time of assay. The pituitary and brain were quickly removed after decapitation. Brains were dissected on a frosted glass plate placed on top of crushed ice and brain structures, along with the pituitary, were placed in microfuge tubes and quickly frozen in liquid nitrogen. Brain tissue samples, which included hypothalamus, pituitary, hippocampus, cerebellum, and posterior cortex were stored at −70°C until the time of sonication.

Brain tissue processing. Each tissue was added to 0.25–1.0 ml of cold Iscove's culture medium containing 5% fetal calf serum and a cocktail enzyme inhibitor (in mM: 100 amino-*n*-caproic acid, 10 EDTA, 5 benzamidine–HCl, and 0.2 phenylmethylsulfonyl fluoride). Total protein was mechanically dissociated from tissue using an ultrasonic cell disruptor (Heat Systems, Inc., Farmingdale, NY). Sonication consisted of 10 s of cell disruption at the setting 10. Sonicated samples were centrifuged at 14,000 rpm at 4°C for 10 min. Supernatants were removed and stored at 4°C until an ELISA was performed. Bradford protein assays were also performed to determine total protein concentrations in brain sonication samples.

Serial blood sampling procedure. In experiments in which serial blood samples were taken baseline (BL) blood samples were obtained immediately prior to the administration of LPS or saline and blood samples were take 60 and 120 min later. To retrieve blood samples, the rat was removed from its home cage, gently wrapped in a towel, and lightly restrained with a Velcro strap. The tail was exposed and a small nick was made in a lateral tail vein with a scalpel (No. 15 blade), and the tail was gently stroked until a volume of approximately 200–300 μl of whole blood was obtained in microfuge tubes. The entire sampling procedure was accomplished within 2 min of approaching the cage to ensure nonstressed basal values. Samples were spun in a refrigerated centrifuge immediately, and plasma was aliquoted and stored at 20°C until the time of assay.

Measurement of cytokines. Cytokines were measured using commercially available ELISAs for rat IL-1β, TNF-α (R & D Systems, Minneapolis, MN), and IL-6 (BioSource, Camarillo, CA). The ELISAs were run according to the manufacturer's instructions. The rat IL-1β and TNF-α kits have a detection limit of <5 pg/ml and the IL-6 kit has a detection limit of <8pg/ml. The intra- and interassay precision is $<10\%$.

Measurement of plasma endotoxin. Plasma levels of endotoxin were determined by an enzymatic assay, according to the procedure outlined by Bio-Whittaker (Cat. No. 50-648U; Walkersville, MD). The detection limit of the assay is 0.02 EU/ml. Plasma was diluted 1:10 for saline-injected animals or 1:100 for LPS-injected animals. Animals that were injected with LPS, but had no detectable levels of plasma endotoxin, also had no increase in plasma, brain, peritoneal, or spleen cytokine levels compared to saline-injected controls. Presumably, injections were made into an internal organ which resulted in no detectable immune response. Therefore, these animals were eliminated from the study. Approximately 15% of the animals were eliminated from the study due to no detectable endotoxin and they were evenly distributed between groups.

Statistics. Due to size and manageability, the experiments examining the cytokine response 4, 10, and 21 days after IS were run as separate experiments with their own controls and analyzed using a 2 × 2 ANOVA between stress condition (IS vs HCC) and drug administration (saline vs LPS). The experiment examining the cytokine response 24 h after IS was analyzed using a 2 × 2 × 2 ANOVA between stress condition (IS vs HCC), drug administration (saline vs LPS), and time (1 h vs 2 h). Based on the a priori prediction that differences would be observed at the 1-h time point post hoc analysis was done using a Bonferonni corrected *t* test.

RESULTS

Effects of Prior Stress on Plasma Endotoxin

Plasma endotoxin levels for IS and HCC groups administered either LPS or saline are shown in Fig. 1. Low levels of plasma endotoxin were detectable in the saline control subjects. Administration of LPS produced large increases in plasma endotoxin after 1 h. Importantly, prior exposure to IS had no effect on basal or LPS administered plasma endotoxin levels.

Effects of Stress 24 h prior to LPS on Plasma Cytokines

The plasma TNF-α values for the various groups are shown in Fig. 2a. Plasma TNF-α was not detectable in subjects who had not received LPS. However, LPS produced a large elevation in plasma TNF-α measured 1 h later. TNF-α levels at 2 h had substantially diminished, but were still above basal levels. Importantly, prior exposure to IS potentiated the plasma TNF-α increase to LPS at the 1-h time point, with the potentiation no longer evident 2 h after LPS. A 2 × 2 × 2 ANOVA revealed a reliable interaction between stress condition (IS vs HCC), drug administration (sa-

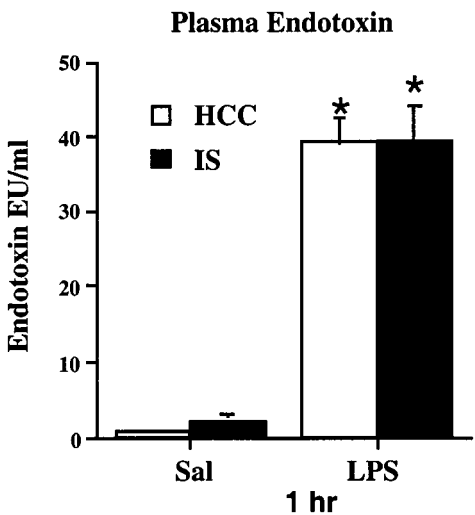

FIG. 1. Circulating plasma endotoxin 1 h after administration of lipopolysaccharide (LPS) or saline (Sal) in home cage control rats (HCCs) or rats exposed to inescapable tailshock (IS) 24 h prior. Bars represent means ($n = 7–8$) plus standard errors. *, significant difference ($p < .05$) from saline-injected animals.

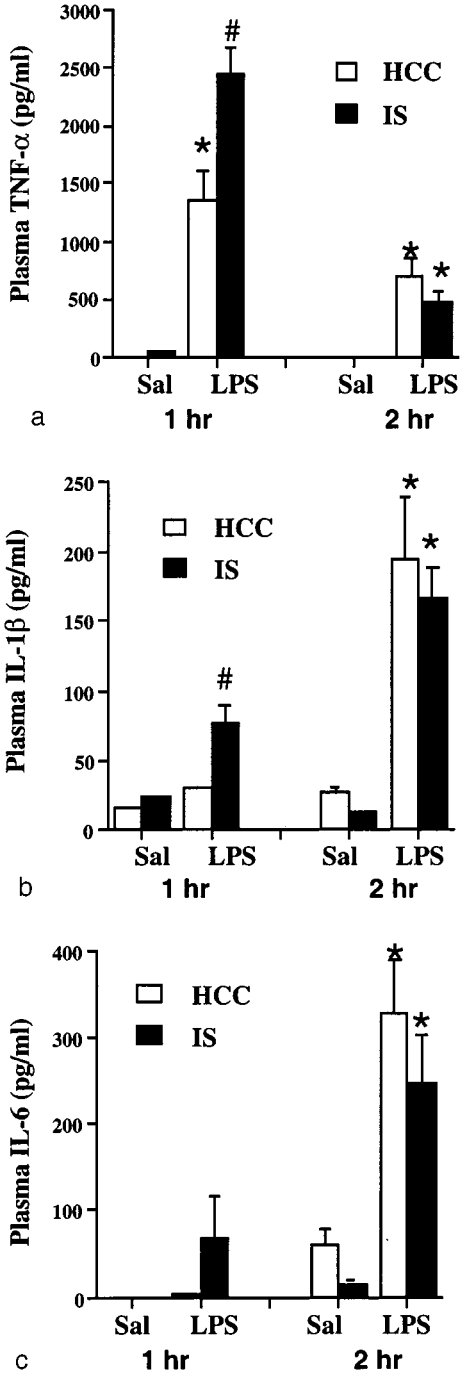

FIG. 2. Plasma levels of TNF-α (a), IL-1β (b), and IL-6 (c) 1 and 2 h after LPS or Sal administration in HCCs or rats exposed to IS 24 h prior. Bars represent means (n = 7–8) plus standard errors. *, significant difference ($p < .05$) from saline-injected animals; #, significant difference ($p < .05$) from saline- and HCC LPS-injected animals.

line vs LPS), and time (1 h vs 2 h) after LPS administration [$F(1, 1,55) = 9.004$; $p < .05$]. Post hoc analyses revealed a significant difference between HCC and IS animals administered LPS at 1 h ($p < .05$), but not at 2 h ($p = .43$). There were no statistical differences between saline groups at either time point.

Plasma IL-1β showed a different pattern (Fig. 2b). Plasma levels of IL-1β were detectable in the saline control subjects. Prior exposure to IS had no effect on basal levels of IL-1β. Although the plasma IL-1β response to LPS increased from the 1-h to the 2-h time point, IS again facilitated the cytokine response to LPS at the 1-h time point, but not at the 2-h time point. A 2 × 2 × 2 ANOVA did not reveal a reliable interaction between stress condition (IS vs HCC), drug administration (saline vs LPS), and time (1 h vs 2 h) after LPS administration [$F(1, 1,55) = .607$; $p = .44$]. However, post hoc analyses based on a priori predictions revealed a statistical difference between HCC and IS animals administered LPS at 1 h ($p < .05$), but not at 2 h ($p = .66$). There was no statistical reliable difference between saline groups at either timepoint. The pattern for plasma IL-6 was similar (Fig. 2c), but the post hoc analysis was not reliable at 1 h ($p = .13$) or 2 h ($p = .52$).

Effects of Stress 24 h prior to LPS on Brain IL-1β Protein

Brain and pituitary IL-1β levels are showed in Figs. 3a–3e. Tissue levels of IL-1β were detectable in the saline control subjects. Prior exposure to IS had no effect on basal IL-1β levels 24 h later. Tissue IL-1β response to LPS increased from the 1-h to the 2-h time point in HCC animals, and once again IS facilitated the cytokine response to LPS at the 1-h time point, but not at the 2-h time point. A 2 × 2 × 2 ANOVA did not reveal a reliable interaction between stress condition (IS vs HCC), drug administration (saline vs LPS), and time (1 h vs 2 h) after LPS administration in any brain region. However, post hoc analyses revealed a statistically significant difference between HCC and IS animals administered LPS at 1 h for the hypothalamus ($p = .05$), cerebellum ($p < .05$), and pituitary ($p < .05$), but not at 2 h ($p = .83$), ($p = .56$), and ($p = .55$), respectively. No statistically significant differences were observed between HCC and IS animals 1 h after LPS administered in the hippocampus ($p = .09$) and cortex ($p = .11$), or at the 2-h time point ($p = .65$) and ($p = .34$), respectively.

Effects of Stress 4, 10, and 21 Days prior to LPS-Induced Plasma IL-1β

As previously shown, plasma levels of IL-1β were detectable in the saline control subjects and prior exposure to IS had no effect on basal levels of IL-1β. Plasma IL-1β responses to LPS increased from the 1- to the 2-h time point. Animals injected with LPS 4 days after exposure to IS had a very similar response to animals that had been exposed to IS 24 h before LPS. That is, IS enhanced plasma IL-1β 1 h, but not 2 h, after LPS (Fig. 4a). A 2 × 2 ANOVA revealed an interaction between stress condition (IS vs HCC) and drug administration (saline vs LPS) 1 h after LPS administration [$F(1, 25) = 7.55$; $p < .05$]. LPS administration 10 or 21 days after IS did not result in significant differences in plasma IL-1β compared to controls (Figs. 4b and 4c).

DISCUSSION

Exposure to a single session of IS resulted in the enhancement of proinflammatory cytokine release in response to LPS administered 24 h later. Prior exposure to IS

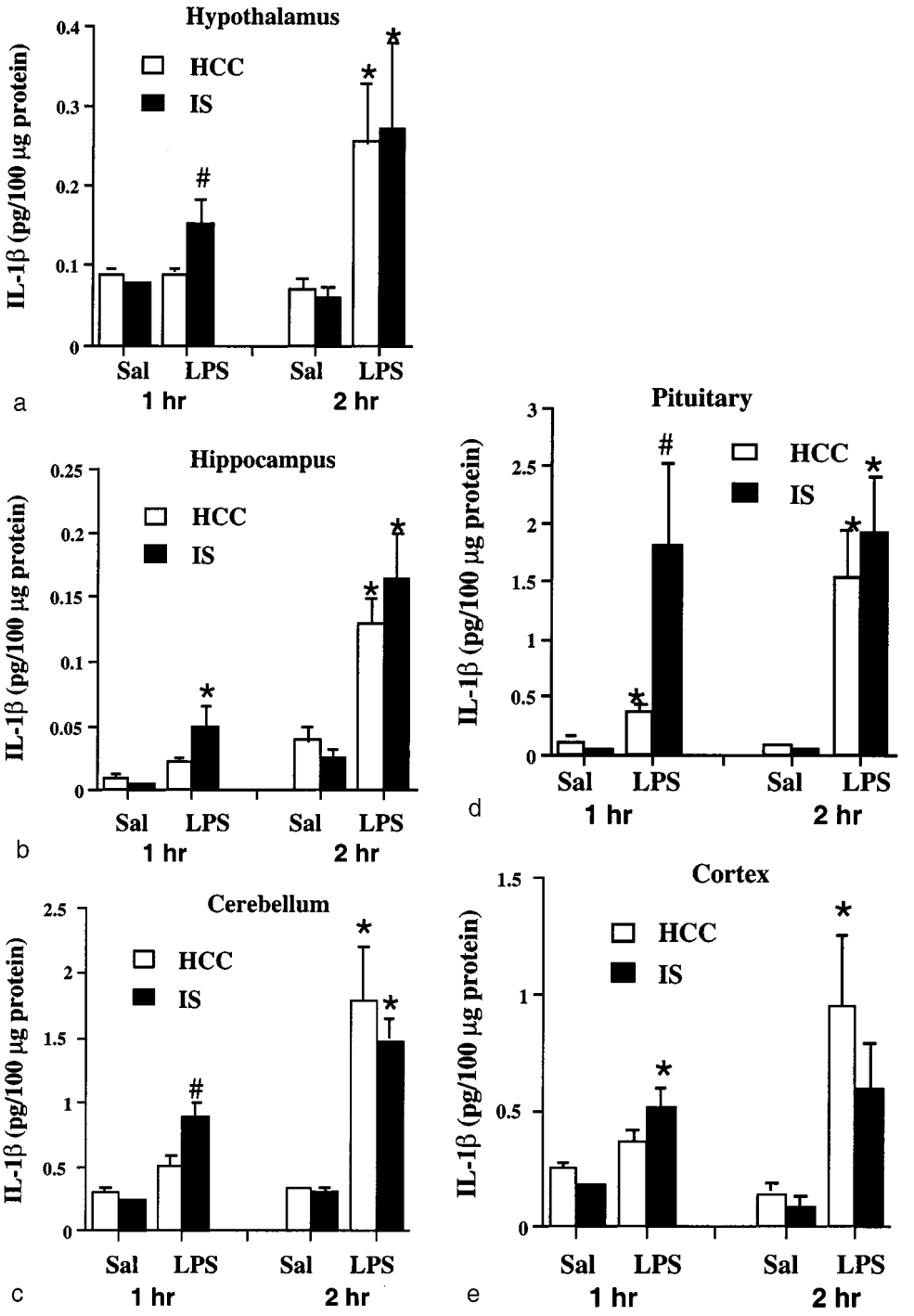

FIG. 3. IL-1β levels in the hypothalamus (a), hippocampus (b), cerebellum (c), pituitary (d), and cortex (e) 1 and 2 h after LPS or Sal administration in HCCs or rats exposed to IS 24 h prior. Bars represent means ($n = 7–8$) plus standard errors. *, significant difference ($p < .05$) from saline-injected animals; #, significant difference ($p < .05$) from saline- and HCC LPS-injected animals.

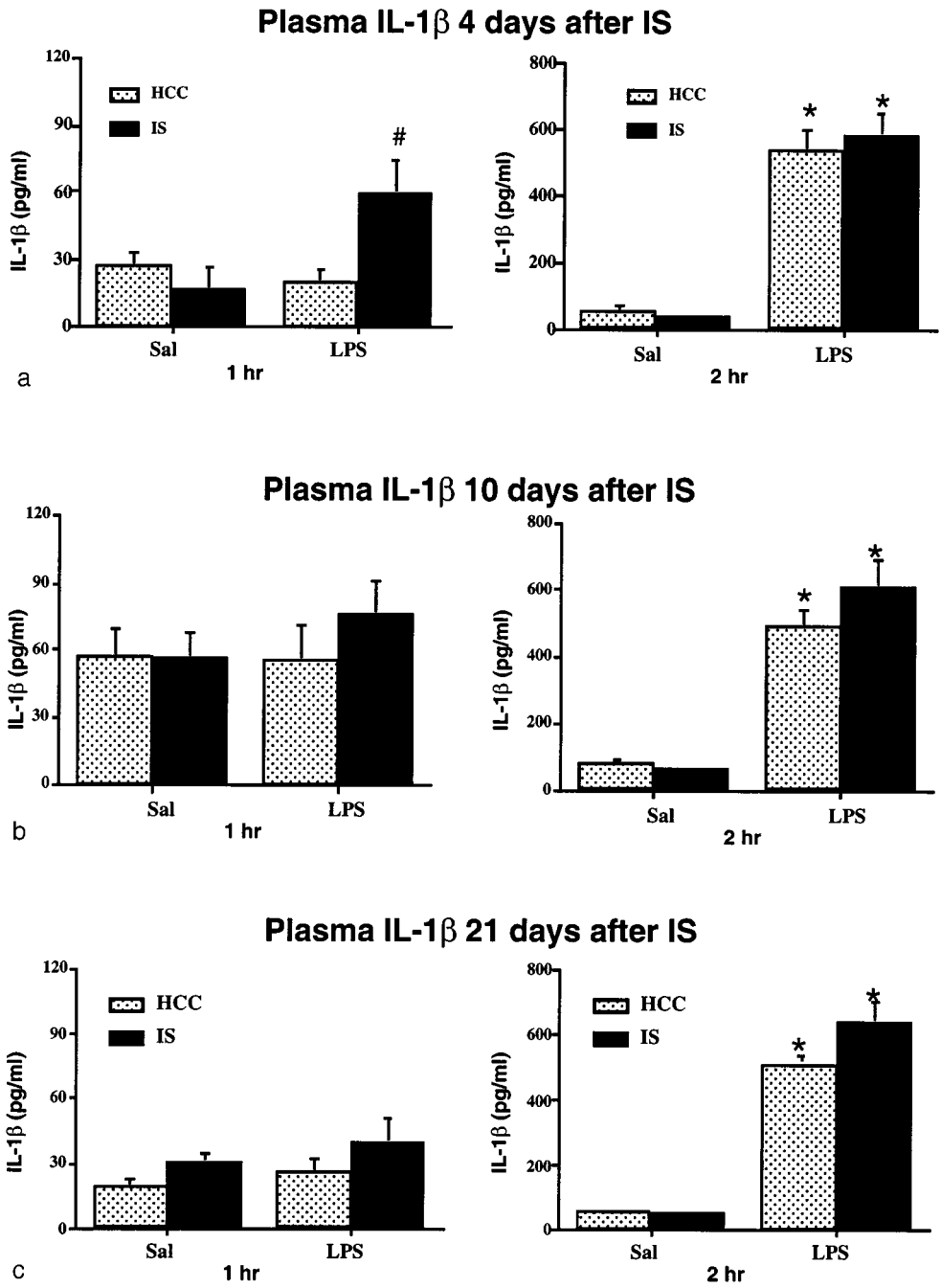

FIG. 4. Plasma IL-1β levels 1 and 2 h after LPS or Sal administration in HCCs or rats exposed to IS 4 days (a), 10 days (b), or 21 days (c) prior. Bars represent means ($n = 6–8$) plus standard errors. *, significant difference ($p < .05$) from saline-injected animals; #, significant difference ($p < .05$) from saline- and HCC LPS-injected animals.

significantly increased plasma IL-1β and TNF-α 1 h after immune stimulation, while showing a tendency in this direction with regard to IL-6. Since in response to LPS IL-1β stimulates the release of IL-6 (LeMay, Otterness, Vander, & Kluger, 1990b; Romero Schettini, Lechan, Dinarello, & Reichlin, 1993; Luheshi et al., 1996), it is the last in the cascade of proinflammatory cytokines to be induced. Thus, a slightly later time point may be needed to observe a significant enhancement in IL-6 levels. All of these cytokines were significantly elevated 2 h after LPS stimulation, but IS did not potentiate the cytokine responses at this time point. This pattern suggests that prior exposure to IS results in a more rapid release of proinflammatory cytokines. While there was no difference in cytokine levels 2 h after LPS administration, more time points would be needed to determine whether IS alters peak cytokine values.

A more rapid production of brain IL-1β was also observed in IS animals. This may reflect the more rapid peripheral immune response, since peripheral IL-1β has been shown to stimulate the production of central IL-1β (Laye et al., 1994; Quan et al., 1994). However, LPS has been shown to bind to brain endothelial cells and stimulate the release of IL-1β and IL-6 (Fabry et al., 1993; Corsini et al., 1996) and so it is possible that the enhanced central cytokine response to LPS is due to IS sensitization of central pathways. In this study IS resulted in a more rapid release of cytokines both peripherally and centrally, but more studies are needed to determine which cell types are sensitized after IS.

Exposure to IS resulted in facilitation of proinflammatory cytokine release as measured by the plasma IL-1β response to LPS for a period of days. LPS administration 4 days after IS resulted in a more rapid increase in plasma IL-1β compared to controls, similar to what was observed when LPS stimulation occurred 24 h after IS. However, the enhanced plasma IL-1β response was no longer present by 10 days after IS. It should also be noted that the 2-h IL-1β levels in the 4-, 10-, and 21-day post-IS studies were approximately three times larger than those in the previous 24-h experiment. Further studies have shown that this is due to the method of blood collection, serial tail vein nicks vs decapitation (unpublished observation).

One potential explanation for the more rapid increase in peripheral and central cytokines after an ip injection of LPS in animals that had received IS could be that the transport of the endotoxin from the peritoneal cavity to the blood stream was more rapid in IS animals. While a complete time course was not conducted to determine exactly when endotoxin levels began to increase in the blood after LPS, no difference was found in endotoxin levels 1 h after LPS between IS and control animals, which is the time point at which the enhancement in cytokine levels was observed. Therefore, it is unlikely that the more rapid induction of proinflammatory cytokines can be explained by a shift in the kinetics of endotoxin transport from the peritoneal cavity in animals exposed to IS.

Previous research has shown that stress enhances certain types of immune cell activity. Persoons, Schornagel, Breve, Berkenbosch, and Kraal (1995) have shown that IL-1β and TNF-α release from LPS-stimulated alveolar macrophages are enhanced immediately following 20 min of electric footshock. *In vivo* blockade of the autonomic nervous system or β-adrenoceptors completely blocked the stress-induced alterations in alveolar macrophage activity, suggesting that the sympathetic nervous system is involved in the stress-induced enhancement of IL-β and TNF-α. Chronic cold water stress has also been shown to enhance TNF-α and IL-6 production from LPS-stimulated peritoneal macrophages collected soon after stress (Chancellor-

Freeland et al., 1995; Zhu et al., 1995). *In vivo* pretreatment with the substance P antagonist RP67,580 blocked the cold water stress-induced increase in IL-6 (Zhu et al., 1995) and pretreatment with capsaicin diminished the stress-induced enhancement of IL-6 and TNF-α (Chancellor-Freeland et al., 1995), suggesting that substance P is involved in the macrophage stress response. These studies suggest that immediately after acute and/or chronic stress the innate immune response is enhanced. The present data support the notion that stress enhances the innate immune response and adds the new findings that these effects occur *in vivo* and are long-lasting, since LPS was administered 24 h to 4 days after exposure to the stressor.

While the mechanism by which IS sensitizes the cytokine response to LPS is unknown, a number of changes are known to occur in IS animals and some of these changes have the potential to alter the innate immune response. For example, exposure to IS has been shown to elevate positive acute phase proteins (Deak et al., 1997), increase core body temperature, and cause a small elevation in basal corticosterone levels (Fleshner et al., 1995). Each of these changes has been shown to enhance innate immune function (Liao, Keiser, Scales, Kunkel, & Kluger, 1995; Hasday, 1996; Wilckens & De Rijk, 1997; Jiang et al., 1999), but it is unclear whether any single or combination of these changes could result in a more rapid release of cytokines as observed in this study.

Stress has been thought to suppress cytokine responses to infection because high levels of glucocorticoids inhibit cytokine production and release (Berkenbosch, Wolvers, & Derijk, 1991; Fantuzzi, Di Santo, Sacco, Benigni, & Ghezzi, 1995). Indeed, the *in vivo* proinflammatory cytokine response to LPS is inhibited if the LPS is administered during or immediately after stress, when glucocorticoid levels are high (Goujon et al., 1995). However, in the present studies, LPS was administered after the large acute endocrine response to the stressor had subsided, and the cytokine response in the periphery and brain was enhanced. It has also been known that stress exacerbates inflammatory diseases (Mei-Tal et al., 1970; Thomason et al., 1992) such as psoriasis, asthma, and arthritis, which are known to result from immune activation. In addition, recent studies have suggested that stress can enhance some functional aspects of immune function for a period of days. Deak et al. (1999) have shown that stress facilitates recovery from subcutaneous bacterial challenge and Dhabhar and McEwen (1996) have shown that stress produces large and long-lasting enhancement of skin delayed-type hypersensitivity responses. These data along with the current finding that stress sensitizes the cytokine response to LPS suggests that at least part of the immune response is enhanced after an organism encounters a stressor, and an enhanced immune response after a stressor (e.g., predator–prey encounter) may be important in preventing or containing infection.

The present data add to the growing literature demonstrating cross-sensitization between stressors and stimuli that activate peripheral immune cells (Tilders & Schmidt, 1999). It has previously been shown that exposure to IL-1β and TNF-α sensitize subsequent endocrine, behavioral, and neurochemical responses to the same cytokine (Schmidt, Janszen, Wouterlood, & Tilders, 1995; Merali, Lacosta, & Anisman, 1997; Hayley, Brebner, Lacosta, Merali, & Anisman, 1999) and to footshock (Tilders & Schmidt, 1998). The present experiments indicate that cross-sensitization also occurs in the reverse direction, namely that exposure to a stressor can sensitize the response to a stimulus that activates cells of the immune system. Moreover, prior work has utilized IL-1β and TNF-α as sensitizing agents, and here it has been shown

that released IL-1β and TNF-α can themselves be sensitized by prior exposure to a stressor.

However, the existing data make it clear that there are multiple and different mechanisms of sensitization. Some of the sensitization effects that have been reported grow slowly following presentation of the sensitizing agent, and are not present until several weeks later (Schmidt et al., 1995). In contrast, other sensitization phenomena develop quickly (Hayley et al., 1999), and the very same event can induce both rapid and delayed sensitization, depending on the response to the event that is measured (Hayley et al., 1999). Rapid and delayed sensitizations have been argued to depend on different mechanisms (Tilders & Schmidt, 1999), and the cross-sensitization between IS and LPS seems to involve the more rapid sensitization.

Cross-sensitization between an initial immune-activating stimulus such as LPS or a cytokine and a subsequent stressor has been argued to be of potential importance for understanding depression (Tilders & Schmidt, 1999) and anxiety (Anisman & Merali, 1999). The experience of stressful life events has been implicated in the etiology of anxiety and affective disorders (Hammen, Davila, Brown, Ellicott, & Gitlin, 1992). Thus, it has been suggested that individuals who have received an immune stimulus might react to a stressor experienced during the cross-sensitization period in an exaggerated manner, thereby exacerbating the anxiogenic and depressogenic impact of the stressor. Interestingly, it has been suggested that the induction of proinflammatory cytokines in the periphery, and therefore in the brain, might also lead to depressed mood (Connor & Leonard, 1998) and anxiety (Connor, Song, Leonard, Merali, & Anisman, 1998). Thus, the cross-sensitization demonstrated here, in which an initial exposure to a stressor exaggerates the peripheral and central cytokine response to a bacterial stimulus, might also have implications for the etiology of anxiety or depression.

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DEPARTMENT OF HEALTH

Irritable Bowel Syndrome (IBS) Issue Brief

INCLUDING IBS AND IBS-D

OCTOBER 2022

Introduction

This briefing was prepared in response to petitions to consider adding irritable bowel syndrome (IBS) and irritable bowel syndrome with diarrhea (IBS-D) as new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used identify any ongoing or completed clinical trials.

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Symptom severity can range from debilitating to mild or moderate. Further, IBS is often associated with additional somatic comorbidities (conditions that affect the body), psychiatric conditions, and visceral sensitivity (Enck et al., 2016).

IBS is thought to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the gut. The associated problem between the brain and the gut leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both (Ford et al., 2020).

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes, IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools is loose, or watery and more than a quarter of a patient's stools are hard and lumpy (Chey et al., 2015).

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis is irritable bowel disease (IBD). Unlike IBS, which is characterized by a gut-brain disorder, IBD, which encompasses Crohn's disease (CD) and Ulcerative colitis (UC), is characterized by chronic relapsing inflammation and immune activity (Abdul Rani et al., 2016). However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological comorbidities, specifically depression and anxiety (Abdul Rani et al., 2016). Further, studies have found that depression can increase a patient's probability for developing increased inflammation (Fagundes et al., 2013, Johnson et al., 2002). Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development (Abdul Rani et al., 2013). However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent (Abdul et al., 2016). Finally, both IBD and IBS patients experience abnormal gut microbiota (Abdul et al., 2016). However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease (Abdul et al., 2016). Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks. Ultimately, more large-scale research is needed to define a clear connection.

Epidemiology

IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years (Chey et al., 2015). Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion (Chey et al., 2015). Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms (Chey et al., 2015).

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity (Chey et al., 2015).

Diagnosis

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or inflammatory bowel disease. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale (Chey et al., 2015).

Diagnostic Criteria for Irritable Bowel Syndrome (IBS) With Subtypes includes:

Recurrent abdominal pain or discomfort at least three days a month associated with two or more of the following: reduced abdominal pain with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (Chey et al., 2015).

IBS with constipation (IBS-C) is defined as hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements. IBS with diarrhea (IBS-D) is defined as loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements. Mixed IBS (IBS-M) is defined as hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements (Chey et al., 2015).

While diagnosis of IBS-D or IBS-C is relatively straightforward, the diagnosis of patients with IBS-M presents a unique challenge. Therefore, a detailed history of a patients mixed bowel patterns is required to better understand the underlying disease state (Chey et al., 2015). Further, the consideration of all prescription and over-the-counter medications is needed to determine how they might affect IBS symptoms (Chey et al., 2015).

In addition to the identification of symptom-based criteria, a detailed assessment to eliminate the potential for alternative disease is required to finalize the diagnosis. A patient with clear IBS symptoms combined with an absence of diagnostic markers indicative of other gastrointestinal related disorders, can be diagnosed as having IBS with some level of accuracy (Chey et al., 2015).

Current Therapies

Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates) (Chey et al., 2015). A meta-analysis of the low-FODMAP diet found

that the diet was effective at improving patient well-being and reducing symptoms (van Lanen et al., 2021). However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP (van Lanen et al., 2021). Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established (van Lanen et al., 2021).

Medications

A doctor may recommend medication to relive IBS symptoms dependent on the type of IBS a patient is suffering from.

Antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume (Chey et al., 2015). However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit of loperamide compared to the placebo group for the overall reduction of IBS symptoms (Chey et al., 2015). Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic (Chey et al., 2015).

Serotonin agents such as Alosetron, a 5-HT_3 antagonist has been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies (Chey et al., 2015). Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo.

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools (Chey et al., 2015). Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms (Chey et al., 2015). Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it has not been shown to improve abdominal pain or bloating (Chey et al., 2015). Stimulant laxatives have also been used as a therapy for IBS-C patients, but there have been few randomized controlled trials evaluating its efficacy (Chey et al., 2015).

Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel, and abdominal symptoms in IBS-C patients (Chey et al., 2015). Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls (Chey et al., 2015).

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity

compared to placebo controls (Chey et al., 2015). Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea (Lacy et al., 2009). As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximize effects are felt (Chey et al., 2015).

The use of probiotics and antibiotics has been explored as a treatment for IBS (Chey et al., 2015). Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence (Ford et al., 2014). However, there was some variability in the probiotics used and grouping methods employed that limited comparability (Ford et al., 2014). As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation regarding the use of specific probiotic preparations for IBS (Chey et al., 2015). Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients (Menee et al., 2012). However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms (Chey et al., 2015). Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern (Chey et al., 2015).

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain (Dekel et al., 2013). However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS (Chey et al., 2015). Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms (Ford et al., 2014). However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS (Hussain et al., 2006). However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture (Manheimer et al., 2012). Studies evaluating herbal remedies have yielded mixed results. There is a lack of an understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary interventions, medication, and behavioral strategies to maximize treatment of IBS (Chey et al., 2015).

Pre-clinical Research

Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the CB1 receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system (Hill et al., 2017, Brugnatelli et al., 2020). Pre-clinical studies have shown a direct connection

between the endocannabinoid system and regulation of gastrointestinal motility (Storr et al., 2008). In fact, activation of the cannabinoid 1 (CB1) and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility (Hasenoehrl et al., 2016). Additionally, research by Vianna et al., 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility. Despite the promising pathophysiologic mechanism, studies examining the impact of an endocannabinoid deficiency on IBS are limited.

Clinical Trials

A clinical trial by Wong et al. in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS (Wong et al., 2011). In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, Wong et al. attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial conducted by Wong et al. in 2012 failed to reproduce the findings seen in 2011 (Wong et al. 2012). In addition, a study by Klooker at al., 2011, showed that the cannabinoid receptor agonist delta-9-tetrahydrocannabinols (THC) had no effect on rectal distension or rectal sensitivity in healthy volunteers and IBS patients. Moreover, a placebo-controlled crossover study (a study where patients receive both the treatment and the placebo at different times during a study) reported no significant difference in IBS patient pain scores between CBD and placebo treatments. However, this study was small scale and only recruited women for the study (Anne-Claire B. et al., 2021). Finally, a small clinical trial investigating the impact of cannabidiol therapy on IBS patients found at the group level there was no difference in the pain score of those who received the cannabidiol therapy compared to those who did not receive the cannabidiol therapy (van Orten-Luiten et al., 2021). Overall, while some studies, such as the 2011, Wong et al. have shown the promising potential for dronabinol, several more recent studies have failed to reproduce these findings. Thus, more large-scale clinical trials are needed.

Ongoing Clinical Trials

A search for current ongoing clinical trials was conducted on clinicaltrials.gov. Search terms specific to cannabis and IBS were used to identify clinical trials. Search terms for IBS included Irritable Bowel Syndrome, IBS, IBS-D, IBS-C, and IBS-M. Search terms for Cannabis included cannabis, THC, marijuana, and dronabinol. Currently there are no ongoing clinical trials investigating the potential role of cannabis as a treatment for IBS.

Observational Studies

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS (Choi et al., 2022). The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis (Choi et al., 2022). When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users (Choi et al., 2022). However, Choi et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission (Choi et al. 2022). Therefore, the authors found that cannabis use had no impact on IBS-specific 30-day hospital readmission rates but did reduce total hospitalization cost and charges.

Adejumo et al. conducted a national survey, using the international classification of disease, 9th edition codes to identify individuals with Cannabis Use Disorder (CUD) and IBS. They found that patients with CUD were significantly more likely to have IBS compared to patients without CUD (Adejumo et al. 2019). These finding suggest that the abnormal use of cannabis may either contribute to the development or exacerbation of IBS and its symptoms. Adding to this, a study of 31,272 patients by Patel et al., 2020, found that patients with CUD had a higher odd for IBS hospitalization compared to patients without Cannabis Use Disorder (Patel et al. 2020). This suggests the use of cannabis among those with CUD may be associated with the development of IBS or exacerbation of IBS symptoms. Therefore, while there is a potential benefit associated with the use of cannabis, the improper use of cannabis poses some risk to the development and aggravation of IBS.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers), reported that cannabis use may decrease inpatient health-care utilization in IBS patients. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users (Desai et al., 2020). Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users (Desai et al., 2020, Choi et al., 2022). In contrast, a study by Adeyinka et al., 2019, reported a higher likelihood of hospitalization among people who use cannabis conflicting with prior reports of a shortened stay. This paper also noted that an elevated state of anxiety might countermand the effects of cannabis on the endocannabinoid system (Adeyika et al., 2019). In conclusion, while cannabis as a therapy for IBS shows promise, the data remains inconclusive and more large-scale clinical trial research is needed.

In contrast to IBS, IBD research suggests that the use of small doses of cannabis can help reduce inflammation and reduces the overall IBD symptomology (McCallum et al., 2014, Perisetti et al., 2020). However, consumption of cannabis at high levels can exacerbate IBD symptoms and increase a patient's likelihood to be hospitalized due to severe IBD (UC and CD) (McCallum et al., 2014, Perisetti et al., 2020). Therefore, extreme cause should be taken when using cannabis as a therapy for IBD.

National Medical Organization Recommendations

In 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

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Depressive Symptoms Enhance Stress-induced Inflammatory Responses

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Abstract

Depression is a risk factor for morbidity and mortality, and immune dysregulation may be partially responsible for this link. Proinflammatory cytokines such as interleukin 6 (IL-6) are reliable predictors of quality of life, morbidity, and many causes of mortality. The current study evaluated relationships between depressive symptoms, as assessed by the CES-D, and stress-induced inflammation. The participants, 138 healthy adults, were evaluated at rest, and after a standardized laboratory speech and mental arithmetic stressor. Compared with individuals with fewer depressive symptoms, those with more depressive symptoms produced more IL-6 in response to the stressor, as well as significantly higher levels of IL-6 both 45 minutes and 2 hours after the stressor. These findings add to our emerging understanding of the complex interactions among stress, depression, and immune dysregulation, and provide one potential pathway to explain relationships between depressive symptoms and disease.

1. Introduction

Depression is a risk factor for morbidity and mortality (Rovner et al., 1991; Wulsin, Vaillant, & Wells, 1999). Both major depression and subthreshold depressive symptoms have been linked to many diseases of older adulthood (Bush et al., 2001; Frasure-Smith et al., 2009; Pan et al., 2011; Satin, Linden, & Phillips, 2009; Wouts et al., 2008). Immune dysregulation may partially contribute to these links. Inflammation is a key immunological mechanism that promotes many age-related diseases including diabetes, certain cancers, cardiovascular disorders, frailty and mortality (Maggio, Guralnik, Longo, & Ferrucci, 2006).

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All authors declare that there are no conflicts of interest.

In this study, we examined how depressive symptoms interact with acute stress to induce proinflammatory cytokine production.

Acute stress produces transient increases in systemic inflammation. Stress-induced elevations in inflammation have been detected among medical students preparing for an academic exam, individuals giving an oral presentation, and couples engaging in a marital disagreement (Heinz et al., 2003; Kiecolt-Glaser et al., 2005; Maes et al., 1998). Standardized experimental performance tasks, such as the Trier Social Stress Test (TSST), promote reliable elevations in interleukin-6 (IL-6) (Carpenter et al., 2010; Pace et al., 2006; Steptoe, Hamer, & Chida, 2007). These stress-induced inflammatory responses may vary in magnitude between individuals.

Prior stress and depression may enhance stress-induced inflammatory rises by sensitizing the inflammatory response to stress (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003). For example, rats that were previously exposed to inescapable tailshock produced larger inflammatory responses to bacterial endotoxin than controls that were not shocked (Johnson et al., 2002). Studies in humans provide preliminary evidence that depression may promote greater stress-induced increases in circulating IL-6. In a study comparing 14 males with a history of early life stress and major depression with 14 controls, major depression patients with early life stress produced a more pronounced plasma IL-6 response to the TSST than controls (Pace et al., 2006). In another study 16 women with a lifetime history of depression showed greater IL-6 increases after giving birth than 50 women without a history of depression (Maes, Ombelet, De Jongh, Kenis, & Bosmans, 2001). These findings provide initial evidence that major depression may enhance systemic inflammation. However, sample size was limited in both studies, and we do not know if these findings extend to those with depressive symptoms more generally.

Minor elevations in depressive symptoms are associated with higher baseline levels of proinflammatory cytokine production (Lutgendorf et al., 1999). Furthermore, in a community sample of older adults, those with more depressive symptoms had a greater IL-6 increase after an annual influenza vaccination compared to those with fewer symptoms, suggesting that even modest elevations in depressive symptoms may sensitize the inflammatory response (Glaser et al., 2003). The current study sought to extend work demonstrating that those with major depression have more pronounced IL-6 elevations in response to a stressor by examining whether stress-induced IL-6 responses are exaggerated among individuals with more depressive symptoms compared with fewer depressive symptoms.

2. Methods

2.1 Subjects

The study data were drawn from the baseline sample of a clinical trial addressing the potential benefits of fish oil. Participants were recruited through advertisements, brochures, and media announcements in the local community. Screening exclusions included a prior history of cancer (except basal or squamous cell), diabetes, chronic obstructive pulmonary disease, autoimmune disease, evidence of liver or kidney failure, symptomatic ischemic heart disease, GERD, ulcerative colitis, smoking status, excessively high triglycerides or LDL cholesterol, more than 3 hours a week of vigorous physical exercise, and a body mass index (BMI) above 40. Individuals could not participate if they were taking medications for depression, anxiety, cholesterol, or blood pressure. The Ohio State Biomedical Research Review Committee approved the project; all subjects gave written informed consent prior to participation.

2.2. Procedure

When participants arrived at the Clinical Research Center (a hospital research unit) at 7:45 a.m., a catheter was inserted in their arm. Once they had eaten a standardized breakfast (after fasting since midnight) and completed questionnaires (approximately 25 minutes after catheter insertion), they sat quietly in a chair for 20 minutes. At the end this relaxation period, blood was drawn to assess baseline IL-6 levels.

Next, subjects participated in the Trier Social Stress Test, a well validated stressor (Kirschbaum, Pirke, & Hellhammer, 1993). Participants were told they would deliver a speech in front of a committee of behavioral experts, and were briefly brought into the room to view the committee before they prepared the speech. Then, in another room, they spent 10 minutes preparing a speech about why they were the best candidate for a job. After that, a research assistant escorted them to a room where they saw a microphone, video camera, and an audience panel of 2 individuals wearing white laboratory coats. While seated, participants gave their 5-minute speech and then performed mental arithmetic serial subtraction tasks for 5 minutes in front of this panel. Then, 45 minutes post-stressor, another blood sample was drawn, followed by another blood draw 2 hours after the stressor.

2.3 Measures

The Center for Epidemiological Studies Depression Scale (CES-D) was used as a measure of depressive symptoms. It has been used extensively as a brief measure of depressive symptomatology (Basco, Krebaum, & Rush, 1997; Radloff, 1977). Studies have shown acceptable test-retest reliability and excellent construct validity (Basco et al., 1997).

We assessed major depression with the Structured Clinical Interview for DSM-IV, nonpatient version (SCID-NP) (First, Spitzer, & Williams, 1995) Inter-rater reliability for SCID-NP diagnoses were calculated using randomly selected audiotapes for 20% of the participants. This substantial interrater agreement was confirmed with McNemar's test for marginal proportions ($p>0.99$ for all diagnoses).

The Childhood Trauma Questionnaire provided data on early childhood abuse and neglect. Widely used, it has excellent normative data for its 5 scales: Physical, Sexual, and Emotional Abuse, and Physical and Emotional Neglect (Bernstein & Fink, 1998). We adopted the Walker cuts (Walker et al., 1999) to make categorical cut-offs (with sensitivity and specificity >.85 for each scale). Then, we created a categorical indicator variable representing any maltreatment (exceeding ≥ CTQ cut point threshold)(Walker et al., 1999).

We used the **Beck Anxiety Inventory** to assess both cognitive and physiological symptoms (Beck, Epstein, Brown, & Steer, 1988). This scale has been shown to have sound psychometric properties such as factorial validity, internal consistency, and test-retest stability.

Whole blood was drawn into a BD vacutainer serum tube (Becton-Dickinson, New Jersey) and allowed to clot at room temperature for 30 minutes. Serum tubes were then centrifuged for 10 minutes at 2700rpm. Serum was stored at -86OC until assayed in duplicate levels for IL-6 cytokine using MSD 96-well Multispot Custom Cytokine Kits (Meso Scale Discovery, Maryland) . Plates were read using an MSD Sector Imager 2400. A four parameter logistic fit standard curve was derived using the MSD Software and IL-6 concentrations were extrapolated from the standard curve. The IL-6 sensitivity was 0.26 pg/ml. The CV for intra-assay precision had a range of 5.64-6.70%. The CV for inter-assay precision had a range of 5.16-10.2%.

2.4 Analytic Method

All analyses were run using mixed models regression and restricted maximum likelihood estimation. IL-6 was log transformed before analysis. We adjusted for key potential confounds including age, BMI, and sex. We examined residuals from all analyses to confirm that they were distributed normally.

We hypothesized that individuals who had more depressive symptoms would have greater increased IL-6 in response to the stressor than those with fewer depressive symptoms. We ran a repeated measures analysis with depressive symptoms modeled as a continuous variable to test this hypothesis. There was considerable variability in correlations over the three segments. Hence, we employed an unstructured within-subjects covariance matrix for all repeated measures analyses. The Kenward-Roger option was used to correct the degrees of freedom in the model, which brought Type I errors rates back to the nominal level. All tests used a two-sided, α=0.05 significance level.

3. Results

Table 1 reports descriptive information for the participants. Table 2 summarizes the results of the repeated measures analysis that assessed whether changes in IL-6 over time differed depending on depressive symptoms.

Overall, IL-6 increased in response to the Trier Social Stress Test. There was a significant interaction between depressive symptoms and time. Compared to those with fewer depressive symptoms, individuals with more depressive symptoms had a greater IL-6 response to the Trier Social Stress Test. Specifically, individuals with more depressive symptoms displayed greater increases in IL-6 from baseline to 45 minutes post-stressor and baseline to 2 hours post-stressor (Figure 1). Depressive symptoms were unrelated to baseline levels of IL-6. However, those who had more depressive symptoms had significantly higher IL-6 levels both 45 minutes post-stressor and 2 hours post-stressor than those with fewer depressive symptoms. We ran an additional analysis controlling for baseline levels of IL-6, and all significance levels remained the same. In sum, those who had more depressive symptoms had greater IL-6 increases in response to the stressor and higher levels of IL-6 after the stressor than those with fewer depressive symptoms.

In ancillary analyses, we adjusted for a history of maltreatment, menopausal status, and anxiety levels. None of these variables were associated with changes in IL-6, and the significance levels of all results remained the same. When we dichotomized BMI at 30, it was not significantly associated with changes in IL-6. Furthermore, it did not interact with depressive symptoms.

4. Discussion

Individuals with more depressive symptoms had larger stress-induced increases in IL-6 to a standardized laboratory speech and mental arithmetic stressor. They also had significantly higher levels of IL-6 after the stressor than those with fewer depressive symptoms. With a considerably larger sample, this study extends work linking major depression to greater stress-induced increases in IL-6 by demonstrating that those who have more depressive symptoms show an exaggerated IL-6 response to a laboratory stressor.

Depression has been linked to premature mortality among those with cancer, heart disease, stroke, and diabetes (Bush et al., 2001; Frasure-Smith et al., 2009; Pan et al., 2011; Satin et al., 2009; Wouts et al., 2008). Elevated inflammation is a risk factor for these diseases (De Martinis, Franceschi, Monti, & Ginaldi, 2006; Maggio et al., 2006). Accordingly, these

findings may provide one potential pathway to explain relationships between depressive symptoms and morbidity and premature morality.

Proinflammatory cytokines can act on the brain to induce sickness behaviors (Ahles et al., 2002; Bower, Ganz, Aziz, & Fahey, 2002; Luecken, Kraft, Appelhans, & Enders, 2009; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Although there is ample evidence that depressive symptoms can elevate inflammation, there is also considerable evidence that inflammation contributes to depressive symptoms (Miller, Maletic, & Raison, 2009; Raison, Capuron, & Miller, 2006). The association between inflammation and depressive symptoms has been found in a variety of different populations (Alesci et al., 2005; Bouhuys, Flentge, Oldehinkel, & van den Berg, 2004; Miller, Stetler, Carney, Freedland, & Banks, 2002; Musselman et al., 2001). Minor elevations in depressive symptoms may be a catalyst for stress-induced inflammatory rises that subsequently promote more depressive symptoms through a feedback loop.

Mechanistically, both autonomic and neuroendocrine function may promote stress-induced inflammation. Norepinephrine enhances proinflammatory cytokines by inducing nuclear factor B (NF- B) transcription, an intracellular signaling molecule that regulates proinflammatory cytokine gene expression (Bierhaus et al., 2003; Straub & Härle, 2005). Furthermore, higher levels of parasympathetic activity can reduce inflammation via the cholinergic anti-inflammatory pathway that induces acetylcholine release (Tracey, 2009).

Our sample consisted of healthy adults. Accordingly, we do not know if these findings could be detected among those with chronic diseases. Furthermore, our sample was predominately college educated and white. Future studies that are more diverse are needed in order to ensure our findings generalize across different ethnic and socioeconomic groups. Finally, the type of stressor we used may have influenced the results. The stressor we imposed evokes negative self-evaluation (Kirschbaum et al., 1993), which may be particularly stressful for those with more depressive symptoms (Giesler, Josephs, & Swann Jr, 1996). In future work, it would be interesting to see if other types of acute stressors elicit similar inflammatory responses.

In sum, those with more depressive symptoms exhibited enhanced inflammation to a stressor compared with those with fewer depressive symptoms. Accordingly, depressive symptoms may enhance the stress response system in ways that promote excessive inflammation. These findings add to our emerging understanding of the complex interactions among stress, depression, and immune dysregulation.

Acknowledgments

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Highlights

Compared with individuals with fewer depressive symptoms, those with more depressive symptoms produced more IL-6 in response to a laboratory stressor, as well as significantly higher levels of IL-6 both 45 minutes and 2 hours after the stressor.

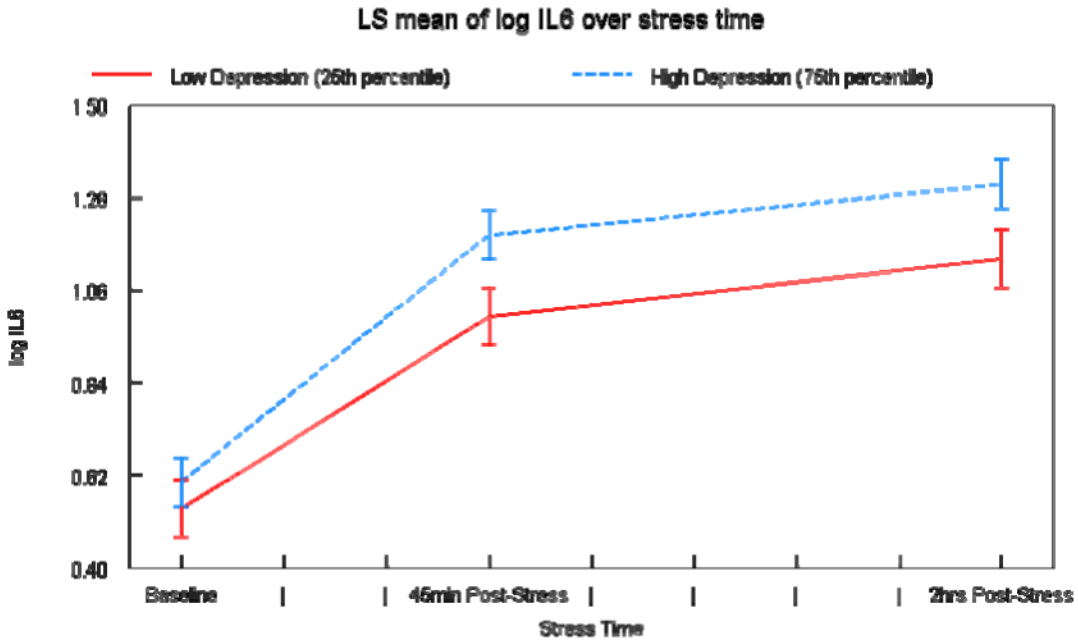

Figure 1.
Mean (± SEM) IL-6 across experimental periods in people with more and fewer depressive symptoms based on the 75th and 25th percentile scores on the CES-D. The 25% represents a score of "2" on the CES-D and the 75% represents a score of "10." These are both well below the clinical threshold for depression, which is "16."

Table 1

Sample Population Characteristics

	Total (N=138)		
Variable	***n***	***M***	***SD***
IL6		3.79	3.84
Log IL6		1.01	0.81
Age (yrs)		51.04	7.75
BMI (kg/m^2)		30.59	4.50
CESD		7.58	8.10
Current depression			
No	119		
Yes	4		
Race			
White	109		
Black	22		
Asian	4		
Native American	2		
Other	1		
Sex			
Female	93		
Male	45		
Menopause			
No	56		
Yes	45		
NA	37		
Marital Status			
Single	19		
Married	92		
Common Law	3		
Separated	3		
Divorced	16		
Widowed	5		
Education			
Some high school	7		
Some college	32		
College graduate	52		
Graduate/Professional	47		
Income			
< 25 K	11		
25 K- 50 K	34		
50 K- 75 K	35		
75 K- 100 K	26		

	Total (N=138)		
Variable	***n***	***M***	***SD***
> 100 K	24		
Prefer not to answer	8		

Table 2
Interleukin 6 across time based on CES-D scores

Effect	Time point	Log IL6	
		Estimate	p
CESD total score		0.008	0.240
Period	Baseline		
	Post stress 45 minutes	0.424	<0.001
	Post stress 2 hours	0.565	<0.001
CESD × Period	Baseline		
	Post stress 45 minutes	0.017	0.016
	Post stress 2 hours	0.014	0.035
Change per unit depression	Baseline	0.008	0.240
	Post stress 45 minutes	0.024	0.001
	Post stress 2 hours	0.022	0.002
Slope change per unit depression	Baseline to 45 minutes	0.017	0.016
across time points	Baseline to 2 hours	0.014	0.035
	45 minutes to 2 hours	−0.002	0.757

2. Relevant Medical or scientific evidence pertaining to the disease or condition

Content for this section was borrowed heavily from the Minnesota Department of Health's Issue Brief on Irritable Bowel Syndrome, which was published in October 2022 in support of its decision to add Irritable Bowel Syndrome to the state's list of Qualifying Conditions for Medical Marijuana. For more information, we encourage you to contact the Minnesota Department of Health's Office of Medical Cannabis at:

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IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years.[1] Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion.[2] Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms.[3]

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity.[4]

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or IBD. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale.[5]

[1] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954
[2] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954
[3] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954
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[5] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

Irritable Bowel Syndrome: a clinical review

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Review

Irritable Bowel Syndrome
A Clinical Review

William D. Chey, MD; Jacob Kurlander, MD; Shanti Eswaran, MD

IMPORTANCE Irritable bowel syndrome (IBS) affects 7% to 21% of the general population. It is a chronic condition that can substantially reduce quality of life and work productivity.

OBJECTIVES To summarize the existing evidence on epidemiology, pathophysiology, and diagnosis of IBS and to provide practical treatment recommendations for generalists and specialists according to the best available evidence.

EVIDENCE REVIEW A search of Ovid (MEDLINE) and Cochrane Database of Systematic Reviews was performed for literature from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*.

FINDINGS The database search yielded 1303 articles, of which 139 were selected for inclusion. IBS is not a single disease but rather a symptom cluster resulting from diverse pathologies. Factors important to the development of IBS include alterations in the gut microbiome, intestinal permeability, gut immune function, motility, visceral sensation, brain-gut interactions, and psychosocial status. The diagnosis of IBS relies on symptom-based criteria, exclusion of concerning features (symptom onset after age 50 years, unexplained weight loss, family history of selected organic gastrointestinal diseases, evidence of gastrointestinal blood loss, and unexplained iron-deficiency anemia), and the performance of selected tests (complete blood cell count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate colorectal cancer screening) to exclude organic diseases that can mimic IBS. Determining the predominant symptom (IBS with diarrhea, IBS with constipation, or mixed IBS) plays an important role in selection of diagnostic tests and treatments. Various dietary, lifestyle, medical, and behavioral interventions have proven effective in randomized clinical trials.

CONCLUSIONS AND RELEVANCE The diagnosis of IBS relies on the identification of characteristic symptoms and the exclusion of other organic diseases. Management of patients with IBS is optimized by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral interventions.

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CME Quiz at jamanetworkcme.com and **CME Questions** page 965

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal condition. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits, in the absence of any other disease to cause these sorts of symptoms. Pooled population-based prevalence estimates of IBS vary globally, in part related to differences in study populations, diagnostic criteria, and study methodology. In North America, the population prevalence of IBS is approximately 12%.[1] IBS is most prevalent in South America (21.0%) and least prevalent in Southeast Asia (7.0%).[1] In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent among women than men, whereas there appears to be greater parity in Asia.[2] Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea.[2] It appears that IBS prevalence decreases with age. In the United States, patients are equally distributed among IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), whereas in Europe, IBS-C or IBS-M may be more prevalent.[3]

This clinical review covers the epidemiology, natural history, pathophysiology, diagnosis, and management of IBS.

Methods

Evidence to support this clinical review was obtained from searches performed by a medical librarian of MEDLINE and the Cochrane Database of Systematic Reviews from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*. This search strategy yielded 1303 articles after limiting to the English language. We selected 139 articles for inclusion. When available, systematic reviews and meta-analyses were used to summarize the available evidence.

FODMAP *fermentable oligosaccharides, disaccharides, monosaccharides, and polyols*

IBS *irritable bowel syndrome*

IBS-C *IBS with constipation*

IBS-D *IBS with diarrhea*

IBS-M *IBS with a mixed bowel pattern*

Burden of Illness and Natural History

Multiple comorbidities are associated with IBS, including somatic pain syndromes (fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain),[4] other gastrointestinal disorders (gastroesophageal reflux disease[5] and dyspepsia[6]), and psychiatric disorders (major depression, anxiety, and somatization),[7] raising the possibility of shared pathogenesis.

In most patients, IBS is a chronic relapsing disease in which symptoms may vary over time. A systematic review showed that during long-term follow-up of clinic-based IBS patients, 2% to 18% worsened, 30% to 50% remained unchanged, and 12% to 38% improved.[8] Previous surgery, longer duration of disease, higher somatic scores, and comorbid anxiety and depression all predicted worse outcomes. After a negative diagnostic evaluation result, a patient receiving a diagnosis of IBS has a less than 5% risk of receiving an alternative organic diagnosis in the future.[8]

Over time, patients may migrate between different IBS subtypes,[9] most commonly from IBS-C or IBS-D to IBS-M; switching between IBS-C and IBS-D occurs less commonly.[10] Many of the "natural history" studies in IBS are affected by treatments introduced by the patient or clinician. Thus, it is difficult to know how much symptom variation is the consequence of medical intervention vs the true natural history of IBS.

IBS significantly reduces health-related quality of life and work productivity.[11] Among patients with IBS, 13% to 88% seek care. Individuals who seek care have more distress and less social support than those who do not.[12] In the United States, IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually, with total direct and indirect expenditures exceeding $20 billion.[13,14]

Pathophysiology

The pathogenesis of IBS, like the clinical phenotype, is heterogeneous (**Box 1**). IBS likely encompasses a number of diseases with distinct pathophysiology that present with similar symptoms. During the past 40 years, a number of factors that contribute to the pathophysiology of IBS have emerged. Traditionally, the pathogenesis of IBS has focused on abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress. Although one or more of these abnormalities are demonstrable in the majority of IBS patients, none can account for symptoms in all of them. More recently, altered gut immune activation, intestinal permeability, and intestinal and colonic microbiome have been identified in some IBS patients.[15,16]

Box 1. Pathophysiology of Irritable Bowel Syndrome (IBS)

Environmental Contributors to IBS Symptoms

Early life stressors (abuse, psychosocial stressors)

Food intolerance

Antibiotics

Enteric infection

Host Factors Contributing to IBS Symptoms

Altered pain perception

Altered brain-gut interaction

Dysbiosis

Increased intestinal permeability

Increased gut mucosal immune activation

Visceral hypersensitivity

Supporting a role for these factors is the increased prevalence of IBS symptoms in inflammatory conditions such as celiac disease[17] and inflammatory bowel diseases[18] and following severe acute gastroenteritis.[19] The intestinal mucosa of some IBS patients shows increased activation of the innate and adaptive immune systems.[20,21] Increased small bowel and colonic permeability has also been observed in patients with IBS-D[22] and is associated with visceral hypersensitivity.[23] The fecal microbiota of IBS patients differ significantly from that of controls, likely reflecting the influence of genetics, diet, stress, infection, and drugs or antibiotics.[24]

IBS symptoms that arise after acute gastroenteritis or so-called postinfectious IBS present an interesting developmental model. Host factors such as genetics, immune function, microbiome, and psychological status, as well as environmental factors such as stress, severity of infection, or treatment with antibiotics, could predispose to the development of chronic IBS symptoms.[25] It is important to identify patients with postinfectious IBS because, unlike typical IBS, which tends to be a chronic relapsing condition, it spontaneously resolves in roughly half of patients within 6 to 8 years of the index infection.[25]

Many patients identify food as a trigger for their IBS symptoms. Various reviews of how specific dietary constituents can cause gastrointestinal symptoms are available.[26-29] The contribution of true food allergies to IBS is small.[30] Conversely, food intolerances are common in IBS patients. Increasingly, rapidly fermentable, osmotically active, short-chain carbohydrates (including fructose, lactose, fructans and galactans, and sugar alcohols) have been recognized as an important trigger of IBS symptoms. Poorly absorbed carbohydrates can exert osmotic effects and lead to increased fermentation in the small bowel or colon, which can exacerbate symptoms

Box 2. Features of Irritable Bowel Syndrome

Typical Features

Loose/frequent stools

Constipation

Bloating

Abdominal cramping, discomfort, or pain

Symptom brought on by food intake/specific food sensitivities

Symptoms dynamic over time (change in pain location, change in stool pattern)

Concerning Features for Organic Disease

Symptom onset after age 50 y

Severe or progressively worsening symptoms

Unexplained weight loss

Nocturnal diarrhea

Family history of organic gastroenterological diseases, including colon cancer, celiac disease, or inflammatory bowel disease

Rectal bleeding or melena

Unexplained iron-deficiency anemia

Box 3. Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes[a]

Recurrent abdominal pain or discomfort[b] at least 3 d/mo in the last 3 mo associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Subtyping IBS by Predominant Stool Pattern

1. IBS with constipation—hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements
2. IBS with diarrhea—loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Mixed IBS—hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

[a] Criterion fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.

[b] "Discomfort" means an uncomfortable sensation not described as pain.

in IBS patients who have underlying abnormalities in gut function and sensation.[29] On the other hand, healthy individuals with normal gut function and sensation rarely experience symptoms after a meal.

Psychosocial factors may also predispose to the development of IBS. Women with IBS are more likely to have experienced verbal, sexual, or physical abuse, which can contribute to the development of the disease through brain-gut and mucosal immune dysfunction.[31] For some IBS patients, recurrent abdominal pain may begin in childhood and reflect learned-illness behaviors.[32] These experiences may lead to persistent changes in the brain-gut axis, resulting in the perception of otherwise unconscious interoceptive input from the gastrointestinal tract.[33] A subset of IBS patients have hypersensitivity to rectal balloon distention and increased activation of brain regions associated with emotional arousal and endogenous pain modulation.[34] In another subset of IBS patients, hypervigilance and catastrophizing are important features that lead to gastrointestinal and nongastrointestinal symptom amplification.[35]

Diagnosis

The diagnosis of IBS is based on the presence of characteristic symptoms and the exclusion of selected organic diseases (**Box 2**). The cardinal features of IBS according to the current diagnostic standard, the Rome III criteria, include abdominal pain or discomfort and altered bowel habits (**Box 3**). IBS patients can experience constipation, diarrhea, or both. Identification of a patient's predominant bowel complaint plays an important role in both the selection of diagnostic testing and treatment. The Rome III criteria emphasize the importance of stool consistency to distinguish between the 3 subtypes of IBS (Box 3)[36] because it correlates with patients' complaints of constipation or diarrhea and colonic transit better than stool frequency.[37] It can be assessed with the Bristol Stool Form Scale, a validated instrument that allows reporting of stool appearance from a score of 1 (hard and lumpy stool) to 7 (entirely liquid).[38] Bloating (subjective sensation of abdominal fullness) and distention (objective increase in abdominal girth) are also common and bothersome complaints reported by more than 80% of IBS patients.[39] However, many individuals without IBS also report these complaints.[40]

Although identifying patients with IBS-D or IBS-C is straightforward, patients with IBS-M present unique challenges. A detailed history can help determine whether a mixed bowel pattern represents the underlying disease state or is the consequence of medical intervention. It is important to consider all prescription and over-the-counter medications and supplements that could affect IBS symptoms (**Box 4**). A stool diary can help identify patterns among the chaotic bowel habits that many IBS patients report. Many IBS-M patients report periods without a bowel movement or with only small, hard stools, followed by periods of multiple stools of variable consistency that they interpret as "diarrhea." Most of these patients actually have IBS-C, with periods of progressive stool accumulation culminating in bowel purging. A radiograph demonstrating fecal loading can help confirm this clinical suspicion.

Along with an assessment of symptom-based criteria, one should be conducted for the presence of concerning features that identify patients who should undergo a more detailed evaluation to exclude organic disease[41] (Box 2, **Box 5**). Although the presence of concerning features may identify patients more likely to have an organic disease, most patients will ultimately have a negative evaluation result. Thus, the value of concerning features lies in their negative, rather than their positive, predictive value. Evidence suggests that a diagnosis of IBS can be confidently made for patients who fulfill symptom-based criteria and have no concerning features because the yield of extensive diagnostic testing is low.[42] Nonetheless, most health care professionals view IBS as a diagnosis of exclusion[43] and are uncomfortable relying solely on symptoms to diagnose it.

There are several diseases that should be considered in patients with IBS symptoms. A meta-analysis of 5 studies found a 4-fold

Box 4. Commonly Used Treatments That Can Exacerbate Irritable Bowel Syndrome Symptoms

Over-the-Counter
Antihistamines
Calcium
Iron
Magnesium
Nonsteroidal anti-inflammatory drugs
Wheat bran

Prescription
Antibiotics
Antidepressants
Antiparkinsonian drugs
Antipsychotics
Calcium-channel blockers
Diuretics
Metformin
Opioids
Sympathomimetics

Box 5. Diagnostic Testing for Patients With Suspected Irritable Bowel Syndrome (IBS) and No Concerning Features

All IBS Subtypes
Complete blood cell count
Age-appropriate colorectal cancer screening

IBS With Diarrhea
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
When colonoscopy performed, obtain random biopsies
SeHCAT, fecal bile acids, or serum C_4 where available

IBS, Mixed
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
Stool diary
Consider abdominal radiography to evaluate for stool accumulation

IBS With Constipation
If severe or medically refractory, refer to gastroenterology specialist for physiologic testing

Abbreviations: SeHCAT, tauroselcholic (selenium 75) acid; TtG, tissue translutaminase.

increased likelihood of biopsy-proven celiac disease in patients with IBS symptoms.[44] The prevalence of celiac disease in these patients varies by region, and although studies from Europe have demonstrated a higher prevalence of the disease, those from the United States have not.[45] Decision analysis suggests that routine screening for celiac disease in IBS patients becomes cost-effective at a prevalence of greater than or equal to 1%.[46] Given the potential long-term consequences of missing celiac disease, clinicians caring for patients with IBS should have a low threshold to screen for it, particularly in individuals with IBS-D.[41]

Recent literature has identified that a small subset of patients with suspected IBS-D have microscopic colitis. A recent case-control study found that age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new drugs, and comorbid autoimmune diseases were associated with an increased risk of microscopic colitis (Box 2).[47] When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be performed to rule out microscopic colitis (Box 5).[41]

Inflammatory bowel diseases, including ulcerative colitis and Crohn disease, are of concern when a patient with IBS symptoms is evaluated. Even low-grade inflammation could alter permeability and sensitize visceral afferent neurons, leading to alterations in motility and visceral sensation.[18] Studies suggest that more than a third of patients with inflammatory bowel disease fulfill the Rome criteria for IBS.[18] It is unclear how many patients with inflammatory bowel disease and overlapping IBS symptoms have concerning features (Box 2). From a pragmatic standpoint, the important question is how often inflammatory bowel disease is ultimately identified in patients who have typical IBS symptoms and no concerning features. A prospective US study that included more than 900 nonconstipated IBS patients and healthy controls undergoing colonoscopy found inflammatory bowel disease in less than 1% of IBS patients and none of the controls.[48] These data argue against routine colonoscopy in patients with typical IBS symptoms and no concerning features. Noninvasive biomarkers may provide a more cost-effective means by which to screen for inflammatory bowel disease than colonoscopy. A recent systematic review and meta-analysis suggested that fecal calprotectin, a biochemical assay for intestinal inflammation, was effective and cost-effective in identifying inflammatory bowel disease.[49] Another systematic review and meta-analysis found that a C-reactive protein level of less than 0.5 mg/dL or fecal calprotectin level of less than 40 µg/g conferred a less than 1% risk of inflammatory bowel disease in patients with typical IBS symptoms.[50]

Perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit.[51] Evidence of bile acid malabsorption may be present in up to a third of patients with IBS-D symptoms.[52] At present, clinicians can assess for bile acid malabsorption by instituting an empirical trial with a bile acid sequestrant. Several tests have been developed to identify such malabsorption, including the SeHCAT (tauroselcholic [selenium 75] acid) retention test, serum C4 measurement, and fecal bile acid measurement. However, these tests are not widely available in the United States. It is hoped that eventually bile acid malabsorption testing will identify IBS-D patients more likely to benefit from a bile acid sequestrant.

For IBS-C patients, colorectal cancer is a common concern. A meta-analysis that included 8 cross-sectional surveys found that constipation was actually associated with a lower prevalence of colorectal cancer (odds ratio, 0.56; 95% CI, 0.36-0.89). This analysis also found no significant increase in colorectal cancer risk among constipated patients vs nonconstipated controls in 3 cohort studies (odds ratio, 0.80; 95% CI, 0.61-1.04).[53] However, a more recent case-control study found that patients with chronic constipation have a significantly higher prevalence and incidence of colorectal cancer and benign colorectal neoplasms.[54] The limited prospective literature suggests that the risk of colorectal cancer is less than 1% in patients

Table. Summary of Therapies for Irritable Bowel Syndrome[a]

Treatment	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Over-the-Counter			
Fiber: psyllium	Moderate	Best suited for IBS-C	Bloating, gas
Laxatives: polyethylene glycol	Very low	Beneficial for constipation but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidiarrheals: loperamide	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Low	Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics	Similar to placebo
Antispasmodics: peppermint oil	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription			
Antidepressants: TCAs, SSRIs, SNRIs	High	TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents			
Linaclotide	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Lubiprostone	Moderate	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaximin	Moderate	Improves global symptoms, pain, and bloating in nonconstipated IBS patients	Similar to placebo
5-HT_3 receptor antagonists: alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other Therapies			
Psychological/behavioral therapy	Very low	Benefits for global IBS symptoms in all subgroups	Similar to placebo

Abbreviations: GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Quality of Evidence were taken from Ford et al.[59] Quality of the evidence was reported as very low, low, moderate, or high based on the number and quality of available clinical trials and reproducibility of the results. Evidence judged to be of very low quality was from case series and nonrandomized trials while evidence judged to be of high quality was taken from randomized placebo-controlled trials with reproducible results.

with typical IBS symptoms and no concerning features and not increased compared with that in healthy controls. As such, in patients with typical IBS symptoms and no concerning features, age-appropriate colorectal cancer screening is the most logical recommendation.

An underrecognized condition in patients with IBS-C symptoms is dyssynergic defecation, a constipation-associated condition that arises from the inability to coordinate the abdominal wall, anal sphincter, and pelvic floor muscles in a way that enables normal defecation.[55] Although a sense of incomplete evacuation after a bowel movement or the need for digital maneuvers to facilitate defecation may increase the likelihood of dyssynergia, symptoms generally do not accurately identify affected patients.[56] Dyssynergia can cause abdominal symptoms such as pain, discomfort, and bloating, which are relevant to IBS-C. Preliminary data suggest that correction of dyssynergia with biofeedback can improve both bowel and abdominal symptoms.[57] Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia with a digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging.

Management

General Management Recommendations

A trusting patient-physician relationship is the cornerstone of managing IBS patients. Actively listening, not interrupting, using empathy, setting realistic expectations ("helping" rather than "curing"), and using nonverbal techniques such as making eye contact, nodding, leaning forward, and using open body posture can help build this relationship.[58] The clinician must understand the patient's goals for the visit and avoid focusing only on the gastrointestinal symptoms. Performing a physical examination establishes the ritual of touch, which many patients identify with a thorough and caring physician. It is critical to assign a confident diagnosis and provide education regarding the causes, natural history, and treatment of IBS.

Because IBS is a symptom-based disorder, treatments can address abdominal symptoms such as pain, cramping, bloating, or bowel symptoms, including diarrhea and constipation (Box 2). Traditionally, first-line IBS therapies have focused on over-the-counter medications aimed at improving diarrhea (eg, loperamide, probiotics) or constipation (eg, fiber supplements, laxatives). Benefits of this strategy include improving altered bowel habits, widespread availability, low cost, and an excellent safety record. However, over-the-counter medications offer little benefit for global, or overall, IBS symptoms or abdominal symptoms such as pain and bloating. The **Table** provides a summary of commonly used IBS treatments, along with recently published recommendations and evidence quality assessments from the American College of Gastroenterology Functional Bowel Disorders Task Force.[59] During the last 5 years, lifestyle and dietary interventions have become an increasingly important first-line treatment option.

Exercise

Physically active individuals move their bowels more often and have more rapid colon transit than sedentary individuals.[60] Further-

more, a randomized clinical trial found that a structured exercise intervention led to greater improvements in overall IBS symptoms than usual care.[61] Thus, IBS patients should be encouraged to increase their physical activity. A simple recommendation is to take a 20-minute walk (roughly 1 mile) each day. Distance and pace can be gradually increased as tolerated.

Diet

Patients often associate their IBS symptoms with eating a meal. Up to 90% of IBS patients restrict their diet to prevent or improve their symptoms.[62] True food allergies are uncommon in IBS. On the other hand, food intolerances or sensitivities are frequently reported. At present, there is emerging evidence that supports diets for IBS patients that are gluten free and low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).

The effect of gluten was assessed by a randomized, double-blind, placebo-controlled, rechallenge trial in 34 IBS patients with a history of gluten sensitivity.[63] During 6 weeks, overall IBS symptoms were not adequately controlled in 68% of patients receiving gluten vs 40% receiving a gluten-free diet ($P < .001$). Gluten worsened pain, bloating, and stool consistency, as well as "tiredness." Another study in IBS-D patients reported increased stool frequency, as well as altered gut permeability and immune activation, in the presence of gluten.[64] These data have led some to conclude that gluten is the primary cause of symptoms after ingestion of wheat. However, wheat contains fructans and other proteins that might also cause symptoms in IBS patients. In a recent Australian study of 37 IBS patients with wheat sensitivity, symptom relief was more closely associated with exclusion of poorly absorbed carbohydrates than gluten.[65] It is also likely that widespread negative media reports about gluten have increased the chance of a "nocebo" response, contributing to the perceived negative effects of eating gluten-containing foods.

Short-chain, poorly absorbed, highly fermentable carbohydrates are collectively known as FODMAPs and are found in such foods as wheat, onions, some fruits and vegetables, sorbitol, and some dairy. FODMAPs lead to increased small intestinal and colonic water secretion and fermentation, which causes increased production of short-chain fatty acids and gas.[66] Aside from increased flatulence, FODMAPs do not cause gastrointestinal symptoms in healthy adults.[67] Conversely, FODMAPs are an important trigger of meal-related symptoms in IBS patients, possibly as a consequence of underlying abnormalities in gut physiology and visceral sensation.[29] A randomized clinical trial in 30 IBS patients found lower overall symptom scores on the low-FODMAP diet vs a typical Australian diet ($P < .001$).[67] Seventy percent of IBS patients felt better while receiving the low-FODMAP diet regardless of IBS subtype. Responders to full FODMAP exclusion should gradually reintroduce FODMAP-containing foods to identify the level of dietary restriction needed to maintain symptom benefit. There are currently few long-term efficacy or safety data for the low-FODMAP diet.

Given the rapidly expanding role of dietary intervention in the primary management of IBS and other gastrointestinal conditions, it is becoming increasingly important for clinicians to become educated and to integrate a trained registered dietitian into the health care team.

Medical Treatments for IBS-D

Antidiarrheals

Antidiarrheal medications such as loperamide inhibit peristalsis, prolong gut transit, reduce fecal volume, and are often used as first-line agents in patients with IBS-D. Two randomized trials enrolling IBS-D and IBS-M patients found no benefit of loperamide over placebo for overall IBS symptoms.[59] However, loperamide reduces stool frequency, increases stool consistency, and can be used prophylactically when a patient anticipates diarrhea. When used long term, loperamide is preferred to diphenoxylate or atropine because it does not cross the blood-brain barrier and thus is less subject to habituation. In practice, many gastroenterologists use bile acid sequestrants such as cholestyramine and colesevelam to treat diarrhea. These agents have not been evaluated in rigorous, randomized trials with IBS patients.

Serotonin Agents: 5-HT_3 Receptor Antagonists

The gut hormone serotonin influences gastrointestinal motility and visceral sensation.[68] Alosetron is a 5-HT_3 antagonist approved in the United States for treating women with severe, disabling IBS-D that has not responded to traditional medical therapies. Alosetron (0.5-1 mg once to twice per day) improves global and individual IBS-D symptoms in women and men for up to a year, with a therapeutic gain over placebo of approximately 15%. Dose-dependent constipation and idiosyncratic ischemic colitis are potential adverse effects of alosetron that have led to a risk management plan requiring US patients and prescribers to acknowledge the risks before dispensation of the medication.[69]

Ondansetron, a 5-HT_3 antagonist that is less potent than alosetron, has been shown to benefit IBS-D in a recent randomized, double-blind, placebo-controlled, crossover study.[70] Ondansetron (4-8 mg 1-3 times per day) significantly improved stool consistency, global IBS symptoms, urgency, stool frequency, and bloating (all comparisons, $P \leq .002$) but not pain.

Antispasmodics

Antispasmodics include drugs with anticholinergic or calcium-channel blocking properties that may improve IBS symptoms by relaxing gut smooth muscle. Acknowledging the poor quality of many trials, a 2011 Cochrane review reported benefits of antispasmodics over placebo for abdominal pain and global assessment.[71] The American College of Gastroenterology Functional Bowel Disorders Task Force recently concluded that "certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS."[59] Because some IBS patients have an exaggerated gastrocolonic reflex that is in part cholinergically mediated,[72] these drugs may be best suited for postprandial abdominal cramping and loose stools. Dose-dependent adverse events, including constipation, fatigue, dry mouth, dizziness, and blurred vision, may occur. Anticholinergics should be avoided in the elderly.

Peppermint oil, which is available over the counter, possesses calcium-channel blocking properties and thus is classified as an antispasmodic. A number of small clinical trials suggest that enteric peppermint oil (187-225 mg 3 times daily) benefits some IBS patients.[73] Although peppermint oil is typically well tolerated, some patients may experience reflux symptoms.[73]

Medical Treatments for IBS-C

Fiber Supplements

The efficacy of fiber for treating IBS has been summarized in recent reviews.[26,74] The most recent meta-analysis reported modest benefits with fiber for global IBS symptoms (relative risk, 0.86; 95% CI, 0.80-0.94; number needed to treat, 10).[74] In a subgroup analysis, soluble fiber (psyllium and ispaghula husk; relative risk, 0.84; 95% CI, 0.73-0.94) but not insoluble fiber (wheat bran) was associated with improved IBS symptoms. Benefits of fiber appear most robust in patients with IBS-C rather than IBS-D. Fiber, which is often used as a first-line therapy, should be started at a nominal dose and gradually titrated upward during weeks to a total daily intake of 20 to 30 g. Wheat bran contains fructans, which, like other FODMAPs, can exacerbate IBS symptoms; thus, wheat bran should be avoided in IBS patients.[26]

Laxative Agents

Osmotic laxatives such as polyethylene glycol are frequently recommended as first-line therapy for IBS-C patients. Clinical trials have demonstrated that it improves bowel complaints, including stool frequency and consistency, but does not reliably improve abdominal pain or bloating.[75] The usual starting dose is 17 g in juice or water, with dose escalation dictated by clinical response. Polyethylene glycol is typically well tolerated but can cause dose-dependent bloating, gas, and loose stools.

Stimulant laxatives are also commonly used in IBS-C patients. Although efficacy has been demonstrated in patients with chronic constipation,[76] to our knowledge there are no randomized, controlled trials in IBS-C patients. Relevant to IBS, the most common adverse effects are abdominal pain and cramping.

Prosecretory Agents

Luminally acting prosecretory agents have been evaluated in IBS-C patients. Lubiprostone is a chloride-channel (ClC-2) activator that stimulates intestinal fluid secretion and improves global, bowel, and abdominal symptoms in IBS-C patients.[77] In 2 phase 3 trials (1711 IBS-C patients), a significantly higher percentage of patients treated with lubiprostone 8 µg twice daily responded compared with those treated with placebo (17.9% vs 10.1%; $P = .001$).[78] A higher dosage of 24 µg has proven effective in patients with chronic idiopathic constipation. To limit dose-dependent nausea (8% with an 8-µg dose and 33% with a 24-µg dose), lubiprostone should be received with food.

Linaclotide is a guanylate cyclase-C agonist that increases production of cyclic guanosine monophosphate. Intracellularly, cyclic guanosine monophosphate increases intestinal chloride secretion via the cystic fibrosis transmembrane regulator, whereas extracellularly it reduces firing of visceral afferent pain fibers.[79] A 2013 meta-analysis that included 3 rigorous randomized clinical trials in IBS-C patients reported a relative risk for response to linaclotide (290 µg once daily) vs placebo of 1.95 (95% CI, 1.3-2.9) and a number needed to treat of 7 (95% CI, 5-11).[80] The maximum benefit for stool frequency occurs within a week of treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks to maximally improve. Diarrhea is the most common adverse effect with linaclotide, reported by 20% of patients.[81] Linaclotide should be received 30 to 60 minutes before breakfast to reduce the likelihood of diarrhea.

Modification of the Microbiota: Probiotics and Antibiotics

Probiotics are live bacteria that, when consumed in sufficient quantities, confer a health benefit to the host. Prebiotics are nutrients, usually carbohydrates, that encourage the growth of probiotic bacteria. Synbiotics are combinations of prebiotics and probiotics. Postbiotics consist of extracts from dead or lysed bacteria. The most robust data have evaluated the role of probiotics for IBS. In a recent meta-analysis including 35 randomized clinical trials, probiotics as a group improved global IBS symptoms (relative risk, 0.79; 95% CI, 0.70-0.89; number needed to treat, 7; 95% CI, 4-12.5), abdominal pain, bloating, and flatulence.[59] However, given the differences in probiotic preparations evaluated, data derived from grouping or directly comparing trials should be interpreted with caution.[82] Higher-quality studies have tended to demonstrate less of a treatment effect. Thus, the current literature does not allow recommendations regarding specific probiotic preparations for IBS.

Rifaximin is a poorly absorbed, broad-spectrum antibiotic that has been evaluated in IBS patients. A recent meta-analysis that included 5 randomized clinical trials that enrolled predominantly nonconstipated IBS patients demonstrated therapeutic gains of 9% to 10% for global symptoms (odds ratio, 1.57; 95% CI, 1.22-2.01) and bloating (odds ratio, 1.55; 95% CI, 1.23-1.96).[83] The 2 phase 3 trials in nonconstipated IBS patients used rifaximin 550 mg 3 times daily for 14 days. Clinical experience suggests that many rifaximin responders will eventually develop recurrent IBS symptoms. Recently released data from a large re-treatment trial suggest that second and third courses yield efficacy similar to that of the first course of rifaximin.[84] The role of other antibiotics in IBS treatment remains unknown, although antimicrobial resistance with repeated courses of systemically absorbed antibiotics may be a concern.

Centrally Acting Interventions

Antidepressants

Because of their effects on pain perception, mood, and motility, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. The efficacy of tricyclic antidepressants, selective serotonin-reuptake inhibitors, and, to a lesser extent, selective norepinephrine-reuptake inhibitors has been evaluated in IBS patients.[85] A meta-analysis identified 17 randomized controlled trials that enrolled 1084 IBS patients who were treated with antidepressants or placebo.[85] Collectively, antidepressants were effective for abdominal pain, with a relative risk of remaining symptomatic of 0.62 (95% CI, 0.43-0.88) and a number needed to treat of 4 (95% CI, 3-6). A subgroup analysis reported a number needed to treat of 4 for both tricyclic antidepressants and selective serotonin-reuptake inhibitors. Adverse events occurred more often in patients receiving an antidepressant (number needed to harm, 9; 95% CI, 5-111). Tricyclic antidepressants can cause dose-dependent constipation, dry mouth and eyes, drowsiness, weight gain, and QT-interval prolongation. Selective serotonin-reuptake inhibitors can cause sexual dysfunction, agitation, nausea, drowsiness, and diarrhea. Although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, there are few data addressing their efficacy for IBS.[86]

The adverse event profiles of different antidepressants can be leveraged to address different IBS subtypes.[87] For example, because tricyclic antidepressants can cause constipation, they may be best suited to IBS-D patients, whereas the prokinetic effects of se-

lective serotonin-reuptake inhibitors might make them a better choice for IBS-C patients. Similarly, tricyclic antidepressants might be a better choice for patients with insomnia, anorexia, or weight loss. On the other hand, selective serotonin-reuptake inhibitors might be a better choice for patients with significant anxiety. When a tricyclic antidepressant is selected to treat IBS, low doses (10-25 mg) should be started at bedtime and gradually titrated upward according to symptom response and tolerability. Selective serotonin-reuptake inhibitors are typically started at the lower range of standard dosing.

Psychological Therapies

Psychological therapies provide an alternative or adjunctive therapy for IBS patients. In a recent meta-analysis, 32 separate trials of highly variable quality, involving more than 2000 patients, evaluated 10 different "psychological therapies,"[85] which were more effective than control therapies, with a number needed to treat of 4 (95% CI, 3-5). In a subgroup analysis, similar numbers needed to treat were reported for cognitive behavioral therapy, hypnotherapy, multicomponent psychotherapy, and dynamic psychotherapy but not other techniques. Despite these encouraging results, variable third-party reimbursement, a lack of clinicians, and poor patient and clinician acceptance have limited widespread adoption of these therapies in clinical practice. Access to behavioral therapy may improve with the development of book-, Internet-, or application-based behavioral programs.[88,89]

Complementary and Alternative Medicine

Despite the paucity of evidence, many IBS patients use complementary and alternative therapies.[90] A meta-analysis of 5 studies demonstrated that acupuncture was no better than sham acupuncture in improving symptoms or quality of life in IBS patients.[91] Studies evaluating Chinese herbal remedies for IBS have yielded mixed results.[90] A clear understanding of the active ingredients and a lack of standardization are significant challenges facing clinicians with an interest in herbal therapies.

Bottom-Line Clinical Messages

1. IBS is a common, symptom-based illness that is defined by the presence of abdominal pain or cramping in association with constipation, diarrhea, or both.
2. The diagnosis of IBS can be confidently established with the use of symptom-based criteria, the exclusion of concerning features, and the judicious use of diagnostic testing.
3. Concerning features that should prompt a more detailed evaluation include new onset of symptoms after age 50 years; unexplained weight loss; a family history of organic gastrointestinal diseases such as colon cancer, inflammatory bowel diseases, or celiac disease; gastrointestinal blood loss; and unexplained iron-deficiency anemia.
4. Successful management of patients with IBS begins with a trusting, positive, patient-physician relationship.
5. A holistic approach that embraces lifestyle changes, dietary interventions, medications, or behavioral strategies offers the greatest likelihood of sustained treatment benefit.

Conclusions

IBS remains an enigmatic cause of significant distress, morbidity, and disability. For the foreseeable future, the diagnosis of IBS will rely on the identification of characteristic symptoms and the exclusion of organic disease mimics. As science advances, it is hoped that the confident diagnosis of IBS will be aided by novel biomarkers that can either rule out specific organic diseases or rule in IBS. An improved understanding of the pathophysiology of IBS will also pave the way for novel nonpharmacologic and pharmacologic therapies. For now, it is important for physicians to understand the role of dietary, lifestyle, and behavioral modification either with or without medical treatments for IBS.

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DEPARTMENT OF HEALTH

Irritable Bowel Syndrome (IBS) Issue Brief

INCLUDING IBS AND IBS-D

OCTOBER 2022

Introduction

This briefing was prepared in response to petitions to consider adding irritable bowel syndrome (IBS) and irritable bowel syndrome with diarrhea (IBS-D) as new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used identify any ongoing or completed clinical trials.

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Symptom severity can range from debilitating to mild or moderate. Further, IBS is often associated with additional somatic comorbidities (conditions that affect the body), psychiatric conditions, and visceral sensitivity (Enck et al., 2016).

IBS is thought to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the gut. The associated problem between the brain and the gut leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both (Ford et al., 2020).

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes, IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools is loose, or watery and more than a quarter of a patient's stools are hard and lumpy (Chey et al., 2015).

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis is irritable bowel disease (IBD). Unlike IBS, which is characterized by a gut-brain disorder, IBD, which encompasses Crohn's disease (CD) and Ulcerative colitis (UC), is characterized by chronic relapsing inflammation and immune activity (Abdul Rani et al., 2016). However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological comorbidities, specifically depression and anxiety (Abdul Rani et al., 2016). Further, studies have found that depression can increase a patient's probability for developing increased inflammation (Fagundes et al., 2013, Johnson et al., 2002). Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development (Abdul Rani et al., 2013). However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent (Abdul et al., 2016). Finally, both IBD and IBS patients experience abnormal gut microbiota (Abdul et al., 2016). However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease (Abdul et al., 2016). Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks. Ultimately, more large-scale research is needed to define a clear connection.

Epidemiology

IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years (Chey et al., 2015). Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion (Chey et al., 2015). Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms (Chey et al., 2015).

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity (Chey et al., 2015).

Diagnosis

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or inflammatory bowel disease. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale (Chey et al., 2015).

Diagnostic Criteria for Irritable Bowel Syndrome (IBS) With Subtypes includes:

Recurrent abdominal pain or discomfort at least three days a month associated with two or more of the following: reduced abdominal pain with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (Chey et al., 2015).

IBS with constipation (IBS-C) is defined as hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements. IBS with diarrhea (IBS-D) is defined as loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements. Mixed IBS (IBS-M) is defined as hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements (Chey et al., 2015).

While diagnosis of IBS-D or IBS-C is relatively straightforward, the diagnosis of patients with IBS-M presents a unique challenge. Therefore, a detailed history of a patients mixed bowel patterns is required to better understand the underlying disease state (Chey et al., 2015). Further, the consideration of all prescription and over-the-counter medications is needed to determine how they might affect IBS symptoms (Chey et al., 2015).

In addition to the identification of symptom-based criteria, a detailed assessment to eliminate the potential for alternative disease is required to finalize the diagnosis. A patient with clear IBS symptoms combined with an absence of diagnostic markers indicative of other gastrointestinal related disorders, can be diagnosed as having IBS with some level of accuracy (Chey et al., 2015).

Current Therapies

Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates) (Chey et al., 2015). A meta-analysis of the low-FODMAP diet found

that the diet was effective at improving patient well-being and reducing symptoms (van Lanen et al., 2021). However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP (van Lanen et al., 2021). Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established (van Lanen et al., 2021).

Medications

A doctor may recommend medication to relive IBS symptoms dependent on the type of IBS a patient is suffering from.

Antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume (Chey et al., 2015). However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit of loperamide compared to the placebo group for the overall reduction of IBS symptoms (Chey et al., 2015). Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic (Chey et al., 2015).

Serotonin agents such as Alosetron, a 5-HT_3 antagonist has been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies (Chey et al., 2015). Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo.

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools (Chey et al., 2015). Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms (Chey et al., 2015). Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it has not been shown to improve abdominal pain or bloating (Chey et al., 2015). Stimulant laxatives have also been used as a therapy for IBS-C patients, but there have been few randomized controlled trials evaluating its efficacy (Chey et al., 2015).

Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel, and abdominal symptoms in IBS-C patients (Chey et al., 2015). Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls (Chey et al., 2015).

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity

compared to placebo controls (Chey et al., 2015). Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea (Lacy et al., 2009). As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximize effects are felt (Chey et al., 2015).

The use of probiotics and antibiotics has been explored as a treatment for IBS (Chey et al., 2015). Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence (Ford et al., 2014). However, there was some variability in the probiotics used and grouping methods employed that limited comparability (Ford et al., 2014). As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation regarding the use of specific probiotic preparations for IBS (Chey et al., 2015). Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients (Menee et al., 2012). However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms (Chey et al., 2015). Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern (Chey et al., 2015).

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain (Dekel et al., 2013). However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS (Chey et al., 2015). Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms (Ford et al., 2014). However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS (Hussain et al., 2006). However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture (Manheimer et al., 2012). Studies evaluating herbal remedies have yielded mixed results. There is a lack of an understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary interventions, medication, and behavioral strategies to maximize treatment of IBS (Chey et al., 2015).

Pre-clinical Research

Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the CB1 receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system (Hill et al., 2017, Brugnatelli et al., 2020). Pre-clinical studies have shown a direct connection

between the endocannabinoid system and regulation of gastrointestinal motility (Storr et al., 2008). In fact, activation of the cannabinoid 1 (CB1) and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility (Hasenoehrl et al., 2016). Additionally, research by Vianna et al., 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility. Despite the promising pathophysiologic mechanism, studies examining the impact of an endocannabinoid deficiency on IBS are limited.

Clinical Trials

A clinical trial by Wong et al. in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS (Wong et al., 2011). In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, Wong et al. attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial conducted by Wong et al. in 2012 failed to reproduce the findings seen in 2011 (Wong et al. 2012). In addition, a study by Klooker at al., 2011, showed that the cannabinoid receptor agonist delta-9-tetrahydrocannabinols (THC) had no effect on rectal distension or rectal sensitivity in healthy volunteers and IBS patients. Moreover, a placebo-controlled crossover study (a study where patients receive both the treatment and the placebo at different times during a study) reported no significant difference in IBS patient pain scores between CBD and placebo treatments. However, this study was small scale and only recruited women for the study (Anne-Claire B. et al., 2021). Finally, a small clinical trial investigating the impact of cannabidiol therapy on IBS patients found at the group level there was no difference in the pain score of those who received the cannabidiol therapy compared to those who did not receive the cannabidiol therapy (van Orten-Luiten et al., 2021). Overall, while some studies, such as the 2011, Wong et al. have shown the promising potential for dronabinol, several more recent studies have failed to reproduce these findings. Thus, more large-scale clinical trials are needed.

Ongoing Clinical Trials

A search for current ongoing clinical trials was conducted on clinicaltrials.gov. Search terms specific to cannabis and IBS were used to identify clinical trials. Search terms for IBS included Irritable Bowel Syndrome, IBS, IBS-D, IBS-C, and IBS-M. Search terms for Cannabis included cannabis, THC, marijuana, and dronabinol. Currently there are no ongoing clinical trials investigating the potential role of cannabis as a treatment for IBS.

Observational Studies

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS (Choi et al., 2022). The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis (Choi et al., 2022). When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users (Choi et al., 2022). However, Choi et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission (Choi et al. 2022). Therefore, the authors found that cannabis use had no impact on IBS-specific 30-day hospital readmission rates but did reduce total hospitalization cost and charges.

Adejumo et al. conducted a national survey, using the international classification of disease, 9th edition codes to identify individuals with Cannabis Use Disorder (CUD) and IBS. They found that patients with CUD were significantly more likely to have IBS compared to patients without CUD (Adejumo et al. 2019). These finding suggest that the abnormal use of cannabis may either contribute to the development or exacerbation of IBS and its symptoms. Adding to this, a study of 31,272 patients by Patel et al., 2020, found that patients with CUD had a higher odd for IBS hospitalization compared to patients without Cannabis Use Disorder (Patel et al. 2020). This suggests the use of cannabis among those with CUD may be associated with the development of IBS or exacerbation of IBS symptoms. Therefore, while there is a potential benefit associated with the use of cannabis, the improper use of cannabis poses some risk to the development and aggravation of IBS.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers), reported that cannabis use may decrease inpatient health-care utilization in IBS patients. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users (Desai et al., 2020). Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users (Desai et al., 2020, Choi et al., 2022). In contrast, a study by Adeyinka et al., 2019, reported a higher likelihood of hospitalization among people who use cannabis conflicting with prior reports of a shortened stay. This paper also noted that an elevated state of anxiety might countermand the effects of cannabis on the endocannabinoid system (Adeyika et al., 2019). In conclusion, while cannabis as a therapy for IBS shows promise, the data remains inconclusive and more large-scale clinical trial research is needed.

In contrast to IBS, IBD research suggests that the use of small doses of cannabis can help reduce inflammation and reduces the overall IBD symptomology (McCallum et al., 2014, Perisetti et al., 2020). However, consumption of cannabis at high levels can exacerbate IBD symptoms and increase a patient's likelihood to be hospitalized due to severe IBD (UC and CD) (McCallum et al., 2014, Perisetti et al., 2020). Therefore, extreme cause should be taken when using cannabis as a therapy for IBD.

National Medical Organization Recommendations

In 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

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3. Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition

Content for this section was borrowed heavily from the Minnesota Department of Health's Issue Brief on Irritable Bowel Syndrome, which was published in October 2022 in support of its decision to add Irritable Bowel Syndrome to the state's list of Qualifying Conditions for Medical Marijuana. For more information, we encourage you to contact the Minnesota Department of Health's Office of Medical Cannabis at:

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Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates).[1] A meta-analysis of the low-FODMAP diet found that the diet was effective at improving patient well-being and reducing symptoms.[2] However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP.[3] Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established.[4]

A doctor may recommend medication to relieve IBS symptoms dependent on the type of IBS a patient is suffering from along with the severity of symptoms.

Like in patients who suffer from IBD, antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume.[5] However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit

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[1] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

[2] van Lanen, A. S., de Bree, A., & Greyling, A. (2021). Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis. *European journal of nutrition*, *60*(6), 3505–3522. https://doi.org/10.1007/s00394-020-02473-0

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[5] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

of loperamide compared to the placebo group for the overall reduction of IBS symptoms.[6] Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic.[7] It should be noted that loperamide is a synthetic opiate designed to block the opioid receptors in the gut. However, at very high doses, the medication can cross the blood-brain barrier and cause opioid-like effects, making it a target for abuse, and can even lead to cardiac arrest.[8]

Serotonin agents such as Alosetron, a 5-HT_3 antagonist, have been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies.[9] Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo. Alosetron was originally approved as a new drug to treat IBS in 2000, but was quickly withdrawn by the FDA due to a high risk of constipation and ischemic colitis.[10] The drug was later reapproved for use by women under more strict prescribing conditions.[11]

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools.[12] Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms.[13]

Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it

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Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel and abdominal symptoms in IBS-C patients.[16] Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls.[17]

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity compared to placebo controls.[18] Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea.[19] As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximum effects are felt.[20]

The use of probiotics and antibiotics has been explored as a treatment for IBS.[21] Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence.[22] However, there was some variability in the probiotics used and grouping methods employed that limited comparability.[23] As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation

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[14] Chey, W. D., Kurlander, J., & Eswaran, S. (2015). Irritable bowel syndrome: a clinical review. JAMA, 313(9), 949–958. https://doi.org/10.1001/jama.2015.0954

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regarding the use of specific probiotic preparations for IBS.[24] Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients.[25] However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms.[26] Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern.[27]

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain.[28] However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS[29]. Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms.[30] However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS.[31] However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture.[32] Studies evaluating herbal remedies have yielded mixed results. There is a lack of understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary

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interventions, medication, and behavioral strategies to maximize treatment of IBS.[33] Furthermore, many medications approved for IBS can have uncomfortable or dangerous side effects or withdrawal symptoms.

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Irritable Bowel Syndrome: a clinical review

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Review

Irritable Bowel Syndrome
A Clinical Review

William D. Chey, MD; Jacob Kurlander, MD; Shanti Eswaran, MD

IMPORTANCE Irritable bowel syndrome (IBS) affects 7% to 21% of the general population. It is a chronic condition that can substantially reduce quality of life and work productivity.

OBJECTIVES To summarize the existing evidence on epidemiology, pathophysiology, and diagnosis of IBS and to provide practical treatment recommendations for generalists and specialists according to the best available evidence.

EVIDENCE REVIEW A search of Ovid (MEDLINE) and Cochrane Database of Systematic Reviews was performed for literature from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*.

FINDINGS The database search yielded 1303 articles, of which 139 were selected for inclusion. IBS is not a single disease but rather a symptom cluster resulting from diverse pathologies. Factors important to the development of IBS include alterations in the gut microbiome, intestinal permeability, gut immune function, motility, visceral sensation, brain-gut interactions, and psychosocial status. The diagnosis of IBS relies on symptom-based criteria, exclusion of concerning features (symptom onset after age 50 years, unexplained weight loss, family history of selected organic gastrointestinal diseases, evidence of gastrointestinal blood loss, and unexplained iron-deficiency anemia), and the performance of selected tests (complete blood cell count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate colorectal cancer screening) to exclude organic diseases that can mimic IBS. Determining the predominant symptom (IBS with diarrhea, IBS with constipation, or mixed IBS) plays an important role in selection of diagnostic tests and treatments. Various dietary, lifestyle, medical, and behavioral interventions have proven effective in randomized clinical trials.

CONCLUSIONS AND RELEVANCE The diagnosis of IBS relies on the identification of characteristic symptoms and the exclusion of other organic diseases. Management of patients with IBS is optimized by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral interventions.

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Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal condition. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits, in the absence of any other disease to cause these sorts of symptoms. Pooled population-based prevalence estimates of IBS vary globally, in part related to differences in study populations, diagnostic criteria, and study methodology. In North America, the population prevalence of IBS is approximately 12%.[1] IBS is most prevalent in South America (21.0%) and least prevalent in Southeast Asia (7.0%).[1] In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent among women than men, whereas there appears to be greater parity in Asia.[2] Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea.[2] It appears that IBS prevalence decreases with age. In the United States, patients are equally distributed among IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), whereas in Europe, IBS-C or IBS-M may be more prevalent.[3]

This clinical review covers the epidemiology, natural history, pathophysiology, diagnosis, and management of IBS.

Methods

Evidence to support this clinical review was obtained from searches performed by a medical librarian of MEDLINE and the Cochrane Database of Systematic Reviews from 2000 to December 2014 for the terms *pathophysiology*, *etiology*, *pathogenesis*, *diagnosis*, *irritable bowel syndrome*, and *IBS*. The range was expanded from 1946 to December 2014 for *IBS*, *irritable bowel syndrome*, *diet*, *treatment*, and *therapy*. This search strategy yielded 1303 articles after limiting to the English language. We selected 139 articles for inclusion. When available, systematic reviews and meta-analyses were used to summarize the available evidence.

FODMAP *fermentable oligosaccharides, disaccharides, monosaccharides, and polyols*

IBS *irritable bowel syndrome*

IBS-C *IBS with constipation*

IBS-D *IBS with diarrhea*

IBS-M *IBS with a mixed bowel pattern*

Burden of Illness and Natural History

Multiple comorbidities are associated with IBS, including somatic pain syndromes (fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain),[4] other gastrointestinal disorders (gastroesophageal reflux disease[5] and dyspepsia[6]), and psychiatric disorders (major depression, anxiety, and somatization),[7] raising the possibility of shared pathogenesis.

In most patients, IBS is a chronic relapsing disease in which symptoms may vary over time. A systematic review showed that during long-term follow-up of clinic-based IBS patients, 2% to 18% worsened, 30% to 50% remained unchanged, and 12% to 38% improved.[8] Previous surgery, longer duration of disease, higher somatic scores, and comorbid anxiety and depression all predicted worse outcomes. After a negative diagnostic evaluation result, a patient receiving a diagnosis of IBS has a less than 5% risk of receiving an alternative organic diagnosis in the future.[8]

Over time, patients may migrate between different IBS subtypes,[9] most commonly from IBS-C or IBS-D to IBS-M; switching between IBS-C and IBS-D occurs less commonly.[10] Many of the "natural history" studies in IBS are affected by treatments introduced by the patient or clinician. Thus, it is difficult to know how much symptom variation is the consequence of medical intervention vs the true natural history of IBS.

IBS significantly reduces health-related quality of life and work productivity.[11] Among patients with IBS, 13% to 88% seek care. Individuals who seek care have more distress and less social support than those who do not.[12] In the United States, IBS accounts for 3.1 million ambulatory care visits and 5.9 million prescriptions annually, with total direct and indirect expenditures exceeding $20 billion.[13,14]

Pathophysiology

The pathogenesis of IBS, like the clinical phenotype, is heterogeneous (**Box 1**). IBS likely encompasses a number of diseases with distinct pathophysiology that present with similar symptoms. During the past 40 years, a number of factors that contribute to the pathophysiology of IBS have emerged. Traditionally, the pathogenesis of IBS has focused on abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress. Although one or more of these abnormalities are demonstrable in the majority of IBS patients, none can account for symptoms in all of them. More recently, altered gut immune activation, intestinal permeability, and intestinal and colonic microbiome have been identified in some IBS patients.[15,16]

Box 1. Pathophysiology of Irritable Bowel Syndrome (IBS)

Environmental Contributors to IBS Symptoms

Early life stressors (abuse, psychosocial stressors)

Food intolerance

Antibiotics

Enteric infection

Host Factors Contributing to IBS Symptoms

Altered pain perception

Altered brain-gut interaction

Dysbiosis

Increased intestinal permeability

Increased gut mucosal immune activation

Visceral hypersensitivity

Supporting a role for these factors is the increased prevalence of IBS symptoms in inflammatory conditions such as celiac disease[17] and inflammatory bowel diseases[18] and following severe acute gastroenteritis.[19] The intestinal mucosa of some IBS patients shows increased activation of the innate and adaptive immune systems.[20,21] Increased small bowel and colonic permeability has also been observed in patients with IBS-D[22] and is associated with visceral hypersensitivity.[23] The fecal microbiota of IBS patients differ significantly from that of controls, likely reflecting the influence of genetics, diet, stress, infection, and drugs or antibiotics.[24]

IBS symptoms that arise after acute gastroenteritis or so-called postinfectious IBS present an interesting developmental model. Host factors such as genetics, immune function, microbiome, and psychological status, as well as environmental factors such as stress, severity of infection, or treatment with antibiotics, could predispose to the development of chronic IBS symptoms.[25] It is important to identify patients with postinfectious IBS because, unlike typical IBS, which tends to be a chronic relapsing condition, it spontaneously resolves in roughly half of patients within 6 to 8 years of the index infection.[25]

Many patients identify food as a trigger for their IBS symptoms. Various reviews of how specific dietary constituents can cause gastrointestinal symptoms are available.[26-29] The contribution of true food allergies to IBS is small.[30] Conversely, food intolerances are common in IBS patients. Increasingly, rapidly fermentable, osmotically active, short-chain carbohydrates (including fructose, lactose, fructans and galactans, and sugar alcohols) have been recognized as an important trigger of IBS symptoms. Poorly absorbed carbohydrates can exert osmotic effects and lead to increased fermentation in the small bowel or colon, which can exacerbate symptoms

Box 2. Features of Irritable Bowel Syndrome

Typical Features

Loose/frequent stools

Constipation

Bloating

Abdominal cramping, discomfort, or pain

Symptom brought on by food intake/specific food sensitivities

Symptoms dynamic over time (change in pain location, change in stool pattern)

Concerning Features for Organic Disease

Symptom onset after age 50 y

Severe or progressively worsening symptoms

Unexplained weight loss

Nocturnal diarrhea

Family history of organic gastroenterological diseases, including colon cancer, celiac disease, or inflammatory bowel disease

Rectal bleeding or melena

Unexplained iron-deficiency anemia

Box 3. Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes[a]

Recurrent abdominal pain or discomfort[b] at least 3 d/mo in the last 3 mo associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

Subtyping IBS by Predominant Stool Pattern

1. IBS with constipation—hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements
2. IBS with diarrhea—loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Mixed IBS—hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

[a] Criterion fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.

[b] "Discomfort" means an uncomfortable sensation not described as pain.

in IBS patients who have underlying abnormalities in gut function and sensation.[29] On the other hand, healthy individuals with normal gut function and sensation rarely experience symptoms after a meal.

Psychosocial factors may also predispose to the development of IBS. Women with IBS are more likely to have experienced verbal, sexual, or physical abuse, which can contribute to the development of the disease through brain-gut and mucosal immune dysfunction.[31] For some IBS patients, recurrent abdominal pain may begin in childhood and reflect learned-illness behaviors.[32] These experiences may lead to persistent changes in the brain-gut axis, resulting in the perception of otherwise unconscious interoceptive input from the gastrointestinal tract.[33] A subset of IBS patients have hypersensitivity to rectal balloon distention and increased activation of brain regions associated with emotional arousal and endogenous pain modulation.[34] In another subset of IBS patients, hypervigilance and catastrophizing are important features that lead to gastrointestinal and nongastrointestinal symptom amplification.[35]

Diagnosis

The diagnosis of IBS is based on the presence of characteristic symptoms and the exclusion of selected organic diseases (**Box 2**). The cardinal features of IBS according to the current diagnostic standard, the Rome III criteria, include abdominal pain or discomfort and altered bowel habits (**Box 3**). IBS patients can experience constipation, diarrhea, or both. Identification of a patient's predominant bowel complaint plays an important role in both the selection of diagnostic testing and treatment. The Rome III criteria emphasize the importance of stool consistency to distinguish between the 3 subtypes of IBS (Box 3)[36] because it correlates with patients' complaints of constipation or diarrhea and colonic transit better than stool frequency.[37] It can be assessed with the Bristol Stool Form Scale, a validated instrument that allows reporting of stool appearance from a score of 1 (hard and lumpy stool) to 7 (entirely liquid).[38] Bloating (subjective sensation of abdominal fullness) and distention (objective increase in abdominal girth) are also common and bothersome complaints reported by more than 80% of IBS patients.[39] However, many individuals without IBS also report these complaints.[40]

Although identifying patients with IBS-D or IBS-C is straightforward, patients with IBS-M present unique challenges. A detailed history can help determine whether a mixed bowel pattern represents the underlying disease state or is the consequence of medical intervention. It is important to consider all prescription and over-the-counter medications and supplements that could affect IBS symptoms (**Box 4**). A stool diary can help identify patterns among the chaotic bowel habits that many IBS patients report. Many IBS-M patients report periods without a bowel movement or with only small, hard stools, followed by periods of multiple stools of variable consistency that they interpret as "diarrhea." Most of these patients actually have IBS-C, with periods of progressive stool accumulation culminating in bowel purging. A radiograph demonstrating fecal loading can help confirm this clinical suspicion.

Along with an assessment of symptom-based criteria, one should be conducted for the presence of concerning features that identify patients who should undergo a more detailed evaluation to exclude organic disease[41] (Box 2, **Box 5**). Although the presence of concerning features may identify patients more likely to have an organic disease, most patients will ultimately have a negative evaluation result. Thus, the value of concerning features lies in their negative, rather than their positive, predictive value. Evidence suggests that a diagnosis of IBS can be confidently made for patients who fulfill symptom-based criteria and have no concerning features because the yield of extensive diagnostic testing is low.[42] Nonetheless, most health care professionals view IBS as a diagnosis of exclusion[43] and are uncomfortable relying solely on symptoms to diagnose it.

There are several diseases that should be considered in patients with IBS symptoms. A meta-analysis of 5 studies found a 4-fold

Box 4. Commonly Used Treatments That Can Exacerbate Irritable Bowel Syndrome Symptoms

Over-the-Counter
Antihistamines
Calcium
Iron
Magnesium
Nonsteroidal anti-inflammatory drugs
Wheat bran

Prescription
Antibiotics
Antidepressants
Antiparkinsonian drugs
Antipsychotics
Calcium-channel blockers
Diuretics
Metformin
Opioids
Sympathomimetics

Box 5. Diagnostic Testing for Patients With Suspected Irritable Bowel Syndrome (IBS) and No Concerning Features

All IBS Subtypes
Complete blood cell count
Age-appropriate colorectal cancer screening

IBS With Diarrhea
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
When colonoscopy performed, obtain random biopsies
SeHCAT, fecal bile acids, or serum C_4 where available

IBS, Mixed
C-reactive protein or fecal calprotectin
IgA TtG +/− quantitative IgA
Stool diary
Consider abdominal radiography to evaluate for stool accumulation

IBS With Constipation
If severe or medically refractory, refer to gastroenterology specialist for physiologic testing

Abbreviations: SeHCAT, tauroselcholic (selenium 75) acid; TtG, tissue translutaminase.

increased likelihood of biopsy-proven celiac disease in patients with IBS symptoms.[44] The prevalence of celiac disease in these patients varies by region, and although studies from Europe have demonstrated a higher prevalence of the disease, those from the United States have not.[45] Decision analysis suggests that routine screening for celiac disease in IBS patients becomes cost-effective at a prevalence of greater than or equal to 1%.[46] Given the potential long-term consequences of missing celiac disease, clinicians caring for patients with IBS should have a low threshold to screen for it, particularly in individuals with IBS-D.[41]

Recent literature has identified that a small subset of patients with suspected IBS-D have microscopic colitis. A recent case-control study found that age older than 50 years, nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new drugs, and comorbid autoimmune diseases were associated with an increased risk of microscopic colitis (Box 2).[47] When colonoscopy is performed in patients with suspected IBS-D, random colon biopsies should be performed to rule out microscopic colitis (Box 5).[41]

Inflammatory bowel diseases, including ulcerative colitis and Crohn disease, are of concern when a patient with IBS symptoms is evaluated. Even low-grade inflammation could alter permeability and sensitize visceral afferent neurons, leading to alterations in motility and visceral sensation.[18] Studies suggest that more than a third of patients with inflammatory bowel disease fulfill the Rome criteria for IBS.[18] It is unclear how many patients with inflammatory bowel disease and overlapping IBS symptoms have concerning features (Box 2). From a pragmatic standpoint, the important question is how often inflammatory bowel disease is ultimately identified in patients who have typical IBS symptoms and no concerning features. A prospective US study that included more than 900 nonconstipated IBS patients and healthy controls undergoing colonoscopy found inflammatory bowel disease in less than 1% of IBS patients and none of the controls.[48] These data argue against routine colonoscopy in patients with typical IBS symptoms and no concerning features. Noninvasive biomarkers may provide a more cost-effective means by which to screen for inflammatory bowel disease than colonoscopy. A recent systematic review and meta-analysis suggested that fecal calprotectin, a biochemical assay for intestinal inflammation, was effective and cost-effective in identifying inflammatory bowel disease.[49] Another systematic review and meta-analysis found that a C-reactive protein level of less than 0.5 mg/dL or fecal calprotectin level of less than 40 µg/g conferred a less than 1% risk of inflammatory bowel disease in patients with typical IBS symptoms.[50]

Perfusion of bile acids into the colon stimulates water and electrolyte secretion and accelerates transit.[51] Evidence of bile acid malabsorption may be present in up to a third of patients with IBS-D symptoms.[52] At present, clinicians can assess for bile acid malabsorption by instituting an empirical trial with a bile acid sequestrant. Several tests have been developed to identify such malabsorption, including the SeHCAT (tauroselcholic [selenium 75] acid) retention test, serum C4 measurement, and fecal bile acid measurement. However, these tests are not widely available in the United States. It is hoped that eventually bile acid malabsorption testing will identify IBS-D patients more likely to benefit from a bile acid sequestrant.

For IBS-C patients, colorectal cancer is a common concern. A meta-analysis that included 8 cross-sectional surveys found that constipation was actually associated with a lower prevalence of colorectal cancer (odds ratio, 0.56; 95% CI, 0.36-0.89). This analysis also found no significant increase in colorectal cancer risk among constipated patients vs nonconstipated controls in 3 cohort studies (odds ratio, 0.80; 95% CI, 0.61-1.04).[53] However, a more recent case-control study found that patients with chronic constipation have a significantly higher prevalence and incidence of colorectal cancer and benign colorectal neoplasms.[54] The limited prospective literature suggests that the risk of colorectal cancer is less than 1% in patients

Table. Summary of Therapies for Irritable Bowel Syndrome[a]

Treatment	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Over-the-Counter			
Fiber: psyllium	Moderate	Best suited for IBS-C	Bloating, gas
Laxatives: polyethylene glycol	Very low	Beneficial for constipation but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidiarrheals: loperamide	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Low	Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics	Similar to placebo
Antispasmodics: peppermint oil	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription			
Antidepressants: TCAs, SSRIs, SNRIs	High	TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents			
Linaclotide	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Lubiprostone	Moderate	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaximin	Moderate	Improves global symptoms, pain, and bloating in nonconstipated IBS patients	Similar to placebo
5-HT_3 receptor antagonists: alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other Therapies			
Psychological/behavioral therapy	Very low	Benefits for global IBS symptoms in all subgroups	Similar to placebo

Abbreviations: GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Quality of Evidence were taken from Ford et al.[59] Quality of the evidence was reported as very low, low, moderate, or high based on the number and quality of available clinical trials and reproducibility of the results. Evidence judged to be of very low quality was from case series and nonrandomized trials while evidence judged to be of high quality was taken from randomized placebo-controlled trials with reproducible results.

with typical IBS symptoms and no concerning features and not increased compared with that in healthy controls. As such, in patients with typical IBS symptoms and no concerning features, age-appropriate colorectal cancer screening is the most logical recommendation.

An underrecognized condition in patients with IBS-C symptoms is dyssynergic defecation, a constipation-associated condition that arises from the inability to coordinate the abdominal wall, anal sphincter, and pelvic floor muscles in a way that enables normal defecation.[55] Although a sense of incomplete evacuation after a bowel movement or the need for digital maneuvers to facilitate defecation may increase the likelihood of dyssynergia, symptoms generally do not accurately identify affected patients.[56] Dyssynergia can cause abdominal symptoms such as pain, discomfort, and bloating, which are relevant to IBS-C. Preliminary data suggest that correction of dyssynergia with biofeedback can improve both bowel and abdominal symptoms.[57] Thus, patients with medically refractory IBS-C symptoms should be referred to a specialist for evaluation of dyssynergia with a digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging.

Management

General Management Recommendations

A trusting patient-physician relationship is the cornerstone of managing IBS patients. Actively listening, not interrupting, using empathy, setting realistic expectations ("helping" rather than "curing"), and using nonverbal techniques such as making eye contact, nodding, leaning forward, and using open body posture can help build this relationship.[58] The clinician must understand the patient's goals for the visit and avoid focusing only on the gastrointestinal symptoms. Performing a physical examination establishes the ritual of touch, which many patients identify with a thorough and caring physician. It is critical to assign a confident diagnosis and provide education regarding the causes, natural history, and treatment of IBS.

Because IBS is a symptom-based disorder, treatments can address abdominal symptoms such as pain, cramping, bloating, or bowel symptoms, including diarrhea and constipation (Box 2). Traditionally, first-line IBS therapies have focused on over-the-counter medications aimed at improving diarrhea (eg, loperamide, probiotics) or constipation (eg, fiber supplements, laxatives). Benefits of this strategy include improving altered bowel habits, widespread availability, low cost, and an excellent safety record. However, over-the-counter medications offer little benefit for global, or overall, IBS symptoms or abdominal symptoms such as pain and bloating. The **Table** provides a summary of commonly used IBS treatments, along with recently published recommendations and evidence quality assessments from the American College of Gastroenterology Functional Bowel Disorders Task Force.[59] During the last 5 years, lifestyle and dietary interventions have become an increasingly important first-line treatment option.

Exercise

Physically active individuals move their bowels more often and have more rapid colon transit than sedentary individuals.[60] Further-

more, a randomized clinical trial found that a structured exercise intervention led to greater improvements in overall IBS symptoms than usual care.[61] Thus, IBS patients should be encouraged to increase their physical activity. A simple recommendation is to take a 20-minute walk (roughly 1 mile) each day. Distance and pace can be gradually increased as tolerated.

Diet

Patients often associate their IBS symptoms with eating a meal. Up to 90% of IBS patients restrict their diet to prevent or improve their symptoms.[62] True food allergies are uncommon in IBS. On the other hand, food intolerances or sensitivities are frequently reported. At present, there is emerging evidence that supports diets for IBS patients that are gluten free and low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).

The effect of gluten was assessed by a randomized, double-blind, placebo-controlled, rechallenge trial in 34 IBS patients with a history of gluten sensitivity.[63] During 6 weeks, overall IBS symptoms were not adequately controlled in 68% of patients receiving gluten vs 40% receiving a gluten-free diet ($P < .001$). Gluten worsened pain, bloating, and stool consistency, as well as "tiredness." Another study in IBS-D patients reported increased stool frequency, as well as altered gut permeability and immune activation, in the presence of gluten.[64] These data have led some to conclude that gluten is the primary cause of symptoms after ingestion of wheat. However, wheat contains fructans and other proteins that might also cause symptoms in IBS patients. In a recent Australian study of 37 IBS patients with wheat sensitivity, symptom relief was more closely associated with exclusion of poorly absorbed carbohydrates than gluten.[65] It is also likely that widespread negative media reports about gluten have increased the chance of a "nocebo" response, contributing to the perceived negative effects of eating gluten-containing foods.

Short-chain, poorly absorbed, highly fermentable carbohydrates are collectively known as FODMAPs and are found in such foods as wheat, onions, some fruits and vegetables, sorbitol, and some dairy. FODMAPs lead to increased small intestinal and colonic water secretion and fermentation, which causes increased production of short-chain fatty acids and gas.[66] Aside from increased flatulence, FODMAPs do not cause gastrointestinal symptoms in healthy adults.[67] Conversely, FODMAPs are an important trigger of meal-related symptoms in IBS patients, possibly as a consequence of underlying abnormalities in gut physiology and visceral sensation.[29] A randomized clinical trial in 30 IBS patients found lower overall symptom scores on the low-FODMAP diet vs a typical Australian diet ($P < .001$).[67] Seventy percent of IBS patients felt better while receiving the low-FODMAP diet regardless of IBS subtype. Responders to full FODMAP exclusion should gradually reintroduce FODMAP-containing foods to identify the level of dietary restriction needed to maintain symptom benefit. There are currently few long-term efficacy or safety data for the low-FODMAP diet.

Given the rapidly expanding role of dietary intervention in the primary management of IBS and other gastrointestinal conditions, it is becoming increasingly important for clinicians to become educated and to integrate a trained registered dietitian into the health care team.

Medical Treatments for IBS-D

Antidiarrheals

Antidiarrheal medications such as loperamide inhibit peristalsis, prolong gut transit, reduce fecal volume, and are often used as first-line agents in patients with IBS-D. Two randomized trials enrolling IBS-D and IBS-M patients found no benefit of loperamide over placebo for overall IBS symptoms.[59] However, loperamide reduces stool frequency, increases stool consistency, and can be used prophylactically when a patient anticipates diarrhea. When used long term, loperamide is preferred to diphenoxylate or atropine because it does not cross the blood-brain barrier and thus is less subject to habituation. In practice, many gastroenterologists use bile acid sequestrants such as cholestyramine and colesevelam to treat diarrhea. These agents have not been evaluated in rigorous, randomized trials with IBS patients.

Serotonin Agents: 5-HT_3 Receptor Antagonists

The gut hormone serotonin influences gastrointestinal motility and visceral sensation.[68] Alosetron is a 5-HT_3 antagonist approved in the United States for treating women with severe, disabling IBS-D that has not responded to traditional medical therapies. Alosetron (0.5-1 mg once to twice per day) improves global and individual IBS-D symptoms in women and men for up to a year, with a therapeutic gain over placebo of approximately 15%. Dose-dependent constipation and idiosyncratic ischemic colitis are potential adverse effects of alosetron that have led to a risk management plan requiring US patients and prescribers to acknowledge the risks before dispensation of the medication.[69]

Ondansetron, a 5-HT_3 antagonist that is less potent than alosetron, has been shown to benefit IBS-D in a recent randomized, double-blind, placebo-controlled, crossover study.[70] Ondansetron (4-8 mg 1-3 times per day) significantly improved stool consistency, global IBS symptoms, urgency, stool frequency, and bloating (all comparisons, $P \leq .002$) but not pain.

Antispasmodics

Antispasmodics include drugs with anticholinergic or calcium-channel blocking properties that may improve IBS symptoms by relaxing gut smooth muscle. Acknowledging the poor quality of many trials, a 2011 Cochrane review reported benefits of antispasmodics over placebo for abdominal pain and global assessment.[71] The American College of Gastroenterology Functional Bowel Disorders Task Force recently concluded that "certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS."[59] Because some IBS patients have an exaggerated gastrocolonic reflex that is in part cholinergically mediated,[72] these drugs may be best suited for postprandial abdominal cramping and loose stools. Dose-dependent adverse events, including constipation, fatigue, dry mouth, dizziness, and blurred vision, may occur. Anticholinergics should be avoided in the elderly.

Peppermint oil, which is available over the counter, possesses calcium-channel blocking properties and thus is classified as an antispasmodic. A number of small clinical trials suggest that enteric peppermint oil (187-225 mg 3 times daily) benefits some IBS patients.[73] Although peppermint oil is typically well tolerated, some patients may experience reflux symptoms.[73]

Medical Treatments for IBS-C

Fiber Supplements

The efficacy of fiber for treating IBS has been summarized in recent reviews.[26,74] The most recent meta-analysis reported modest benefits with fiber for global IBS symptoms (relative risk, 0.86; 95% CI, 0.80-0.94; number needed to treat, 10).[74] In a subgroup analysis, soluble fiber (psyllium and ispaghula husk; relative risk, 0.84; 95% CI, 0.73-0.94) but not insoluble fiber (wheat bran) was associated with improved IBS symptoms. Benefits of fiber appear most robust in patients with IBS-C rather than IBS-D. Fiber, which is often used as a first-line therapy, should be started at a nominal dose and gradually titrated upward during weeks to a total daily intake of 20 to 30 g. Wheat bran contains fructans, which, like other FODMAPs, can exacerbate IBS symptoms; thus, wheat bran should be avoided in IBS patients.[26]

Laxative Agents

Osmotic laxatives such as polyethylene glycol are frequently recommended as first-line therapy for IBS-C patients. Clinical trials have demonstrated that it improves bowel complaints, including stool frequency and consistency, but does not reliably improve abdominal pain or bloating.[75] The usual starting dose is 17 g in juice or water, with dose escalation dictated by clinical response. Polyethylene glycol is typically well tolerated but can cause dose-dependent bloating, gas, and loose stools.

Stimulant laxatives are also commonly used in IBS-C patients. Although efficacy has been demonstrated in patients with chronic constipation,[76] to our knowledge there are no randomized, controlled trials in IBS-C patients. Relevant to IBS, the most common adverse effects are abdominal pain and cramping.

Prosecretory Agents

Luminally acting prosecretory agents have been evaluated in IBS-C patients. Lubiprostone is a chloride-channel (ClC-2) activator that stimulates intestinal fluid secretion and improves global, bowel, and abdominal symptoms in IBS-C patients.[77] In 2 phase 3 trials (1711 IBS-C patients), a significantly higher percentage of patients treated with lubiprostone 8 µg twice daily responded compared with those treated with placebo (17.9% vs 10.1%; $P = .001$).[78] A higher dosage of 24 µg has proven effective in patients with chronic idiopathic constipation. To limit dose-dependent nausea (8% with an 8-µg dose and 33% with a 24-µg dose), lubiprostone should be received with food.

Linaclotide is a guanylate cyclase-C agonist that increases production of cyclic guanosine monophosphate. Intracellularly, cyclic guanosine monophosphate increases intestinal chloride secretion via the cystic fibrosis transmembrane regulator, whereas extracellularly it reduces firing of visceral afferent pain fibers.[79] A 2013 meta-analysis that included 3 rigorous randomized clinical trials in IBS-C patients reported a relative risk for response to linaclotide (290 µg once daily) vs placebo of 1.95 (95% CI, 1.3-2.9) and a number needed to treat of 7 (95% CI, 5-11).[80] The maximum benefit for stool frequency occurs within a week of treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks to maximally improve. Diarrhea is the most common adverse effect with linaclotide, reported by 20% of patients.[81] Linaclotide should be received 30 to 60 minutes before breakfast to reduce the likelihood of diarrhea.

Modification of the Microbiota: Probiotics and Antibiotics

Probiotics are live bacteria that, when consumed in sufficient quantities, confer a health benefit to the host. Prebiotics are nutrients, usually carbohydrates, that encourage the growth of probiotic bacteria. Synbiotics are combinations of prebiotics and probiotics. Postbiotics consist of extracts from dead or lysed bacteria. The most robust data have evaluated the role of probiotics for IBS. In a recent meta-analysis including 35 randomized clinical trials, probiotics as a group improved global IBS symptoms (relative risk, 0.79; 95% CI, 0.70-0.89; number needed to treat, 7; 95% CI, 4-12.5), abdominal pain, bloating, and flatulence.[59] However, given the differences in probiotic preparations evaluated, data derived from grouping or directly comparing trials should be interpreted with caution.[82] Higher-quality studies have tended to demonstrate less of a treatment effect. Thus, the current literature does not allow recommendations regarding specific probiotic preparations for IBS.

Rifaximin is a poorly absorbed, broad-spectrum antibiotic that has been evaluated in IBS patients. A recent meta-analysis that included 5 randomized clinical trials that enrolled predominantly nonconstipated IBS patients demonstrated therapeutic gains of 9% to 10% for global symptoms (odds ratio, 1.57; 95% CI, 1.22-2.01) and bloating (odds ratio, 1.55; 95% CI, 1.23-1.96).[83] The 2 phase 3 trials in nonconstipated IBS patients used rifaximin 550 mg 3 times daily for 14 days. Clinical experience suggests that many rifaximin responders will eventually develop recurrent IBS symptoms. Recently released data from a large re-treatment trial suggest that second and third courses yield efficacy similar to that of the first course of rifaximin.[84] The role of other antibiotics in IBS treatment remains unknown, although antimicrobial resistance with repeated courses of systemically absorbed antibiotics may be a concern.

Centrally Acting Interventions

Antidepressants

Because of their effects on pain perception, mood, and motility, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. The efficacy of tricyclic antidepressants, selective serotonin-reuptake inhibitors, and, to a lesser extent, selective norepinephrine-reuptake inhibitors has been evaluated in IBS patients.[85] A meta-analysis identified 17 randomized controlled trials that enrolled 1084 IBS patients who were treated with antidepressants or placebo.[85] Collectively, antidepressants were effective for abdominal pain, with a relative risk of remaining symptomatic of 0.62 (95% CI, 0.43-0.88) and a number needed to treat of 4 (95% CI, 3-6). A subgroup analysis reported a number needed to treat of 4 for both tricyclic antidepressants and selective serotonin-reuptake inhibitors. Adverse events occurred more often in patients receiving an antidepressant (number needed to harm, 9; 95% CI, 5-111). Tricyclic antidepressants can cause dose-dependent constipation, dry mouth and eyes, drowsiness, weight gain, and QT-interval prolongation. Selective serotonin-reuptake inhibitors can cause sexual dysfunction, agitation, nausea, drowsiness, and diarrhea. Although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, there are few data addressing their efficacy for IBS.[86]

The adverse event profiles of different antidepressants can be leveraged to address different IBS subtypes.[87] For example, because tricyclic antidepressants can cause constipation, they may be best suited to IBS-D patients, whereas the prokinetic effects of se-

lective serotonin-reuptake inhibitors might make them a better choice for IBS-C patients. Similarly, tricyclic antidepressants might be a better choice for patients with insomnia, anorexia, or weight loss. On the other hand, selective serotonin-reuptake inhibitors might be a better choice for patients with significant anxiety. When a tricyclic antidepressant is selected to treat IBS, low doses (10-25 mg) should be started at bedtime and gradually titrated upward according to symptom response and tolerability. Selective serotonin-reuptake inhibitors are typically started at the lower range of standard dosing.

Psychological Therapies

Psychological therapies provide an alternative or adjunctive therapy for IBS patients. In a recent meta-analysis, 32 separate trials of highly variable quality, involving more than 2000 patients, evaluated 10 different "psychological therapies,"[85] which were more effective than control therapies, with a number needed to treat of 4 (95% CI, 3-5). In a subgroup analysis, similar numbers needed to treat were reported for cognitive behavioral therapy, hypnotherapy, multicomponent psychotherapy, and dynamic psychotherapy but not other techniques. Despite these encouraging results, variable third-party reimbursement, a lack of clinicians, and poor patient and clinician acceptance have limited widespread adoption of these therapies in clinical practice. Access to behavioral therapy may improve with the development of book-, Internet-, or application-based behavioral programs.[88,89]

Complementary and Alternative Medicine

Despite the paucity of evidence, many IBS patients use complementary and alternative therapies.[90] A meta-analysis of 5 studies demonstrated that acupuncture was no better than sham acupuncture in improving symptoms or quality of life in IBS patients.[91] Studies evaluating Chinese herbal remedies for IBS have yielded mixed results.[90] A clear understanding of the active ingredients and a lack of standardization are significant challenges facing clinicians with an interest in herbal therapies.

Bottom-Line Clinical Messages

1. IBS is a common, symptom-based illness that is defined by the presence of abdominal pain or cramping in association with constipation, diarrhea, or both.
2. The diagnosis of IBS can be confidently established with the use of symptom-based criteria, the exclusion of concerning features, and the judicious use of diagnostic testing.
3. Concerning features that should prompt a more detailed evaluation include new onset of symptoms after age 50 years; unexplained weight loss; a family history of organic gastrointestinal diseases such as colon cancer, inflammatory bowel diseases, or celiac disease; gastrointestinal blood loss; and unexplained iron-deficiency anemia.
4. Successful management of patients with IBS begins with a trusting, positive, patient-physician relationship.
5. A holistic approach that embraces lifestyle changes, dietary interventions, medications, or behavioral strategies offers the greatest likelihood of sustained treatment benefit.

Conclusions

IBS remains an enigmatic cause of significant distress, morbidity, and disability. For the foreseeable future, the diagnosis of IBS will rely on the identification of characteristic symptoms and the exclusion of organic disease mimics. As science advances, it is hoped that the confident diagnosis of IBS will be aided by novel biomarkers that can either rule out specific organic diseases or rule in IBS. An improved understanding of the pathophysiology of IBS will also pave the way for novel nonpharmacologic and pharmacologic therapies. For now, it is important for physicians to understand the role of dietary, lifestyle, and behavioral modification either with or without medical treatments for IBS.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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ORIGINAL CONTRIBUTION

Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis

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Abstract

Purpose This review provides an updated overview of observational and intervention studies investigating the effect of a low-FODMAP (fermentable oligo-, di- and monosaccharides, and polyols) diet (LFD) on gastrointestinal (GI) symptoms, quality of life (QoL), nutritional adequacy, and gut microbiome in irritable bowel syndrome (IBS) patients.

Methods We systematically searched available literature until October 2020 for studies that investigated the effect of LFDs on GI symptoms, QoL, nutritional adequacy, and the gut microbiome in IBS patients. The data were represented as standardized mean differences (SMD) for IBS severity, and as mean differences (MD) for IBS-QoL. Meta-analyses were performed for the quantitative analyses using random effects models with inverse variance weighing.

Results Twelve papers (nine parallel trials, three crossover studies) were included for the meta-analysis. The LFD reduced IBS severity by a moderate-to-large extent as compared to a control diet (SMD −0.66, 95% CI −0.88, −0.44, $I^2 = 54\%$). When analyzing only studies that used the validated IBS-SSS questionnaire, a mean reduction of 45 points (95% CI −77, −14; $I^2 = 89\%$) was observed. Subgroup analyses on adherence, age, intervention duration, IBS subtype, outcome measure, and risk of bias revealed no significantly different results. The LFD also increased IBS-QoL scores, when compared with a control diet (MD 4.93; 95% CI 1.77, 8.08; $I^2 = 42\%$).

Conclusions The low-FODMAP diet reduces GI symptoms and improves quality of life in IBS subjects as compared to control diets. Future work is required to obtain definitive answers regarding potential long-term effects of such diets on nutritional adequacy and the gut microbiome.

PROSPERO registration number CRD42020175157.

Keywords Low-FODMAP diet · Irritable bowel syndrome · Exclusion diet · Gastrointestinal symptoms

Abbreviations

CI	Confidence interval
FODMAP	Fermentable oligo-, di- and monosaccharides, and polyols
GI	Gastrointestinal
GRADE	Grading of recommendations, assessment, development and evaluations
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhea
IBS-M	Irritable bowel syndrome with mixed stool pattern
IBS-U	Unspecified irritable bowel syndrome
IBS-SSS	Irritable bowel syndrome severity scoring system
MD	Mean difference
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QoL	Quality of life
RCT	Randomized controlled trial
SD	Standard deviation
SE	Standard error
SMD	Standardized mean difference
NR	Not reported

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that is characterized by abdominal pain, bloating, and altered bowel habits [1]. It is the most commonly diagnosed GI disorder, estimated to affect approximately 11% of the global population [2], with an increased prevalence in women as compared to men [3]. IBS has repeatedly been demonstrated to both reduce quality of life (QoL) [4–6] and increase health care utilization [7–9], leading to a significant economic burden [8–10].

The complex pathophysiology of IBS is not yet fully understood, but is suggested to involve visceral hypersensitivity, low-grade digestive tract inflammation, changes in GI motility, gut microbiota, and the gut–brain axis [1, 11–15]. As a result of this, IBS treatments currently rely on multifactorial approaches that are primarily focused on treating symptoms [13, 14, 16, 17]. Both IBS patients and gastroenterologists have reported a strong association between consumption of specific foods and IBS-related symptoms [4, 18, 19], indicating the need for an effective dietary treatment strategy. As each IBS subtype presents itself with different symptoms, treatment should be based on IBS subtype and symptom severity [1]. The goal of treatment for IBS with predominantly diarrhea (IBS-D) is to reduce the excessive bowel movements, while treatment for IBS with predominantly constipation (IBS-C) will aim for regular bowel movements, each requiring different nutritional approaches [1]. Besides, general advice to IBS patients comprises eating healthily and in small portions, limiting intakes of gas-producing and fermentable foods, alcohol, fat, and spicy foods [1, 20]. Many patients also try diets like the gluten-free and lactose-free diet to relieve symptoms [19]. Yet, there is little evidence for the efficacy of these elimination diets in the absence of specific conditions like lactose or gluten intolerance or celiac disease, and therefore these diets are not generally recommended [19, 21, 22].

However, there is a growing body of evidence for the effectiveness of the low fermentable oligo-, di- and monosaccharides, and polyols (FODMAP) diet (LFD) in managing IBS symptoms [22, 23]. Currently, advisory bodies like the American College of Gastroenterology and the British Dietetic Association advise the LFD to be respectively first- and second-line treatment for IBS [24, 25]. The underlying hypothesis suggests that reducing the intake of these small, indigestible and often fermentable carbohydrates, reduces intestinal osmolarity and gas production; hence, helping to reduce GI symptoms [26, 27]. The LFD starts with a general phase that aims to eliminate all FODMAPs. If symptoms are successfully reduced within 6–8 weeks, specific groups of FODMAPs are reintroduced into the diet. This serves to identify which FODMAPs cause symptoms, so that patients can adapt a personalized long-term diet that effectively reduces IBS symptoms. Owing to its restrictive nature, however, there are concerns about the effect of the LFD on nutritional adequacy, intestinal microbiota, and health-related quality of life [28–31]. Therefore, the LFD should only be followed in consultation with a specialized dietitian.

Since the two most recent meta-analyses that were performed on the effect of an LFD on GI symptoms in IBS patients [22, 23], four new RCTs and two new cross-sectional studies have been published. The purpose of the current work is to provide an updated systematic review and meta-analysis of both observational and intervention studies that investigates the effect of a low-FODMAP diet, as compared to a control diet, on GI symptoms and quality of life in IBS patients.

Methods

The protocol for this systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO, registration number: CRD42020175157), and conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [32].

Search strategy

We systematically searched the electronic databases PubMed/Medline, SCOPUS, and Web of Science until October 1st 2020 for English language records. Titles, abstracts, and keywords were searched for variations and combinations of the following terms: FODMAP(s), saccharides, oligosaccharide, disaccharide, monosaccharide, galacto-oligosaccharides, fructan(s), fructose, galactans, lactose, polyol(s), sorbitol, mannitol, xylitol, maltitol, sweetener(s), sweetening agent, IBS, irritable bowel syndrome, and irritable colon. Separate searches including additional terms related to gut microbiome and nutritional adequacy were also performed (full PubMed search syntaxes in the Supplementary Materials). Intervention and observational studies were included when they respectively examined the effect of the LFD or assessed the association between FODMAP content in the diet and GI complaints or IBS prevalence in adult human subjects with IBS diagnosed according to the Rome III or IV criteria [11, 33].

Papers were excluded when they had an unsuitable intervention (e.g., a co-intervention from which the effects of an LFD could not be distinguished) or control diet, were conducted in children, non-IBS patients or IBS patients

with significant clinical co-morbidities, were conference abstracts, or when English text was unavailable. In the case of multiple papers referencing the same study, relevant data were extracted from both papers and included as a single study in the analysis.

Screening and selection of trials

The systematic search was followed by a two-step screening and selection process. During the first step, titles, abstracts, and keywords of publications were screened separately by two of the authors (ASL and AG) to identify potentially eligible studies. During the second step, the full texts of these publications were examined to gauge eligibility based on the stated inclusion criteria. In cases of inter-reviewer disagreement, questions on study eligibility were resolved through consensus and consultation with the other co-author (AB).

Outcome assessment

The primary outcome of interest was IBS symptom severity, preferably assessed by the widely used and validated IBS Severity Scoring System (IBS-SSS) [34]. The IBS-SSS questionnaire assesses the intensity of GI symptoms during a 10-day period and focuses on abdominal pain, distension, stool frequency and consistency, and interference with daily life. Each of these items is scored on a 0–100 visual analog scale, adding up to a total sum score of 0–500, with higher scores indicating more severe symptoms [34]. Studies using other measures of symptom severity, both validated measures and nonvalidated VAS and Likert scales, were included as well. When no assessment of the overall symptom severity was reported, abdominal pain was used as an outcome of interest [22].

The secondary outcomes of interest were quality of life, gut microbiome effects and impact on measures of nutritional adequacy. Quality of life was measured by the validated IBS-QoL questionnaire [35]. The IBS-QoL questionnaire consists of 34 questions regarding dysphoria, interference, body image, health worry, food avoidance, social reaction, sexual, relationships. The results are averaged and transformed to a 0–100 scale, with increasing scores indicating a better QoL [35]. Owing to heterogeneity in methodology and reporting of data, it was deemed inappropriate to conduct meta-analyses of the gut microbiome and nutritional adequacy data. These outcomes were therefore included as part of the qualitative analysis.

Data extraction and quantification

Data extraction was performed by two authors (ASL, AG) and consisted of information on the year of publication, country of origin, study design, duration, intervention diet, control diet, adherence to the diets, number of cases, number of controls, total sample size, IBS diagnostic criteria, mean age and gender, and IBS subtype distribution. The means (mean value at the end of the intervention and end of control period, respectively) and standard deviations between symptom severity measures and IBS-QoL before and after intervention were collected. If no means and standard deviations were reported in the text, the data were extracted from tables or graphs (using a web-based plot digitizing tool [36]). When these data were not available and whenever possible, the 95% CIs and P values were used to calculate means and standard deviations [37]. Where median values and ranges were reported, they were converted to mean values and standard deviations according to the conversion formulas of Wan et al. and Luo et al. [38, 39]. This was done in one case [40]. Where no end values were reported, change from baseline data were used instead [41, 42]. Where insufficient data were available to calculate or extract the mean and standard deviation, the study was excluded from analysis [43].

Data synthesis and statistical analysis

For the primary outcome, standardized mean differences (SMD) were calculated to allow comparison between the variety of outcome measures used in the studies, and to prevent unnecessary exclusion of study data. The SMD is a unitless measure that can be interpreted as a small, moderate or large magnitude of effect [44]. Meta-analyses were conducted using a random effects model with inverse variance weighing [45]. Where enough data were available (minimum of four studies per subgroup), the potential effects of predefined covariates (IBS subtype, intervention duration, sex, age) on the change in IBS severity measures were examined by means of subgroup analyses. The I^2 statistic was inspected to assess the extent of possible heterogeneity with I^2 values of 25, 50, and 75% considered to be low-, moderate-, and high-level heterogeneity respectively [46]. Data analysis was performed using Review Manager 5 (Version 5.4, Cochrane).

Risk of bias assessment

Publication bias was investigated through visual inspection of funnel plots and Egger's regression test (with $P < 0.1$ indicating asymmetry) [47]. The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias [48]. For this purpose, seven different domains were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. For cross-sectional studies, we used an adapted version of

the Newcastle–Ottawa quality assessment scale [49]. The assessments were carried out independently by two authors (ASL and AG), and differences resolved by consensus.

Results

Quantitative analysis

Included trial characteristics

A total of 5751 records was identified through database searching. After duplicate removal, 4725 records were screened, leading a full-text assessment of 70 studies. After exclusion of 56 studies, 14 original studies were included in the review (Fig. 1). Of these, 12 original parallel or crossover trials reported on IBS symptom severity outcomes (Table 1) and were included in the meta-analysis. The remaining two cross-sectional studies are described in Table 2. One post hoc analysis reported quality of life data from the same study population as a study that was already included. Relevant data were extracted, and the paper was excluded [50].

A total of 772 subjects took part in the nine parallel and three crossover trials that investigated the effect of an LFD on GI symptoms in IBS patients. The number of participants per study ranged from 30 to 104. The study duration ranged from 4 days to 3 months. The mean age ranged from 29 to 51 years. Two studies were controlled diet interventions that provided almost all food to subjects during the intervention. Subjects in the remaining ten studies received dietary education as an intervention. The control diets, provided or prescribed, comprised a traditional IBS diet ($n=4$), the subjects habitual diet ($n=2$), typical diet for the country where the study was carried out ($n=2$), high-FODMAP diet ($n=2$),

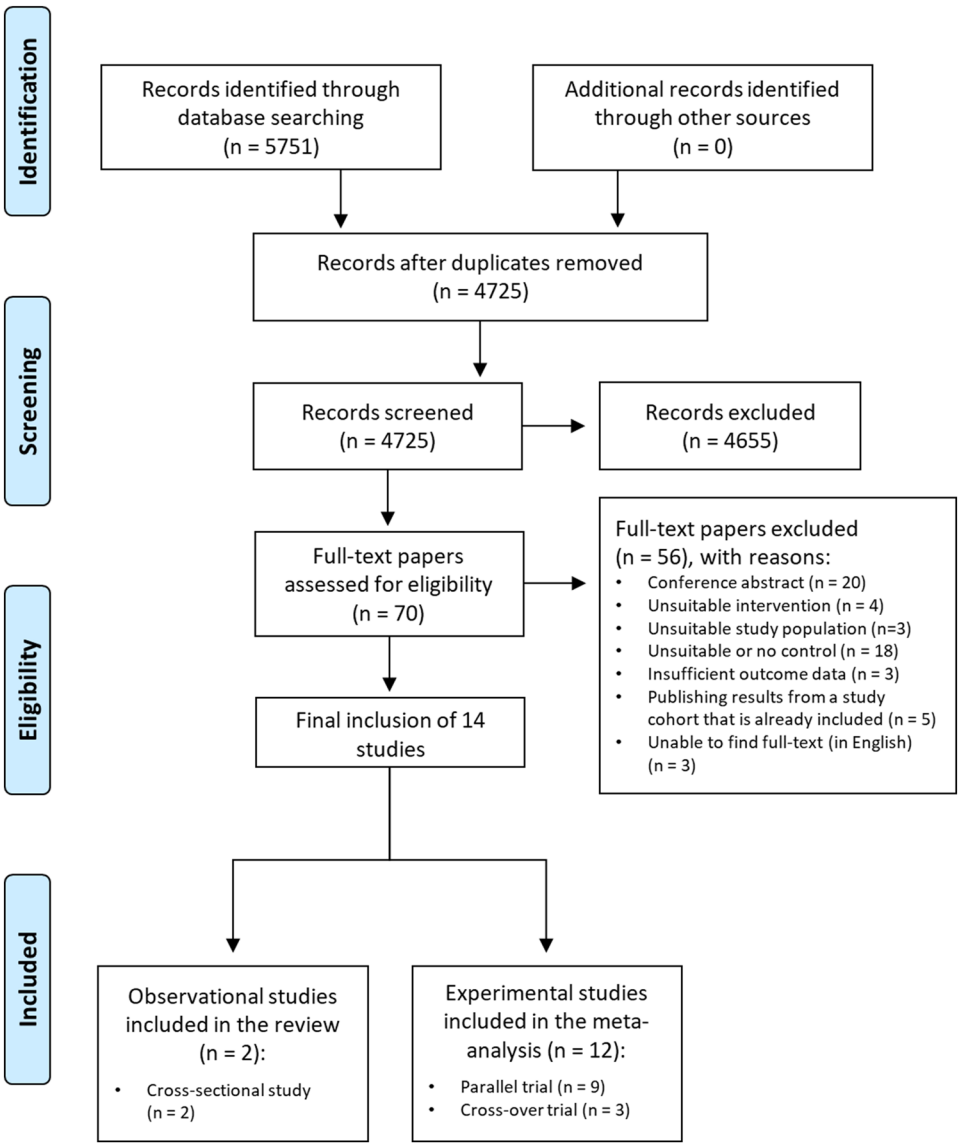

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection procedure

Table 1 Characteristics of experimental studies included in the meta-analysis

First author, year (country)	Study duration	Total case/controls[a]	Type of treatment: intervention vs. control	Age (years)[b]	Female (%)[b]	Predominant IBS subtype (%)[b]	Results
Bohn, 2015 [63] (Sweden)	4 weeks	33/34	Dietary education: LFD vs. traditional IBS diet (NICE and BDA)	42.5	81.3	IBS-M (47)	No significant difference in IBS-SSS was observed between the LFD and control group (246 vs. 23, $P=0.62$)
Eswaran, 2016 [70] (USA)	4 weeks	43/39	Dietary education: LFD vs. traditional IBS diet (NICE)	42.6	70.7	IBS-D (100)	The mean abdominal pain score decreased to 3.4 in the LFD group vs. 4.4 in the mNICE group ($P=0.005$), and the IBS- QoL score increased to 69.3 for the LFD group vs. 59.4 for the mNICE group (P value not reported)
Halmos, 2014 [61] (Australia)	42 days	30/30	Provided diets: LFD vs. typical Australian diet (4.4 g oligosaccharides and 2.6 g polyols/day)	41.0	71.1	IBS-C (43)	Subjects reported lower mean VAS-scores (0–100) for GI symptoms when on an LFD compared to control: 22.8 vs. 44.9 ($P<0.001$)
Harvie, 2017 [52] (New Zealand)	3 months	23/27	Dietary education on LFD vs. no dietary education	41.8	86	IBS-D (64)	Subjects on the LFD had a lower mean IBS-SSS (128 vs. 206) and higher mean IBS-QoL (81 vs. 73) compared to control, after 3 months ($P<0.05$ in both for improvement)
McIntosh, 2017 [64] (Canada)	21 days	18/19	Dietary education: LFD vs. HFD	50.9	86.5	IBS-M (62)	Mean IBS-SSS decreased to 208 in the LFD group vs. 290 in the control group ($P=0.01$)
Ong, 2010 [40] (Australia)	4 days	15/15	Provided diets: LFD (9 g FODMAPs/day) vs. HFD (50 g/day)	40.8	73.3	IBS-C (47)	IBS symptom severity assessed by a self-rating Likert scale was reported to be lower during the LFD (median 2; range 0–7) than during HFD (6; 2–9)
Paduano, 2019 [53] (Italy)	12 weeks	34/28	Dietary education: LFD vs. balanced Mediterranean diet	28.6	83.3	IBS-D (52)	No significant differences were found between the LFD and control diet when looking at mean IBS-SSS (16 vs. 17, $P=0.44$) and IBS-QoL (83 vs. 81, $P=0.27$)
Patcharatrakul, 2019 [62] (Thailand)	4 weeks	30/32	Dietary education: personalized LFD vs. commonly recommended diet to reduce IBS symptoms	51.0	75.8	IBS-C (53)	The mean global IBS symptom severity score (VAS 0–100) after intervention was lower in the LFD group than the control group (38.5 ± 20 vs. 53.5 ± 19, $P<0.01$)

Table 1 (continued)

First author, year (country)	Study duration	Total case/controls[a]	Type of treatment: intervention vs. control	Age (years)[b]	Female (%)[b]	Predominant IBS subtype (%)[b]	Results
Pedersen, 2014 [41] (Denmark)	6 weeks	42/40	Dietary education: LFD including personalized reintroduction vs. unchanged Danish/Western diet	34.6	76.8	IBS-D (45)	There was a significantly greater reduction in mean IBS-SSS in the LFD group than in the control group (133 vs. 34, $P<0.01$). Mean IBS-QoL was not altered significantly (LFD: 8 vs. control: 0.1, $P=0.13$)
Staudacher, 2012 [66] (UK)	4 weeks	16/19	Dietary education: LFD vs. habitual diet	35.1	35.1	NR	The mean overall symptom severity score (0–3 scale) after intervention was lower in the LFD group than in the control group (1.1 vs. 1.7, $P<0.002$)
Staudacher, 2017 [69] (UK)	4 weeks	51/53	Dietary education: LFD vs. sham exclusion diet (comparable in number of restricted foods and difficulty)	34.4	68.6	IBS-D (67)	Mean IBS-SSS was significantly lower for patients on the LFD than the sham diet (173 vs. 224, $P=0.001$). No significant difference was observed between the groups for IBS-QoL (72.4 vs. 70.6, $P=0.057$)
Zahedi, 2018 [42] (Iran)	6 weeks	50/51	Dietary education: LFD (<0.5 g of FODMAPs per meal) vs. traditional IBS diet (BDA)	37.5	50.5	IBS-D (100)	Mean IBS-SSS decreased to a greater extent in the LFD group compared to control (108 vs. 149.8, $P=0.002$). No significant difference was observed between the groups for IBS-QOL (-7.3 vs. -5.35, $P=0.332$)

The data are represented as mean value unless indicated otherwise

BDA British Dietetic Association; *FODMAP* fermentable oligo-, di-, monosaccharides and polyols; *HFD* high-FODMAP diet; *IBS-C* irritable bowel syndrome with constipation; *IBS-D* irritable bowel syndrome with diarrhea; *IBS-M* irritable bowel syndrome with mixed stool pattern; *IBS-QoL* irritable bowel syndrome-associated quality of life; *IBS-SSS* irritable bowel syndrome severity scoring system; *LFD* low-FODMAP diet; *NICE* National Institute for Health and Care Excellence; *NR* not reported

[a]Numbers are retrieved from per-protocol data

[b]Numbers are retrieved from intention-to-treat data

Table 2 Characteristics of observational studies included in the qualitative synthesis

First author, year (country)	Study design	Number of subjects	Diagnostic criteria	Age (years)	Female (%)	Predominant IBS subtype (%)	Quality assessment[a] (number of stars[b])	Results
Lee, 2019 [18] (South Korea)	Cross-sectional	393	Validated modified Korean Rome III	49.4	61.8	IBS-D (43.6)	Poor (3)	High-FODMAP foods were reported by 43.5% of controls[c] and 63.4% of IBS subjects to induce GI symptoms
Pourmand, 2018 [51] (Iran)	Cross-sectional	3362 (number of confirmed IBS cases NR)	Unvalidated modified Persian Rome III	NR	NR	NR	Good (7)	No significant association was found between adherence to the LFD and IBS prevalence

The data are represented as mean value unless indicated otherwise

FODMAP fermentable oligo-, di-, monosaccharides, and polyols; *IBS-D* irritable bowel syndrome with diarrhea; *LFD* low-FODMAP diet; *NR* not reported

[a]According to an adapted Newcastle–Ottawa scale for cross-sectional studies [48]

[b]On a scale from 0 to 10

[c]The control group comprised of symptomatic and nonsymptomatic subjects

balanced Mediterranean diet ($n=1$), or a sham exclusion diet specifically designed for the study ($n=1$).

Effect of LFD on GI symptoms in IBS patients

The LFD was found to reduce IBS severity by a moderate to large extent as compared to a control diet (SMD −0.66, 95% CI −0.88, −0.44, $I^2=54\%$) (Fig. 2). When analyzing studies that used IBS-SSS only, a mean reduction of 45 points (95% CI −76.56, −13.69; $I^2=89\%$) was observed (Fig. 3).

One of the observational studies included in the qualitative analysis observed a larger proportion of IBS subjects to report high-FODMAP foods to induce GI symptoms, as compared to control subjects (63.4% vs. 43.5% respectively) [18] (Table 2). The other observational study reported no association between adherence to the LFD and IBS prevalence [51] (Table 2).

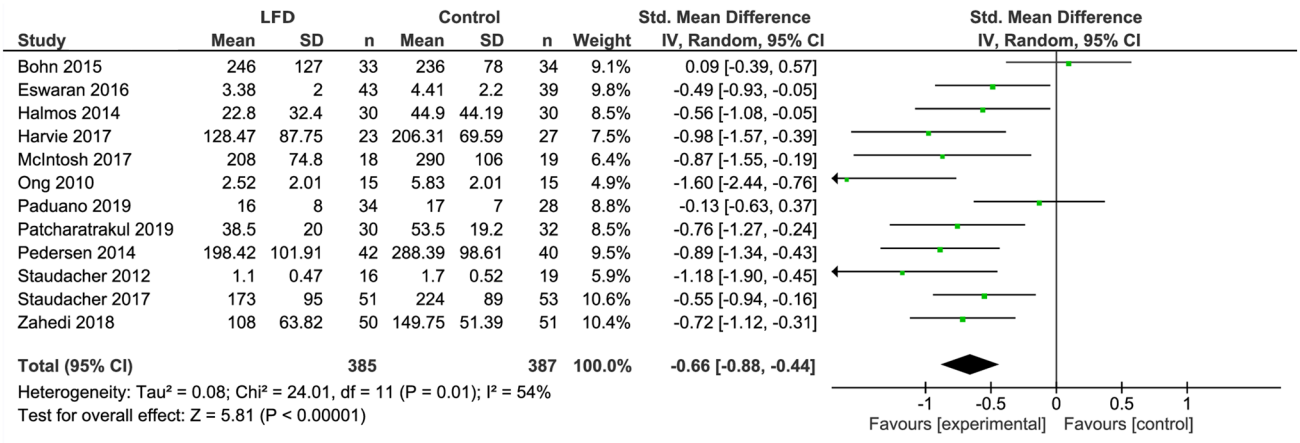

Fig. 2 Forest plot showing standardized mean differences for IBS severity outcome measures

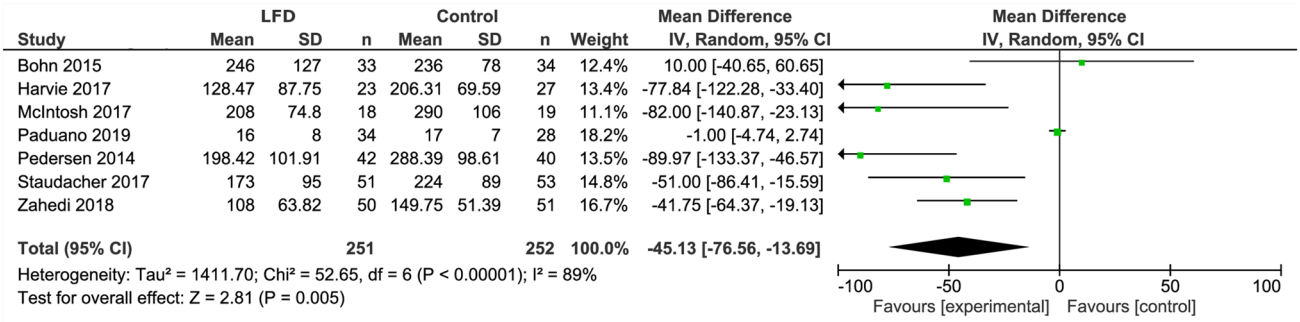

Fig. 3 Forest plot showing mean IBS-SSS scores for studies that used IBS-SSS as outcome

Effect of LFD on QoL in IBS patients

The LFD was associated with higher IBS-QoL scores when compared with a control diet (MD 4.93; 95% CI 1.77, 8.08; $I^2 = 42\%$) (Fig. 4).

Subgroup analyses

Subgroup analyses for age, outcome measure, and adherence revealed no statistically significant differences between subgroups (Table 3, Supplementary Figures 1–6). In all studied subgroups, the change in IBS symptom severity scores remained statistically significant (Table 3, Supplementary Figures 1–6).

Sensitivity analysis, assessment of potential biases, and heterogeneity

Sensitivity analyses, conducted by omitting every study from the meta-analysis, were carried out and did not significantly affect the results (Supplementary Tables 1 and 2). Overall, all included studies had some risk of bias, most notably assessed unclear in allocation concealment and blinding of participants, personnel and of outcome assessment (Supplementary Table 3). Three studies were judged to have a high risk of bias in at least two out of seven areas [41, 52, 53], which all at least include blinding of participants, personnel, and of outcome assessment. Excluding these studies in a subgroup analysis did not affect the SMD (Table 3).

Visual inspection of the funnel plot suggested some publication bias (Fig. 5), which was confirmed by Egger's regression test ($P = 0.087$). The pooled IBS severity measure differences showed moderate heterogeneity ($I^2 = 54\%$) between studies.

Qualitative analysis

Overviews of the systematic searches for studies investigating the effects of the LFD on gut microbiome and nutritional adequacy are presented in Supplementary Figures 7 and 8. For both outcomes, seven studies met the inclusion criteria and were included in the qualitative analysis.

Gut microbiome effects

The methodology employed for fecal microbial analyses varied across studies and included fluorescence in situ hybridization (FISH), quantitative real-time PCR and 16 s rRNA sequencing or combinations thereof.

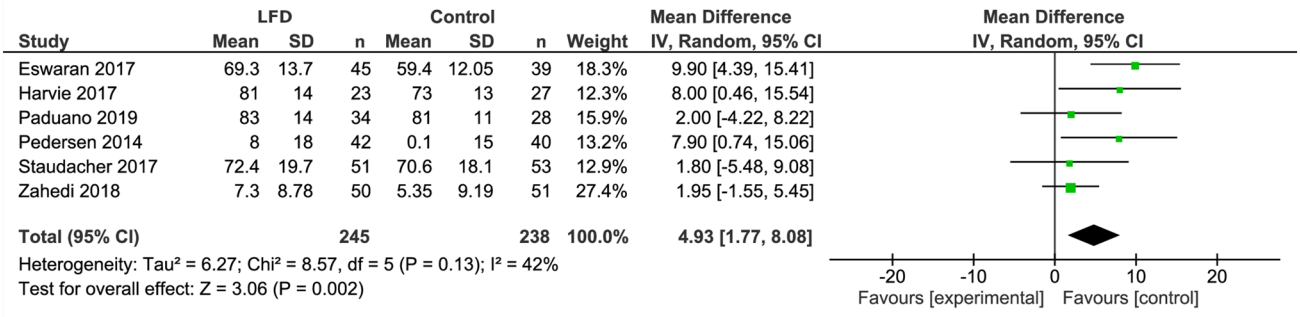

Fig. 4 Forest plot showing mean IBS-QoL values

Table 3 Results of subgroup analyses for different covariates

Covariate	Number of studies	Standardized mean difference	LL	UL	*P* value within group	*P* value between subgroups	I^2 (%)
Adherence	–	–	–	–	–	0.77	54
Reported adherence[a]	6	−0.63	−1.01	−0.24	0.001	–	66
Adherence not reported	6	−0.70	−0.96	−0.43	0.001	–	42
Age	–	–	–	–	–	0.40	54
Below median[b]	6	−0.76	−1.09	−0.43	0.001	–	59
Above median[b]	6	−0.56	−0.87	−0.25	0.001	–	52
Duration	–	–	–	–	–	0.59	50
Median[c]	5	−0.53	−0.88	−0.18	0.003	–	61
Above median[c]	5	−0.65	−0.93	−0.37	0.001	–	39
IBS subtype	–	–	–	–	–	–	–
Majority IBS-D	6	−0.62	−0.84	−0.39	0.001	–	30
Outcome measure	–	–	–	–	–	0.28	13.9
IBS-SSS	6	−0.56	−0.85	−0.27	0.001	–	61
Non-IBS-SSS	6	−0.81	−1.16	−0.46	0.001	–	44
Risk of bias	–	–	–	–	–	–	–
Low risk of bias	9	−0.66	−0.92	−0.40	0.001	–	55

IBS irritable bowel syndrome; *IBS-D* irritable bowel syndrome with diarrhea; *IBS-SSS* IBS symptom severity score; *LL* lower level of 95% confidence interval; *UL* upper level of 95% confidence interval

[a]Adherence was good in all studies that reported adherence

[b]Median age was 40.9 years

[c]Median duration was 4 weeks

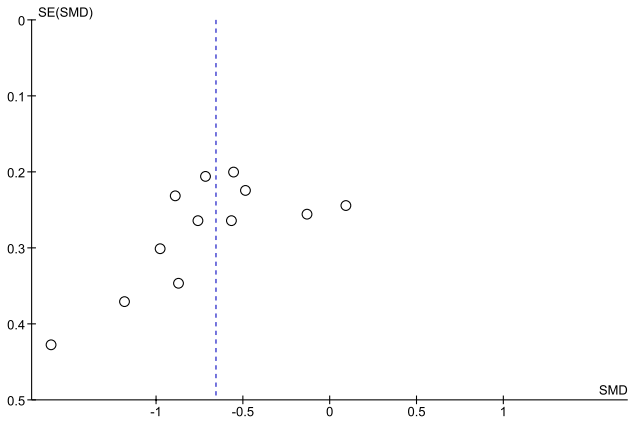

Fig. 5 Funnel plot used to assess risk of publication bias for IBS severity outcome measures

Five of the included studies reported measures of microbial diversity, six studies reported absolute or relative abundances of total bacteria and/or specific taxa and two studies determined a "dysbiosis index". In all five studies that measured it, no influence of the LFD measures on microbial diversity was found. However, in most studies, abundances of bifidobacteria and/or their overarching phylum, actinobacteria were reduced following LFD interventions (Table 4).

Nutritional adequacy

Studies reporting on the effects of the LFD on nutrient intake consisted of two post hoc analyses of previous RCTs, three observational studies and two RCTs that only analyzed changes in macronutrient intakes (Table 5).

In most studies, no differences in the majority of analyzed micronutrient intakes were found. Exceptions were small increases in intakes of vitamin A [54], β-carotene [55], B-vitamins [54–57], and selenium [57] after the LFD as compared to control or habitual diets. Conversely, small decreases in riboflavin [55, 56] and calcium [55] intake were also found.

One RCT found that an LFD intervention resulted in a lower proportion of patients meeting the DRIs for thiamin and iron as compared to control [56], whereas a post hoc analysis of two RCTs found no difference in the proportion of subjects meeting micronutrient DRIs when comparing LFD to control diets [57].

One cross-sectional study reported lower intakes of energy, and all measured food groups, macro- and micronutrients across all quintiles of increasing adherence to an LFD [51].

Table 4 Overview of studies assessing the effect of the LFD on gut microbiome

First author, year (country)	Study design	Number of IBS subjects	Intervention	Study duration	Methodology	Results
Halmos, 2015 [31] (Australia)	Crossover	27	LFD vs. baseline habitual diet vs. Australian diet	6 weeks	qPCR	↓ Total bacterial abundance ↓ *A. muciniphila, Bifidobacteria* absolute abundance ↓ *A. muciniphila,* relative abundance ↓ *Clostridium cluster IV* and *XIVa* absolute and relative abundance
Harvie, 2017 [52] (New Zealand)	Parallel	45	LFD vs. habitual diet	12 weeks	16S rRNA sequencing	↔ α- and β-diversity ↔ In any of 244 observed OTUs
Hustoft, 2017 [71] (Norway)	Crossover	27	LFD (maltodextrin supplement) vs. HFD (FOS)	20 days	GA-map™ Dysbiosis Test	vs. baseline: ↓ Actinobacteria abundance ↓ Bifidobacterium abundance ↓ Clostridium, *F. prausnitzii*, Megasphaera, Pediococcus abundance ↑ Dorea abundance
Bennet, 2018 [72] (Sweden)	Parallel	67	LFD vs. traditional IBS diet	4 weeks	GA-map™ Dysbiosis Test	↑ Dysbiosis Index ↓ Actinobacteria abundance ↓ Bifidobacteria abundance
McIntosh, 2017 [64] (Canada)	Parallel	37	LFD vs. HFD diet	3 weeks	16S rRNA sequencing	↔ α- and β-diversity ↑ Acintobacteria richness and diversity ↑ Firmicutes-, clostridiales richness (IBS-D and IBS-M only) ↓ Bifidobacterial relative abundance
Staudacher, 2012 [66] (UK)	Parallel	41	LFD vs. habitual diet	4 weeks	FISH	↔ Concentrations and proportions of total bacteria, *Bacteroides–Prevotella*, *E. rectale–C. coccoides, F. prausnitzii,* and Lactobacillus–Enterococcus ↓ Concentrations and proportions of bifidobacteria
Staudacher, 2017 [69] (UK)	Parallel	104	LFD vs. sham diet	4 weeks	qPCR and 16S rRNA sequencing	↔ α- and β-diversity ↓ Absolute- and relative abundance of bifidobacteria ↔ Relative abundance of lactobacilli and streptococci
Wilson, 2020 [73] (UK)	Parallel	41	LFD vs. sham diet	4 weeks	FISH and 16S rRNA sequencing	↔ α- and β-diversity ↓ Actinobacteria abundance ↔ Bifidobacteria abundance

All reported changes are for LFD vs. respective control situations

CTRL controls; *FISH* fluorescence in situ hybridization; *FODMAP* fermentable, oligo-, di-, mono-saccharides and polyols; *GOS* Galacto-oligosaccharides; *HFD* high-FODMAP diet; *IBS* irritable bowel syndrome; *LFD* low-FODMAP diet; *OTUs* operational taxonomic units; *qPCR* quantitative polymerase chain reaction; ↑ increase; ↓ decrease; ↔ no change

Discussion

This updated meta-analysis of 12 controlled human intervention studies found that the LFD reduced IBS severity by a moderate to large extent as compared to a control diet (SMD − 0.66, 95% CI − 0.88, − 0.44, $I^2 = 54\%$). Furthermore, the LFD also resulted in higher IBS-QoL scores when compared with a control diet (mean difference 4.93; 95% CI 1.77, 8.08; $I^2 = 42\%$). It should be noted that we used standardized mean differences to include studies that did not use the standard IBS-SSS as an outcome measure. As the SMD can only be interpreted in terms of

Table 5 Studies included to assess nutritional adequacy of the LFD

First author, year (country)	Study design	Number of IBS subjects	Intervention	Study duration	Methodology	Results
Eswaran, 2019 [56] (USA)	Parallel	78	LFD vs. traditional IBS diet (NICE)	4 weeks	3-day food diary (at baseline and last week of intervention period). Post hoc analysis of [70]	Reduction in energy-adjusted carbohydrate (−31.6 g/day), total sugar (− 17.4 g/day), sodium (− 0.5 g/day) (all $P<0.01$) and riboflavin (−0.2 mg/day) intake ($P<0.05$) vs. baseline, compared to no changes in traditional IBS diet; increase in energy-adjusted niacin (0.7 mg/day, $P<0.05$) and vit B6 (0.3 mg/day, $P<0.01$) intake vs. baseline, compared to no changes in traditional IBS diet; fewer patients met the DRIs for thiamin and iron in the LFD group, vs. fewer patients meeting the DRIs for calcium and copper in the control group
O'Keeffe, 2018 [54] (UK)	Prospective follow-up study	103	LFD vs. habitual diet	6–18 month follow-up after initial 6-week LFD	Semi-quantitative FFQ (at follow-up)	No statistically significant differences between groups at long-term follow-up for energy and (micro)nutrient intakes, except for higher folate (398 µg/day vs. 318 µg/day, P = 0.02) and vitamin A (2147 µg/day vs. 1429 µg/day, $P=0.045$) compared to habitual diet

Table 5 (continued)

First author, year (country)	Study design	Number of IBS subjects	Intervention	Study duration	Methodology	Results
Ostgaard, 2012 [55] (Norway)	Prospective follow-up study	114	LFD advice vs. no advice vs. healthy controls	2-year follow-up after LFD advice	Semi-quantitative FFQ (at follow-up)	No difference in calories or macronutrients between LFD guided patients, unguided patients and healthy controls; no difference in micronutrients between LFD guided and unguided patients; lower intakes of riboflavin (1.9 mg/day vs. 2.1 mg/day) and calcium (1065 mg/day vs. 1184 mg/day) and higher intakes of β-carotene (3.9 mg/day vs. 3.6 mg/day) and vitamin B6 (1.7 mg/day vs. 1.6 mg/day) for LFD guided patients vs. healthy controls
Pourmand, 2018 [51] (Iran)	Cross-sectional	3362 (number of confirmed IBS cases NR)	Quintiles of FODMAP intake	–	106-item semi-quantitative food frequency questionnaire	Individuals with the highest adherence to the low FODMAP diet had lower dietary intakes of all measured foods groups and (micro)nutrients ($P < 0.001$)

Table 5 (continued)

First author, year (country)	Study design	Number of IBS subjects	Intervention	Study duration	Methodology	Results
Staudacher, 2019 [57] (UK)	Parallel	130	LFD vs. habitual diet; LFD vs. sham exclusion diet	4 weeks	7-day food record (at baseline and last week of intervention period); diet quality according to Healthy Diet Indicator and Healthy Diet Score; Diet Diversity according to Diet Quality Index-Revised Dietary Diversity and Dietary Diversity Score Post hoc analysis of [66, 69]	Lower intake of starch vs. habitual control diet (109 g/day vs. 128 g/day, $P=0.03$); no difference in micronutrient intakes except for higher intake of vitamin B-12 vs. habitual and sham control diets (6.1 µg/day vs. 3.9 µg/day and 4.7 µg/day respectively, $P<0.01$) and higher intake of selenium vs. sham control diet (52 µg/day vs. 42 µg/day, $P=0.03$); no difference in proportion of patients meeting micronutrient DRIs; overall scores for diet quality were lower after low FODMAP advice vs. habitual control diet ($P<0.01$)
Only macronutrient data						
Böhn, 2015 [63] (Sweden)	Parallel	67	LFD vs. traditional IBS diet (NICE and BDA)	4 weeks	4-day food diary (at screening and during last week of intervention period)	Reduced mean intake of carbohydrates (159.1 g/day vs. 193.1 g/day, $P=0.007$) and dietary fiber (15.1 g vs. 20.2 g, $P=0.003$) vs. traditional IBS diet
Zahedi, 2018 [42] (Iran)	Parallel	101	LFD vs. traditional IBS diet (BDA)	6 weeks	3-day food diary (at baseline and last week of intervention period)	Reduced mean intake of carbohydrates (266.1 g/day vs. 360.9 g/day, $P<0.001$) and increased mean intake of fat (65.2 g/day vs. 51.4 g/day, $P=0.04$) vs. traditional IBS diet

BDA British Dietetic Association; *DRI* dietary reference intakes; *FFQ* food frequency questionnaire; *FODMAP* fermentable oligo-, di-, monosaccharides and polyols; *GI* gastrointestinal; *IBS* irritable bowel; *LFD* low-FODMAP diet; *NICE* National Institute for Health and Care Excellence; *QoL* quality of life

a small, moderate, or large effect, it limits the extent to which conclusions can be derived about clinical relevance of the demonstrated effect. However, when analyzing only studies that used the IBS-SSS as an outcome measure, a mean reduction of 45 points was found (95% CI − 77, − 14) when comparing subjects on the LFD to a control diet. A 50-point reduction in IBS-SSS score is typically considered to be associated with a clinically meaningful improvement [58]. Nevertheless, the LFD was found to have a moderate to high efficacy in reducing GI symptoms in IBS patients. Our findings are in line with the previous meta-analyses [22, 23, 59, 60], and conclusions are more substantiated due to the higher number of controlled intervention studies that could be included in our analyses (12 controlled intervention studies). The two most recent meta-analyses [22, 23] included only one study and four studies, respectively, to assess the effect of the LFD on QoL. Our review includes six controlled intervention studies that assessed QoL and found a statistically significant 5-point improvement when comparing subjects on an LFD to those on a control diet. Whether this reflects a meaningful change in health-related QoL is unclear, as a 10-point change has previously been considered clinically relevant [35].

In subgroup analyses, we found that the demonstrated improvements in IBS symptom severity were consistent between subgroups with different levels of adherence, age, intervention duration, IBS subtype, outcome measure, and risk of bias. Regarding intervention duration, the longest intervention duration was three months, therefore persistence of symptom reduction may need to be researched further. For IBS subtypes, we only had data to perform a subgroup analysis on IBS with predominantly diarrhea (IBS-D), which revealed outcomes similar to the main analysis. Individual studies with a majority of subjects with IBS with predominantly constipation (IBS-C) [40, 61, 62] or IBS with a mixed stool pattern (IBS-M) [63, 64] generally demonstrated similar improvements in IBS symptom severity, although this was not consistent among all studies [41]. More studies are needed to determine whether the efficacy of the LFD is consistent among these different subtypes. It should be noted that all the subgroups in the current meta-analysis were relatively small and as such the outcomes should be interpreted with caution. Future studies with larger sample sizes and clear reporting on adherence assessment, IBS-QoL assessment, IBS subtype, age, sex, and ethnicity are needed to inform in this regard. Furthermore, there are also no studies that investigated a potential dose–response relationship between FODMAP intake and IBS symptom severity in a controlled systematic fashion, indicating a gap in currently available evidence. However, as the threshold for tolerance of FODMAPs and type of FODMAP varies between individuals, carrying out such study would be very complex. This would likely require a large number of patients recruited in a multicenter setting over a prolonged period of time in a collaborated fashion to be feasible.

All studies had some risk of bias, most notably performance bias due to the lack of blinding of participants, personnel, or outcome assessment. Blinding remains a methodological factor in dietary intervention studies that is very difficult to address, especially in LFD trials where IBS subjects may already be familiar with the LFD due to its increasing popularity. However, a subgroup analysis including only studies with the lowest risk of bias ($n = 9$) did not result in a different SMD as compared to the overall analysis. Furthermore, we found indications of publication bias and visual inspection of the funnel plot suggested an absence of studies reporting a low or no effect on IBS symptom severity.

Owing to the LFDs restrictive nature, concerns have been raised over the long-term nutritional adequacy of the LFD [28, 29, 65, 66], as well as its effects on the gut microbiome [28, 31, 67]. As such, we also examined these aspects as part of the qualitative synthesis of this review (Tables 4 and 5). However, it is difficult to draw definitive conclusions regarding these two outcomes. In both cases, there were only a limited number of studies. Along with heterogeneity in analytical measures and outcome reporting, this precluded meta-analyses or direct comparisons of the available data.

In general, different studies demonstrated that substantial nutritional inadequacies do not occur, both during short-term interventions and at long-term follow-up after initial LFD advice [54–57], and may in some cases even lead to small increases in micronutrient intake. Conversely, a cross-sectional study of a large Iranian cohort did find lower intakes of energy, and all measured food groups, macro- and micronutrients across quintiles of increasing adherence to an LFD [51]. However, it is not clear whether the analyses were corrected for energy intake or other potential confounders.

It is important to note that in most of the included studies, subjects received personalized diets and/or nutritional advice under specialist dietetic or nutritionist guidance, which would have helped to maintain a balanced diet. This underscores the importance of specialist counseling where food items are also reintroduced on a timely basis for IBS patients when following an LFD [26]. Furthermore, although the outcomes of the two included long-term follow-up studies [54, 55] are promising, more work is required to conclusively determine the nutritional impact of LFD in individuals that follow it without seeking specialist advice.

The gut microbiome composition is hypothesized to undergo detrimental changes on an LFD, mainly due to decreased fiber intake and availability of prebiotic fructans, causing a reduction in the substrate available for colonic fermentation [66, 68]. Generally, the LFD did not seem to affect measures of overall microbial diversity,

but absolute or relative abundances of actinobacteria were reduced in many cases. Owing to differences in the methodology employed for fecal microbial analyses, it is difficult to compare outcomes between studies. It should also be noted that, since the natural interpersonal variation in gut microbiome composition can result in potentially larger differences than the effect of a dietary intervention, large sample sizes are required to enable robust investigations in this regard. As such, none of the included studies were sufficiently powered to allow for firm conclusions to be drawn. It must also be noted that very few studies have investigated the sustained effects of the LFD on the gut microbiome effects of an LFD (the longest study duration included here was 12 weeks). More work is therefore needed in this regard.

There are some limitations to the current study. First, there was a large variation between studies in control diets, ranging from subjects maintaining their habitual diet without dietary advice to high-FODMAP diets and sham exclusion diets. The FODMAP content of these control diets was often unclear or not reported. The high variety in control diets is also a possible explanation for the moderate heterogeneity observed between studies included in this meta-analysis. Second, half of the included studies did not assess subject adherence to the diet [41, 42, 52, 53, 66, 69]. Other studies assessed adherence via food diaries [40, 62–64, 70] or breath hydrogen tests [61] and reported good adherence. Since adherence is crucial to symptom relief [65], proper reporting in this regard is important to be able to determine the efficacy of an LFD intervention. Also, from a practical point of view, reporting adherence explores the feasibility of following an LFD for IBS patients. Nevertheless, subgroup analyses did not reveal significant differences in effect between studies that reported adherence and studies that did not.

In conclusion, this up-to-date systematic review and meta-analysis found that the low-FODMAP diet reduces gastrointestinal symptoms and improves quality of life in IBS subjects when compared to a control diet. Future research is recommended to obtain definitive answers regarding potential long-term effects of such diets on nutritional adequacy and the gut microbiome. This will require larger RCTs with appropriate controls that report on gut microbiome effects, dietary adherence, IBS-QoL and dose–response effects.

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Data availability Data will remain available for 5 years.

Compliance with ethical standards

Conflict of interest Unilever is a company that manufactures food and beverages, of which some may be considered low-FODMAP.

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Patient Care

Consumer Health Group Warns of Loperamide Abuse, Misuse

January 09, 2019, 08:47 am News Staff – The Consumer Healthcare Products Association (CHPA) wants to ensure family physicians know that improper use of loperamide (Imodium) -- specifically, taking it at very high doses -- can have serious, even fatal, cardiac effects.

In response to this concern, CHPA has launched a Loperamide Safety education campaign that offers clinical resources such as fact sheets for general health care professionals, **emergency health care professionals** and mental health care professionals, as well as for patients. Additional resources for clinicians include FDA drug safety communications and journal articles and case studies about the drug.

Loperamide is an important FDA-approved antidiarrheal medication sold both in OTC formulations and by prescription that is used safely every day by millions of people, said CHPA.

However, recent data suggest that a small but increasing number of people are taking extremely high doses of loperamide in a misguided attempt to self-manage opioid withdrawal or to achieve a euphoric high.

Through this campaign, CHPA hopes to educate health care professionals about loperamide abuse and how they can help prevent misuse/abuse and support patients who may be at risk.

STORY HIGHLIGHTS

- The Consumer Healthcare Products Association (CHPA) wants to ensure family physicians know that improper use of loperamide can have serious cardiac effects, including death.

CHPA has created a Loperamide Safety education campaign that offers clinical resources such as fact sheets for health care professionals and also for patients.

Recent data suggest that a small but increasing number of people are taking extremely high doses of loperamide in a misguided attempt to self-manage opioid withdrawal or to achieve a euphoric high.

About Loperamide

Loperamide is a peripherally acting mu opioid agonist -- specifically, a synthetic opiate that blocks the opioid receptors in the gut. However, at very high doses, the medication can cross the blood-brain barrier and cause opioid-like effects.

According to CHPA's website, "Nonclinical in-vitro and in-vivo (rabbit, guinea pig) cardiac electrophysiological safety assessments of loperamide support a large safety margin at the labeled dose, but at excessive doses, suggest that loperamide can inhibit the potassium channels (hERG) and cardiac sodium channels, which could result in QT and QRS prolongation and induce arrhythmia."

In humans, the loperamide dose and resulting blood level of the drug that lead to serious cardiac events are unknown, CHPA said. But long-term data from the American Association of Poison Control Centers' National Poison Data System suggest that cardiac effects are typically associated with doses of more than 100 mg, although cases have been reported with doses lower than this threshold.

Available data also show that although loperamide abuse is not currently widespread, it is on the upswing. According to an article in a March/April 2017 supplement to the *Journal of the American Pharmacists Association,* 54 case reports of loperamide toxicity were published from 1985 to 2016, with 21 cases reported from 1985 to 2013 and 33 from 2014 to 2016. In addition, 179 cases of intentional

loperamide misuse were reported to the National Poison Data System between 2008 and 2016, with more than half reported after Jan. 1, 2014.

Patient Profile/Signs of Misuse

CHPA's safety campaign website said the low number of reported loperamide abuse cases and limited data make it difficult to pin down a specific patient profile. However, significant evidence links loperamide abuse to substance use disorder (SUD), and available data suggest that patients most at risk for abusing loperamide likely have a history of substance abuse and/or opioid use disorder. And although men in their late 20s and 30s appear to be more likely than other demographic groups to be diagnosed as abusing the drug, loperamide misuse can affect any gender or age group.

There currently is no screening tool specifically for loperamide abuse, said CHPA, but screening tools for SUD are plentiful, including those provided by the Substance Abuse and Mental Health Services Administration's Center for Integrated Health Solutions.

As for signs of loperamide cardiotoxicity, patients may exhibit

- syncope,
- rapid or irregular heartbeat,
- unresponsiveness,
- QT interval prolongation,
- torsades de pointes,
- ventricular arrhythmias, and/or
- cardiac arrest.

Gastrointestinal complications, including nausea, vomiting, constipation and paralyzed intestine, can also be a sign of loperamide overdose, said CHPA. Family physicians who encounter patients with these or other signs of addiction should include loperamide abuse in the differential.

Preventing Loperamide Abuse

As for prevention, CHPA said family physicians should remember that some patients experiencing opioid withdrawal may turn to loperamide to ease their withdrawal symptoms and remain vigilant for signs and symptoms of loperamide toxicity.

It's also important to note that some patients who are abusing loperamide may combine it with other drugs to increase absorption and penetration across the blood-brain barrier.

The safety campaign website recommends family physicians consider their words carefully when discussing loperamide abuse with patients. Being cautious in their approach will help avoid inadvertently letting a patient know that loperamide can be used to manage withdrawal or achieve a high.

If family physicians suspect loperamide abuse but are not able to administer a confirmatory blood test, CHPA recommends asking patients questions such as the following:

- Have you been taking loperamide?
- How much loperamide do you take and how often?
- Are you aware of the serious heart risks associated with taking very high doses of loperamide?

If patients report using more than the approved dose of loperamide, family physicians should educate them about the risks and refer them to an appropriate source of treatment for SUD. The CHPA patient fact sheet may be helpful in this instance, just as the group's clinician-focused fact sheets can be shared with colleagues and office staff to alert them to this important safety issue.

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Program Offers Free Help With Prevention, Treatment, Recovery
(12/19/2018)

CDC Data Show U.S. Life Expectancy Continues to Decline
Suicides, Drug Overdose Deaths Named as Key Contributors
(12/10/2018)

More From AAFP

Chronic Pain Management and Opioid Misuse: A Public Health Concern (Position Paper)

AAFP Chronic Pain Management Toolkit

Ther Adv Gastroenterol
(2010) 3(3) 165–172
DOI: 10.1177/1756283X10362277

Optimizing outcomes with alosetron hydrochloride in severe diarrhea-predominant irritable bowel syndrome

Susan L. Lucak

***Abstract*:** Irritable bowel syndrome (IBS) is a highly prevalent functional gastrointestinal disorder that causes a range of symptoms. Currently, alosetron hydrochloride (Lotronex®), a selective serotonin type 3 receptor antagonist, is the only medication approved for the treatment of severe diarrhea-predominant irritable bowel syndrome (IBS-D) in women who have inadequately responded to conventional therapy. Alosetron has demonstrated efficacy compared with placebo in clinical trials and has been shown to improve overall health-related quality of life (HRQoL). However, rare instances of ischemic colitis and severe complications of constipation have been reported. As a result, in 2000 alosetron was voluntarily withdrawn from the market but was reintroduced in 2002 with a more restricted indication and a requirement that clinicians and patients follow a prescribing program. Although the efficacy and benefit of alosetron has been clearly demonstrated, it has been used sparingly since its reintroduction. This brief review describes the history of alosetron, efficacy of alosetron in the treatment of IBS, the impact of severe IBS on HRQoL, safety considerations, the risk evaluation and mitigation strategy program under which alosetron is now prescribed, and an update on postmarketing surveillance data.

***Keywords*:** Irritable bowel syndrome, diarrhea, 5-HT_3 antagonist, alosetron

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain or discomfort, disturbed bowel function, abdominal distension or bloating, and the passage of mucus. IBS is diagnosed more often in women than in men and typically in patients under 50 years of age [Drossman *et al.* 2002]. Subtypes of the disorder include diarrhea-predominant IBS (IBS-D), constipation-predominant IBS, mixed IBS, and unsubtyped IBS [Longstreth *et al.* 2006]. While the true prevalence of IBS subtypes remains unknown, IBS-D and mixed IBS were the most frequently reported subtypes in two published surveys [Andrews *et al.* 2005; Hungin *et al.* 2005]. Conventional treatments, including antidiarrheals, antispasmodics, and antidepressants, are commonly used for IBS-D [American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009; Drossman *et al.* 2002]; however, no medication in these classes is specifically approved for use in IBS-D. Currently, in the United States, only alosetron is approved for IBS-D, indicated in women with severe IBS-D who have had an inadequate response to conventional therapy.

History of alosetron

Alosetron was introduced in early 2000 for the treatment of women with IBS-D but was voluntarily withdrawn from the market later that year owing to reports of infrequent but serious adverse events associated with its use, specifically ischemic colitis (IC) and complications of constipation (CoC), which included fecal impaction, intestinal obstruction, toxic megacolon, and intestinal perforation [Chang *et al.* 2006]. These adverse events resulted in hospitalizations and rare instances of blood transfusion, surgery, and death [Chang *et al.* 2006; Horton, 2001]. Two deaths were related to CoC; no deaths were related to IC [Chang *et al.* 2006]. After market withdrawal, the US Food and Drug Administration (FDA) received numerous requests from both patients and physicians to

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bring alosetron back to the market [Horton, 2001]. An advisory committee was convened by the FDA to discuss the risks and benefits of alosetron, which resulted in a recommendation for the reapproval of alosetron in June 2002 [Andresen and Hollerbach, 2004; McCarthy, 2002]. Alosetron was subsequently reintroduced for patient use in November 2002 with a lower recommended starting dose (0.5 mg twice daily, instead of 1 mg twice daily) and a more restricted indication specifying it be used in women with 'severe' IBS-D who have had an inadequate response to conventional therapy. For purposes of the more restrictive indication, 'severe' IBS was defined as the presence of one or more of the following: (1) frequent and severe abdominal pain or discomfort; (2) frequent bowel urgency or fecal incontinence; or (3) disability or restriction of daily activities due to IBS. It is important to note that only one of these parameters need be present for IBS to be considered severe [Lewis, 2010]. In addition, alosetron use is now governed by a risk evaluation and mitigation strategy (REMS).

Risk evaluation and mitigation strategy

The REMS includes the Prescribing Program for Lotronex® (PPL), which outlines the responsibilities of the physician and the patient before initiation of alosetron therapy [Prometheus Laboratories, 2008a]. Physicians who enroll in the PPL are required to be qualified to diagnose IBS, to counsel patients on the benefits and risks of alosetron therapy, to sign a physician–patient agreement form, to affix program stickers to alosetron prescriptions, to monitor patients, and to report any serious adverse events to the manufacturer or to the FDA [Prometheus Laboratories, 2008a]. Patients receiving alosetron must sign the physician–patient agreement form, report adverse events, and have the opportunity to participate in a voluntary survey. Finally, pharmacists must confirm that a program sticker is affixed to an alosetron prescription before they dispense the medication and provide an alosetron medication guide [Ameen *et al.* 2008]. These requirements were put in place with the goal of maximizing therapeutic benefit through proper patient selection and reducing the risk of complications or consequences of serious adverse events.

Efficacy of alosetron

Alosetron hydrochloride is a potent, selective serotonin 3 (5-HT_3) receptor antagonist indicated for the treatment of women with chronic (lasting >6 months), severe IBS-D and no anatomic or biochemical abnormalities of the GI tract who have not responded adequately to conventional therapy. Compared with placebo, alosetron demonstrated effectiveness in decreasing fecal urgency and improving stool consistency and frequency in women with IBS-D (Figures 1 and 2) [Krause *et al.* 2007; Lembo *et al.* 2004, 2001]. Alosetron has been shown to significantly improve IBS-related abdominal pain and discomfort in randomized, double-blind clinical trials (Figure 3) [Krause *et al.* 2007; Camilleri *et al.* 2001, 2000].

Impact of irritable bowel syndrome

Numerous studies have indicated that IBS is associated with substantial compromise in health-related quality of life (HRQoL) [American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009]. A survey using the Short Form 36 question general health questionnaire (SF-36) to assess HRQoL revealed scores significantly lower than country-specific normative values for IBS patients from the US ($n = 287$) and the UK ($n = 343$) across each of eight measured domains: physical functioning, role limitations due to physical/emotional components, bodily pain, general health, emotional well-being, energy/fatigue, and social functioning [Hahn *et al.* 1997]. Using the same instrument, Gralnek and colleagues compared HRQoL scores from patients with IBS with scores collected previously from patients with moderate to severe gastroesophageal reflux disease (GERD), diabetes mellitus (DM), dialysis-dependent end-stage renal disease (ESRD), and depression [Gralnek *et al.* 2000]. IBS patients scored significantly lower than GERD patients in seven of the eight SF-36 domains (excluding physical functioning) and significantly lower than DM patients in six of the eight domains (excluding physical functioning and general health perception). In another comparison [Gralnek *et al.* 2000], IBS patients scored significantly lower than ESRD patients in emotional well-being but had similar scores for bodily pain, role limitations due to emotional components, energy/fatigue, and social functioning. Lastly, IBS patients reported significantly worse bodily pain than patients with depression but comparable limitations due to physical components and general health perception [Gralnek *et al.* 2000].

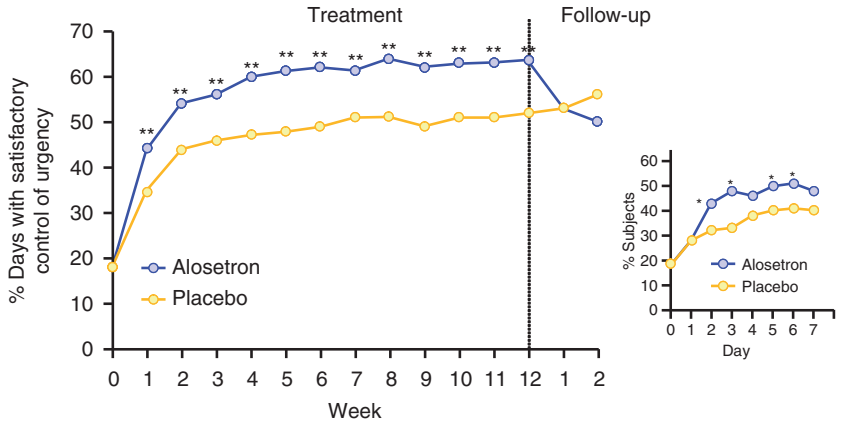

Figure 1. Percentage of days with satisfactory control of urgency throughout a 12-week clinical trial (**$p < 0.003$). Inset shows the percentage of patients with satisfactory urgency control during the first week of treatment (*$p < 0.05$). [Reprinted with permission from Lembo *et al.* 2004].

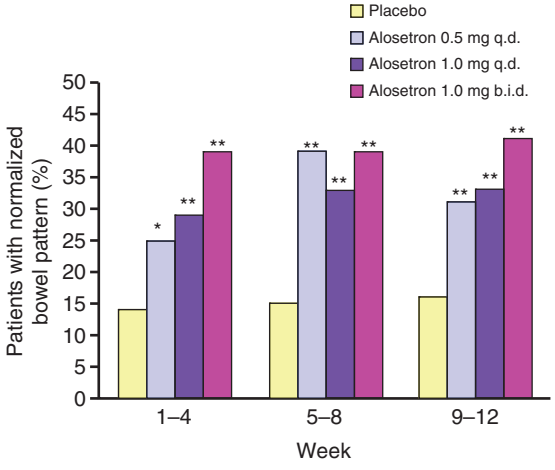

Figure 2. Proportion of patients with normalized bowel pattern (defined as having a stool consistency ≤3 and stool frequency of ≤2 per day (*$p < 0.004$; **$p < 0.001$). [Reprinted with permission from Krause *et al.* 2007].

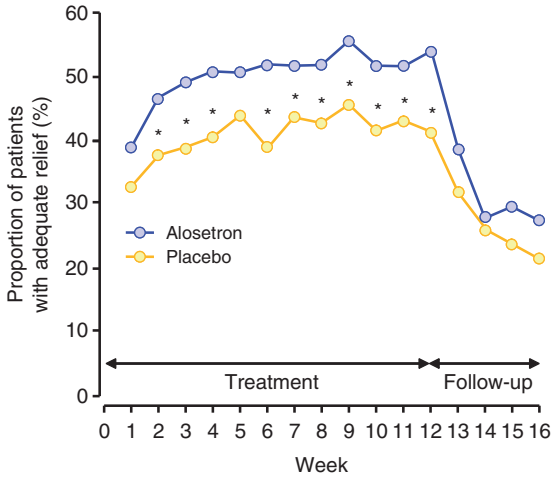

Figure 3. Proportion of patients with adequate relief of abdominal pain and discomfort by week (*$p < 0.05$). [Reprinted with permission from Camilleri *et al.* 2000].

The level of IBS severity also correlates with impairments in HRQoL [American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009; Naliboff *et al.* 1998]. Using an IBS-specific QoL instrument (IBSQoL), Hahn and colleagues found that patients with severe IBS had significantly poorer scores in physical functioning, social functioning, energy/fatigue, mental health, and role limitations due to emotional and physical components than those with moderately severe disease [Hahn *et al.* 1997]. A recent international Internet survey of 1966 IBS patients [Drossman *et al.* 2009] confirmed these earlier findings, showing that patients with severe IBS scored lower than those with less severe disease in all domains of the IBSQoL and had more days of restricted usual/social activities. Patients with severe IBS ($n = 400$) in this survey reported a willingness to risk at least a 1 in 1000 chance of death (24.9%), serious or permanent side effects (18.8%), or mild side effects (65.1%) to be able to take a medication that provided total IBS symptom relief [Drossman *et al.* 2009].

Although traditionally IBS has not been considered a life-threatening disorder, recent data reveal that the negative impact of IBS on patients' lives may be associated with increased suicidal ideation and suicidal behavior [Spiegel *et al.* 2007; Miller *et al.* 2004]. Miller and colleagues assessed

suicidal ideation or suicide attempts specifically linked to bowel problems in IBS and inflammatory bowel disease (IBD) patients followed in the UK National Health Service clinic system [Miller *et al.* 2004]. Investigators questioned patients at all levels of clinical care: primary care (pIBS; 100 patients managed in general practice), secondary care (sIBS; 100 patients referred from primary care), and tertiary care (tIBS; 100 patients referred by another specialist). The control group comprised 100 IBD patients with quiescent, minimally active, or remitted disease. Results showed that patients in the tIBS group were significantly more likely to consider suicide because of their symptoms (38%) than those in the sIBS (16%), pIBS (4%), or IBD (15%) group (tIBS *versus* sIBS [$p = 0.002$] *versus* pIBS [$p < 0.001$] *versus* IBD [$p < 0.001$]). Multiple regression analysis revealed that symptom severity, level of clinical care (i.e. tertiary *versus* secondary *versus* primary), anxiety, and depression were all independent predictors of suicidal ideation [Miller *et al.* 2004]. The potential of IBS, especially in its most severe form, to induce suicidal ideation underscores the seriousness of IBS and the need to optimize treatment outcomes [Miller *et al.* 2004]. To date, studies have not specifically examined the impact of IBS subtypes on HRQoL or suicidal ideation and suicidal behavior; further investigations in this area are needed.

Alosetron and potential for drug–drug interactions

In vivo data suggest that alosetron is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, agents that induce or inhibit these enzymes can alter the clearance of alosetron. For example, concomitant administration of alosetron and fluvoxamine (a selective serotonin reuptake inhibitor) is contraindicated because fluvoxamine strongly inhibits CYP1A2. Fluvoxamine produces approximately six-fold increases in mean alosetron plasma concentrations (AUC) and an approximately three-fold prolongation of its half-life [Lewis, 2010]. Use of alosetron with more moderate CYP1A2 inhibitors, such as quinolone antibiotics or cimetidine, has not been assessed but should be avoided unless clinically necessary given the drug interaction potential. In addition, caution is recommended during concomitant use of alosetron and the strong CYP3A4 inhibitor ketoconazole, which can increase alosetron plasma concentrations by 29% [Lewis, 2010]. Alosetron has not been evaluated in drug-interaction studies with more modest CYP3A4 inhibitors (e.g. clarithromycin, telithromycin, protease inhibitors, voriconazole, itraconazole).

Data from *in vitro* and *in vivo* studies suggest that alosetron is unlikely to inhibit CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 [Lewis, 2010; Koch *et al.* 2004b], nor is it likely to induce the CYP2C19, 2E1, or 3A4 enzymes. No adjustments in alosetron dosing are needed during coadministration of oral contraceptives such as ethinyl estradiol or levonorgestrel or coadministration of fluoxetine, alprazolam, or theophylline [Koch *et al.* 2004a, 2001; D'Souza *et al.* 2001a, 2001b]. It is unknown whether alosetron induces other enzymes.

Alosetron use in pregnancy

Given that alosetron is indicated only for women with IBS-D, its potential influence on pregnancy should be considered. Alosetron belongs to Pregnancy Category B. Preclinical reproduction studies in rats and rabbits (at ~160 and ~240 times the recommended human dose based on body surface area, respectively) have revealed no evidence of impaired fertility or fetal harm from alosetron. Despite this, no randomized, placebo-controlled studies of alosetron have been performed in pregnant women; therefore, it is recommended that alosetron be used during pregnancy only if there is a clear indication of need [Prometheus Laboratories, 2008b].

Safety: association of ischemic colitis and complications of constipation with alosetron

A systematic blinded review performed by Chang and colleagues examined the incidence of IC and CoC in patients treated with alosetron in clinical trials and during postmarketing surveillance of the initial marketing period [Chang *et al.* 2006]. Notably, the randomized, controlled trials examined in the Chang *et al.* analysis included patients with the full spectrum of IBS illness, not just women with severe IBS-D, for whom the drug is now indicated [Chang *et al.* 2006]. Table 1 outlines the screening criteria used to identify IC and CoC that were probably related to alosetron use in this analysis.

Table 1. Screening criteria to identify potential cases of ischemic colitis and serious complications of constipation in patients receiving alosetron (identified from pooled clinical trial data). [Adapted with permission from Chang *et al.* 2006].

Probable ischemic colitis (IC)	Probable serious complications of constipation (CoC)
• Medical history consistent with IC (e.g. abdominal discomfort, hematochezia, diarrhea) and . . . • Supported by the results of colonoscopy or other imaging tests and /or histological evaluation of a relevant tissue biopsy and . . . • No evidence for any more likely diagnosis	• Medical history consistent with serious CoC (e.g. patient complained of constipation) and met regulatory definition of a serious adverse event* • Medical history is supported by hospital or medical records • Colonoscopy results (or other imaging test) do not identify a more likely diagnosis for the patient's symptoms

*Serious adverse event is defined as 'death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect.' Serious adverse events also include: 'important medical events that may not result in death, be life-threatening, or require hospitalization . . . [but] based upon appropriate medical judgment, they may jeopardize the patients and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.'

Clinical trial program

In their pooled analysis of clinical trials, Chang *et al.* [2006] found an increased risk of IC among patients receiving alosetron (0.15%) compared with those receiving placebo (0%, $p = 0.03$; 6.4 cases per 1000 patient years [pt-yr] of alosetron use *versus* 0.0 cases per 1000 pt-yr of placebo use). All patients developing IC associated with alosetron use ($n = 19$) had transient symptoms with no long-term sequelae; the majority of cases (63.1%) occurred within the first 30 days of treatment [Chang *et al.* 2006].

Rates of serious CoC in clinical trials did not differ significantly between alosetron- and placebo-treated patients (3.3 cases per 1000 pt-yr of alosetron use *versus* 1.0 case per 1000 pt-yr of placebo use) [Chang *et al.* 2006]. Of 10 cases of serious CoC that occurred in the program, 90% occurred within the first 90 days of treatment, highlighting the importance of vigilance during the first 3 months of therapy [Chang *et al.* 2006]. All patients were hospitalized, one patient underwent abdominal surgery, and there were no deaths.

Postmarketing surveillance before June 2002

In postmarketing surveillance data collected before June 2002, post-adjudication rates of IC and CoC were 0.96 cases per 1000 pt-yr and 0.59 cases per 1000 pt-yr of use, respectively [Chang *et al.* 2006].

Postmarketing surveillance after reintroduction (November 2002–December 2007)

Postmarketing surveillance data were obtained from REMS reports submitted to the FDA between November 2002 and December 2007 (including spontaneous reports from patients and health care professionals, responses from a voluntary patient survey, and serious adverse event reports from physicians as required by the prescribing program), applying the same adjudication criteria for probable relation to alosetron used by Chang *et al.* (Table 1). Based on these data, 15 cases of IC were confirmed, revealing an IC incidence rate of 1.14 cases per 1000 pt-yr [Ameen *et al.* 2008]. Over that same period, six confirmed cases of CoC were reported, corresponding to an incidence rate of 0.46 per 1000 pt-yr of treatment [Ameen *et al.* 2008].

Sequelae of ischemic colitis and complications of constipation cases in association with alosetron

In the time period prior to its reintroduction, alosetron use was not associated with fatal outcomes resulting from the development of IC but two fatalities did occur as a result of CoC. Since the market reintroduction of alosetron, confirmed cases of IC ($n = 15$) and CoC ($n = 6$) have not resulted in the need for surgical procedures or transfusions, nor have they been associated with fatal outcomes. Moreover, all confirmed events of IC and CoC resolved upon discontinuation of alosetron [Ameen *et al.* 2008]. Thus, IC and CoC events observed over this 5-year period have remained rare, idiosyncratic, unrelated to alosetron dose, and with incidence rates similar to those noted in the postmarketing surveillance prior to its reintroduction [Ameen *et al.* 2008].

Discussion

Since the reapproval and reintroduction of alosetron in 2002, the efficacy, safety, and tolerability of this medication have been well characterized. The alosetron REMS program provides health care professionals and patients with information about alosetron (including new dosing guidelines). Since the introduction of the REMS, no new, clinically relevant safety concerns have been observed. Likewise, reports of IC and CoC since reintroduction have remained rare and stable [Ameen *et al.* 2008; Chang *et al.* 2006] and no confirmed serious outcomes have been reported (e.g. surgeries, transfusions, deaths) to result from these events [Ameen *et al.* 2008; Krause *et al.* 2007; Chang *et al.* 2006]. The risk of developing IC and the pathologic mechanism by which alosetron might cause this adverse event remains unclear [Camilleri, 2007]. Effects of alosetron on colonic mucosal blood flow are unknown; however, submucosal vasomotor reflexes appear to be modulated by 5-HT_4 or 5-HT_{1p} receptors, not 5-HT_3 receptors [Camilleri, 2007]. In experimental settings, 5-HT_3 antagonists do not inhibit normal dilatory responses in preconstricted arterioles during balloon distension [Reed and Vanner, 2003]. Likewise, there is no evidence that 5-HT_3 antagonists cause changes in coagulation factors or platelet or endothelial function [Camilleri, 2007]. Moreover, medical claims data from a large managed care database (United Healthcare) showed that IBS patients have a 3.4 times higher incidence of IC than the general population [Cole *et al.* 2004]. One remaining point of controversy is whether alosetron predisposes patients to developing IC, exacerbates other risk factors for IC, or causes IC.

One unintentional outcome of the REMS is that it has led to a much more restricted usage of alosetron than when it initially came to market. A survey of patients enrolled in the RiskMAP found that 76% of alosetron-treated women who responded to the questionnaire met all three severity criteria for the diagnosis of severe IBS-D, although only one criterion is necessary to receive the diagnosis of 'severe' IBS-D [Miller *et al.* 2006]. This finding indicates that there are likely many more women suffering from less severe IBS-D who may benefit from a trial of alosetron.

Selection of therapy for the IBS patient should be based not only on the severity of GI symptoms (e.g. abdominal pain, fecal urgency) but should also address the impact of the symptoms on the patient's functional status and HRQoL. Routine screening of HRQoL in IBS patients is recommended by the American College of Gastroenterology (ACG) Task Force on IBS, and treatment should be initiated when symptoms reduce functional status and diminish overall HRQoL [American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009]. Indeed, in women with IBS-D, disability or restriction of daily activities due to IBS is an HRQoL parameter that supports the characterization of IBS as severe. Furthermore, recent evidence suggesting increased suicidal ideation and suicidal behavior in patients with IBS, independent of depression or other psychiatric comorbid conditions, underscores the importance of timely treatment of severe IBS [Spiegel *et al.* 2007; Miller *et al.* 2004]. Appropriate use of alosetron across a broader population of patients with severe IBS—not just in those with the severest disease—would likely optimize outcomes in the population of women who suffer from this serious disorder.

Conclusions

Alosetron is currently the only 5-HT_3 receptor antagonist approved for the management of severe IBS-D in women [American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009; Prometheus Laboratories, 2008b]. Several clinical trials have shown that alosetron effectively treats the multiplicity of GI symptoms, including fecal urgency, stool consistency and frequency, and abdominal pain and discomfort, as well as improves HRQoL in patients with IBS-D. Whereas the use of alosetron has been associated with serious but rare adverse events, the incidence of these events has essentially remained rare and stable and they have not resulted in any deaths since alosetron was reintroduced in November 2002. Despite these findings, it appears that only the most severe IBS cases are being treated with alosetron. Outcomes in patients with IBS-D might be optimized through the accurate assessment and diagnosis of IBS severity as it relates to both GI symptomatology and impact on HRQoL. With such an assessment, an appropriate and effective treatment plan can be initiated to improve symptoms and ease the suffering related to IBS.

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Conflict of interest statement

The author declares that she is a speaker and consultant for Prometheus Labs, Inc., Salix, and Takeda pharmaceutical companies; she is also a consultant for Forest Labs/Ironwood. The author serves as a legal expert for Novartis and was a legal expert for GlaxoSmithKline.

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Lubiprostone: chronic constipation and irritable bowel syndrome with constipation

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Expert Opinion

Lubiprostone: chronic constipation and irritable bowel syndrome with constipation

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Lubiprostone is a bicyclic fatty acid metabolite analogue of prostaglandin E1. The FDA has approved lubiprostone for the treatment of chronic constipation in men and women and the treatment of women with irritable bowel syndrome with constipation (IBS-C). Lubiprostone specifically activates type-2-chloride channels on the apical membrane of epithelial cells. Lubiprostone acts locally within the intestinal tract, is rapidly metabolized and has very low systemic bioavailability. Animal studies have demonstrated that lubiprostone increases gastrointestinal fluid secretion in a dose-dependent manner. Clinical studies performed in men and women with chronic constipation using 24 µg of lubiprostone twice-daily demonstrated objective improvement in stool frequency and consistency, as well as symptoms of straining and incomplete evacuation. A multi-center study of patients with IBS-C found that 8 µg of lubiprostone twice-daily improved both global and individual symptoms of irritable bowel syndrome. Lubiprostone is generally well tolerated and serious adverse events are rare. The most common reported side effects are nausea, headache and diarrhea. This monograph provides a brief overview on chloride channel function in the gastrointestinal tract, describes the structure, function, and pharmacokinetics of lubiprostone, and discusses the safety and efficacy of this new medication for the treatment of chronic constipation and IBS-C.

Keywords: chloride, chloride channels, constipation, functional bowel disorders, gastrointestinal motility, intestinal secretion, irritable bowel syndrome, lubiprostone

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1. Introduction

Lubiprostone (Amitiza, Sucampo Pharmaceuticals, Bethesda, MD, USA), a type-2-chloride channel (ClC) activator, was approved by the FDA for the treatment of chronic constipation in men and women (24 µg twice-daily) on 31 January 2006. The FDA subsequently approved lubiprostone, at a dose of 8 µg twice-daily, for the treatment of women who have irritable bowel syndrome with constipation (IBS-C) on 29 April 2008.

Chronic constipation and IBS-C are two of the most common functional bowel disorders encountered by primary care providers and gastroenterologists. The prevalence of constipation in the US is ~ 15%, with women, the elderly, non-Caucasians and patients in lower socioeconomic classes more likely to be affected [1,2]. Chronic constipation markedly affects patients' quality of life and imposes a significant economic burden to the health care system. Several studies have shown that patients with chronic constipation note a reduction in quality of life in several areas, including both physical and psychological domains [3,4].

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The annual cost of evaluating and treating patients with chronic constipation in the US is estimated to be > $7 billion [4]. This figure includes indirect costs attributed to missing school or work and being less productive at school or work, as well as the direct costs of treating constipation (e.g., office visits, diagnostic tests and medications). Although the natural history of chronic constipation is not as well studied as other functional bowel disorders, most patients with chronic constipation remain symptomatic when surveyed 18 – 20 months after initial evaluation [5].

Irritable bowel syndrome (IBS) is also frequently encountered by all types of health care providers, and prevalence in the US is estimated to be 9 – 22% [6-8]. Similar to chronic constipation, women are more likely than men to be diagnosed with IBS [6-8]. In addition, IBS imposes a significant burden on both patients and society. Patients with IBS suffer from a dramatic reduction in quality of life [9] and conservative estimates are that annual US health care costs for the evaluation and treatment of IBS exceed $20 billion [10]. On average, health care costs for IBS patients are 50% higher than patients of similar age and sex who do not have IBS [11].

The definition of constipation has evolved over the past decade and at present is based on several different symptoms rather than exclusively on stool frequency. Patients with constipation often describe a constellation of symptoms that includes hard or lumpy stools, infrequent stools, straining, feelings of incomplete evacuation, and rectal or perianal fullness or discomfort. The recently released Rome III criteria have attempted to take these various symptoms into consideration (**Table 1**). Pathophysiologically, constipation is generally classified as either primary (e.g., colonic inertia, pelvic floor dysfunction, normal transit constipation, IBS-C) or secondary in nature (e.g., metabolic, endocrine, surgical, psychiatric) (**Table 2**) [12,13].

The definition of IBS has also changed considerably over the past several decades. The Rome III criteria define IBS as a chronic disorder characterized by abdominal pain or discomfort associated with disordered defecation (constipation, diarrhea, or mixed symptoms of alternating constipation and diarrhea). Symptoms should have developed at least 6 months before the patient first presents for formal evaluation. Abdominal pain or discomfort should be present at least 3 days per month for 3 months and should be associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency, and/or onset associated with a change in stool form. According to the Rome III criteria, the subgrouping of IBS patients is predicated on differences in stool consistency (**Table 3**) [12].

Treating patients with chronic constipation and IBS-C can be frustrating because symptoms do not accurately reflect the underlying pathophysiology nor do they predict response to treatment. Life-style modifications (e.g., drinking more water, exercising and adding dietary fiber) are frequently recommended by health care providers as the first step in therapy. Although safe, these treatments are usually ineffective except in patients who are fiber deficient [14,15]. Over-the-counter medications are generally used next, and these include bulk laxatives (e.g., psyllium), osmotic laxatives (e.g., magnesium citrate), emollients (e.g., docusate sodium) and stimulant laxatives (e.g., cascara). Although some patients note an improvement in symptoms, there is little evidence to support the long-term efficacy of these agents [13]. Patients with persistent symptoms despite this step-wise approach generally seek out medical consultation. After an appropriate evaluation has been performed, medical therapy is usually recommended, which may include osmotic agents (e.g., polyethylene glycol, lactulose) or a type-2-ClC activator (e.g., lubiprostone). The safety and efficacy of osmotic agents have been carefully reviewed in two recent monographs and will not be discussed further [13,16]. The remainder of this review focuses on lubiprostone.

2. ClCs

ClCs are located throughout the body in virtually all cell types, including epithelial, nerve and muscle cells, where they play a critical role in normal cellular function [17]. They are pore forming proteins that allow the transport of chloride ions, the predominant anion in the extracellular fluid, across cell membranes.

In the gastrointestinal (GI) tract, a number of different ClCs play a critical role in fluid transport, depolarization of smooth muscle cells, postsynaptic transmission, and the maintenance of both cell volume and intracellular pH [18]. At present, nine separate ClCs have been identified (ClC-0 – ClC7, ClC-Ka and ClC-Kb). One of the most important ClCs is the cystic fibrosis transmembrane conductance regulator. Genetic defects in cystic fibrosis transmembrane conductance regulator may lead to the development of cystic fibrosis symptoms owing to defective Cl^- uptake into cells with resultant increased viscosity of secretions and mucus impaction [18]. This review focuses on the ClC-2 channel, as this is the ClC selectively activated by lubiprostone.

The ClC-2 channel is distributed throughout the GI tract, including the stomach, small intestine and colon. It is an α-helical transmembrane protein that is highly selective for Cl^- and is not permeable to larger anions or to cations [19]. Essential functions of the ClC-2 channel include fluid transport and secretion, regulating cell volume and pH, and maintaining the membrane potential of the cell [17-19]. ClC-2 channels are localized to the apical (luminal) cell membrane in human intestine [20]. Activation of ClC-2 is probably regulated by second messenger induced phosphorylation.

Table 1. Rome III criteria for chronic constipation (modified from [12]).

Symptom onset at least 6 months before diagnosis
Presence of symptoms for the past 3 months (see below)
Insufficient criteria for irritable bowel syndrome
Loose stools are rarely present without the use of laxatives
Symptoms include two or more of the following during at least 25% of defecations:
Straining
Lumpy or hard stools
Sensation of incomplete evacuation
Sensation of anorectal obstruction or blockade
Manual maneuvers to facilitate evacuation
Less than three bowel movements a week

Table 2. Common causes of constipation.

Primary
Slow transit constipation
Pelvic floor dyssynergia
Irritable bowel syndrome with constipation
Normal transit constipation
Secondary
Anatomical obstruction
Medications (opioids, tricyclic antidepressants, anticholinergic agents)
Metabolic disorders
Neurologic/myopathic disorders
Psychiatric (somatization, anxiety, depression)
Idiopathic

Table 3. Rome III criteria for IBS (modified from [12]).

Symptom onset at least 6 months before diagnosis
Presence of symptoms for the past 3 months (see below)
Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months with two or more of the following symptoms:
Improvement with defecation
Onset associated with a change in stool frequency
Onset associated with a change in stool form
The constipation subtype of IBS is further classified by:
Hard or lumpy stools with at least 25% of bowel movements
Loose (mushy) or watery stool < 25% of bowel movements

IBS: Irritable bowel syndrome.

3. Pharmacology of lubiprostone

3.1 Structure

The formal chemical name of lubiprostone is difluoropentyl-2-hydroxy-6-oxooctahydrocyclopenta-heptanoic acid [21]. It is a white, odorless crystal and powder that is soluble in ethanol but insoluble in water. Lubiprostone is classified as a prostone, a bicyclic fatty acid compound derived from a metabolite of prostaglandin E1. Lubiprostone can tautomerize between two different forms: lubiprostone II is the active form (**Figure 1**).

3.2 Pharmacokinetics and metabolism

The pharmacokinetic properties of lubiprostone were evaluated in a study of fasted healthy male volunteers [21]. After ingesting a 72 µg dose of radio-labeled lubiprostone, 60% of the radio-label was recovered in the urine in 24 h, 63% was recovered in the urine by day 7 and 30% was recovered in the stool at the end of 1 week. Lubiprostone could not be detected in plasma, urine or stool, and it is thought that the measured radioactivity represents a compound labeled as M3, which is the active metabolite of lubiprostone. Peak plasma levels occur ~ 1.14 h after oral administration of a single 24 µg dose, and the half-life of lubiprostone (t½) has been estimated at ~ 3 h [21].

Lubiprostone is metabolized within the GI tract through microsomal carbonyl reductase; the cytochrome P450 system is not involved. In contrast to the parent drug, M3 is absorbed and ~ 94% is bound to human plasma proteins. The half-life of M3 is ~ 0.9 – 1.4 h. Although not tested in large studies, gender does not seem to influence the metabolism of lubiprostone. No studies have been conducted to assess the pharmacokinetic profile of lubiprostone in patients with hepatic or renal impairment. Studies are in progress to evaluate the pharmacokinetics of lubiprostone in the pediatric population. In summary, lubiprostone seems to act locally within the GI tract, has a fairly quick onset of action and is rapidly metabolized on the apical (luminal) surface of epithelial cells.

3.3 Mechanism of action

Lubiprostone specifically activates ClC-2 channels on the apical membrane of epithelial cells [20,22,23]. Highly specific inhibitors of ClC-2 channels are not available, and thus blocking experiments cannot be performed. Activation of ClC-2 channels causes an efflux of chloride into the lumen of the GI tract, followed by an efflux of sodium ions to maintain isoelectric neutrality. Sodium efflux occurs through a paracellular pathway and not through the apical membrane. Water then follows sodium along the paracellular pathway to maintain isotonic equilibrium. Animal studies have demonstrated that lubiprostone increases intestinal fluid secretion in a dose-dependent manner [24].

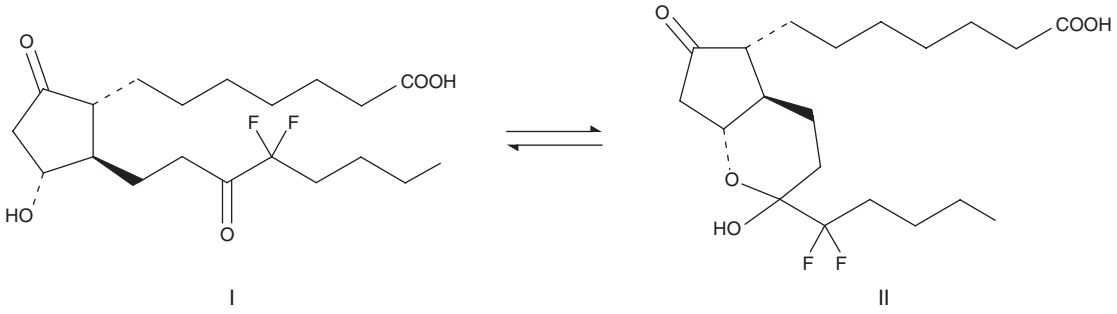

Figure 1. Structure of lubiprostone.

Because lubiprostone is a metabolite of prostaglandin E1, researchers have investigated whether lubiprostone can directly stimulate smooth muscle, possibly through prostaglandin receptors. Two separate animal studies have not shown any evidence of a direct stimulatory effect of lubiprostone on GI smooth muscle [25,26]. Cuppoletti *et al.*, using cultured human uterine smooth muscle cells, found that lubiprostone decreased calcium levels, did not change cAMP levels and caused hyperpolarization of the cells [26]. These effects were directly opposite to those of prostaglandins E1 and E2, which caused an increase in both calcium and cAMP, and depolarization of the muscle cells. However, a recent study by Bassil *et al.* found that lubiprostone induced contraction of rat and human stomach longitudinal muscle, but inhibited electrical field stimulated contractions of colonic circular smooth muscle [27]. The stimulatory effects of lubiprostone on longitudinal muscle were blocked by a prostaglandin EP_1 receptor antagonist, whereas the inhibition of circular smooth muscle was reduced by a prostaglandin EP_4 antagonist. These findings raise the possibility that lubiprostone's actions may not be entirely due to activation of the ClC-2 channels.

In summary, lubiprostone stimulates ClC-2 channels and promotes intestinal fluid secretion. Although the final details of lubiprostone's mechanism of action are still lacking with regard to improvement in symptoms of constipation, one theory is that the secretion of fluids into the GI tract promotes increased transit through the small intestine and colon, possibly through stimulation of local receptors sensitive to stretch and distention [28,29]. The direct effects of lubiprostone on smooth muscle are unclear given contradictory results. Further studies are required to determine the extent of direct smooth muscle activation by lubiprostone.

4. Effects on reproduction and development

Animal studies have not shown evidence of a direct teratogenic effect of lubiprostone [21,30]. More specifically, when rats received 332 times the standard human dose or rabbits received 33 times the standard human dose, no teratogenic effects were noted. However, lubiprostone administered at 6 – 10 times the recommended dose to guinea pigs was associated with an increase in the rate of fetal loss. This was thought to be the result of significant weight loss in the pregnant animals, rather than a direct effect on the fetus [21,30]. Fetal loss did not occur in similarly designed experiments involving mice and rats. Owing to the adverse effects observed in the guinea pig model, however, and the lack of well-controlled studies in pregnant women, the FDA has rated lubiprostone as pregnancy category "C".

5. Clinical studies in chronic constipation

5.1 Randomized controlled trials

The safety and efficacy of lubiprostone were evaluated in a multi-center, double-blind, placebo-controlled, dose-ranging study of 129 subjects with symptoms of chronic constipation [31]. Constipation was defined as fewer than three spontaneous bowel movements (SBM) a week, together with one or more of the following symptoms occurring at least 25% of the time: hard stools, straining or feelings of incomplete evacuation. After a 2-week washout period, patients who had a minimum of 6 months of symptoms were randomized to receive either lubiprostone (24, 48 or 72 µg/day) or placebo for three consecutive weeks. All patients underwent either a colonoscopy or a flexible sigmoidoscopy and barium enema to exclude an organic cause for their symptoms. The patients were predominantly female (≥ 84% in each treatment arm) and Caucasian (≥ 81% in each treatment arm). The mean age was 48.3 years; 10% were at least 65 years of age. Using a modified intention to treat analysis, patients in the treatment groups were found to have a significant increase in the average number of weekly SBMs during the first ($p = 0.006$) and second week of the study ($p = 0.014$), and over the entire study period ($p = 0.046$) when compared to placebo, although no difference was noted at week 3 ($p = 0.298$). Each of the three treatment arms showed significant improvement in SBM frequency at

week 2 of the study compared with placebo ($p \leq 0.020$), but only the 48 µg treatment group showed a statistically significant improvement over the entire treatment period ($p = 0.015$). A larger percentage of patients in each treatment arm had an SBM in 24 h of initial dosing of lubiprostone compared to placebo; the difference for the two highest dosing groups was statistically significant (placebo group = 27.3%; 48 µg = 59.4%, $p = 0.009$; 72 µg = 63.6%, $p = 0.003$). Several measures of constipation were assessed each week during the trial period using 4- and 5-point scales. The lubiprostone treatment group experienced a statistically significant improvement over the entire treatment period when compared to baseline in the mean degree of straining ($p < 0.005$), stool consistency ($p < 0.0001$), abdominal bloating ($p = 0.035$), severity of constipation ($p = 0.010$) and overall rating of treatment effectiveness ($p = 0.045$). Abdominal discomfort and bloating improved but did not reach statistical significance ($p = 0.136$). Finally, no differences were noted between the groups with regard to the use of rescue medications (bisacodyl pills or sodium phosphate enemas).

During this 3-week study, no significant differences were found between the two groups with regard to vital signs, physical examination, electrocardiograms (ECG) or blood work (complete blood count, electrolytes, blood urea nitrogen/creatinine, glucose). There were no drug-related serious adverse events during the trial. Sixty-nine percent of patients in the lubiprostone group experienced at least one adverse event compared to 39% of patients taking placebo ($p = 0.006$). Twelve (9%) patients reported adverse events of severe intensity. Of these events, ten were experienced by more than one patient and included: headache (two patients in the 72 µg arm), diarrhea (four patients in the 72 µg arm), abdominal pain (one patient in the placebo arm and one patient in the 48 µg group), and nausea (one patient in each of the lubiprostone 48 and 72 µg groups). Overall, nausea was the most common adverse event reported by 31% of patients taking lubiprostone but none taking placebo. Most patients rated the nausea as mild or moderate in nature. Four percent of study patients discontinued the study because of nausea. Diarrhea occurred in ~ 10% of patients taking lubiprostone but none taking placebo.

The results of two separate Phase III multi-center trials reinforce the findings of the initial dose-ranging study [32,33]. Patients were classified as having symptoms of chronic constipation using modified Rome II criteria as previously described [31]. The first study involved 242 subjects (mean age = 48.6 years; 90% women; > 84% Caucasian) from 20 centers across the US [32]. Patients were randomized to twice-daily lubiprostone (24 µg) or placebo taken with food after a 2-week baseline period. Prescription and over-the-counter constipation remedies were prohibited during the washout and study periods, although bisacodyl suppositories or sodium phosphate enemas were available as 'rescue' therapy for those subjects without a bowel movement for three or more consecutive days. Compared to placebo, the treatment group had more SBMs during week 1 (5.7 versus 3.5, $p = 0.0001$), and the effect was sustained during each of the subsequent weeks of the study. A larger percentage of patients on lubiprostone had an SBM in 24 h (56.7 versus 36.9%, $p = 0.0024$) and in 48 h (80.0 versus 60.7%, $p = 0.0013$). The need for rescue medications was similar in both groups at baseline but decreased in the lubiprostone group by the end of the study period (35.6 versus 50.8%, $p = 0.0357$). Symptom scores were significantly improved with lubiprostone compared to placebo for weeks 1 – 4 for stool consistency ($p < 0.0001$), straining ($p \leq 0.0001$) and constipation severity ($p \leq 0.0003$). Abdominal bloating was improved in the lubiprostone treated group compared to placebo during weeks 1 – 2 ($p \leq 0.031$), whereas abdominal discomfort scores were significantly improved for weeks 2 – 4 ($p \leq 0.045$). Seventy percent of subjects on lubiprostone reported at least one adverse event compared to 50.8% of patients on placebo ($p = 0.0026$). The most common treatment-related adverse event was nausea, occurring in 31.7% of the lubiprostone group and 3.3% of the placebo group ($p < 0.001$). Five percent of patients discontinued the study due to nausea.

The second Phase III trial included 237 subjects (mean age = 45.8 years; 88% women) [33]. Patients on lubiprostone experienced significant improvement in the frequency of weekly bowel movements (5.9 versus 4.00, $p < 0.0001$). Similar to the previously described studies, patients on lubiprostone reported improvements in subjective measures of constipation, and more patients experienced an SBM in the first 24 h in the lubiprostone group than the placebo group (61 versus 31%, $p < 0.0001$). Nausea, headache and diarrhea were again the most commonly reported adverse effects. Mild to moderate nausea occurred more frequently in the lubiprostone treated group than in the placebo group in the second study (21 versus 4.2%; p-value not reported) [34]. No serious adverse events were reported; fifteen lubiprostone patients withdrew from the second trial.

Sudden cessation of a medication may result in a worsening of symptoms above baseline, a phenomena referred to as a 'rebound effect'. The potential for rebound constipation developing following lubiprostone withdrawal was evaluated in 128 subjects (mean age and gender not reported) with symptoms of chronic constipation treated with lubiprostone (24 µg) twice-daily for 4 weeks [35]. After the initial 4-week study period, subjects were then randomized to receive three more weeks of lubiprostone or placebo. A rapid and sustained improvement in SBM similar to that seen in the other trials was observed (1.4 a week at baseline versus 6.3, 5.9 and 5.5 at weeks 1, 2 and 3, respectively; $p < 0.0001$ at all weeks). Three weeks after randomization to placebo or to

continued lubiprostone, the SBM frequency declined in the placebo group (3.04 versus 5.59; p = 0.0464) but remained improved compared to baseline (3.0 versus 1.4; p = 0.0223), arguing against significant rebound constipation after lubiprostone withdrawal.

5.2 Open-label studies

Three large, open-label studies have been conducted to assess the long-term efficacy of lubiprostone in the treatment of chronic constipation. 308 patients were entered into one 24-week study, whereas another 572 patients were entered into two separate 48-week trials. The severity of constipation, bloating and abdominal discomfort were periodically assessed among all 880 patients [36]. Statistically significant improvements were reported for all symptoms throughout the trial periods (p < 0.0001). Constipation severity improved in all three studies by an average of 26% at weeks 4 – 6 (n = 828), 29% at week 24 (n = 512) and 28% at week 48 (n = 281). Bloating improved by an average of 18% at weeks 4 – 6 (n = 829), and 20% at weeks 24 (n = 512) and 48 (n = 282). Abdominal discomfort improved by an average of 15% at week 1 (n = 619), 18% at week 24 (n = 512) and 17% at week 48 (n = 282).

5.3 Gender differences

Women have accounted for most subjects in all of the clinical trials of lubiprostone performed until now. A subgroup analysis of the 4-week controlled trials was performed to evaluate efficacy in men [37]. Pooled data yielded 27 male placebo subjects and 32 lubiprostone subjects. Male subjects taking lubiprostone experienced 5.69 – 6.05 SBMs a week compared to 2.55 – 3.23 in the placebo group (p < 0.0489 at week 3, p = 0.0503 at week 4). These rates were higher compared to females in the trials (4.99 – 5.75 SBM/week). Fifty percent of male subjects taking lubiprostone experienced at least one side effect compared to 33.3% of men taking placebo (exact details of adverse effects were not reported).

6. IBS with constipation

The safety and efficacy of lubiprostone in the treatment of IBS-C was first evaluated in a multi-center, double-blind, placebo-controlled dose-ranging study involving 195 patients [38]. Patients who met Rome III criteria for IBS-C were randomized to 12 weeks of treatment with either placebo or one of three different doses of lubiprostone (8, 16 or 24 µg b.i.d.) after a 4-week screening period. The primary end point was the change in abdominal pain/discomfort during the first 4 weeks of therapy. Secondary end points included the frequency of SBM, stool consistency, straining at stool and abdominal bloating. Laboratory tests (complete blood count, electrolytes, blood urea nitrogen/creatinine, glucose), EKGs, symptom diaries and IBS-quality of life scores were monitored throughout the study. Most patients were women (92%) and Caucasian (83%). At 1 and 2 months, patients treated with any dose of lubiprostone had a greater improvement in mean abdominal pain and discomfort scores compared to placebo (p = 0.023 and 0.039, respectively). At 3 months, there was no difference in the response rates for abdominal pain and discomfort in patients treated with lubiprostone compared to placebo. As well, symptoms of bloating were not improved. A greater number of adverse events were noted with the higher doses of lubiprostone. Patients treated with the 24 µg b.i.d. dose of lubiprostone had the greatest improvement in symptoms; however, they also had the greatest number of adverse events. Although not the focus of this study, IBS quality of life scores were not statistically better in the lubiprostone group compared to the placebo group, although this dose-ranging study was not powered to accurately measure changes in quality of life scores. Overall, the authors concluded that the 8 µg twice-daily dose provided the best combination of efficacy and safety.

The results of two separate Phase III studies evaluating the safety and efficacy of lubiprostone in patients with IBS and constipation were recently published in an abstract form [39]. These two studies enrolled 1171 adults diagnosed with IBS-C using the Rome II criteria and randomized them to receive either 12 weeks of b.i.d. lubiprostone (8 µg) or placebo dosed with food. Most patients were women (91.6%), and were between the ages of 18 and 65 (91.7%). The primary efficacy variable was a global question rating overall IBS symptoms, whereas a 7-point balanced scale was used to rate changes in individual symptoms. Patients reporting at least moderate relief for 4 out of 4 weeks or patients reporting significant relief 2 out of 4 weeks were considered monthly responders, and patients had to be a monthly responder for at least 2 out of the 3 months to qualify as an overall responder (**Table** 4). The authors reported that patients receiving lubiprostone were nearly twice as likely as those receiving placebo to achieve overall response (17.9 versus 10.1%; p = 0.001). Secondary end points including abdominal pain, bloating, straining, stool consistency and constipation were all significantly improved in the lubiprostone group compared to the placebo group (p < 0.05 for all end points). Lubiprostone was generally well tolerated. The most common treatment-related side effects were nausea (8 versus 4% in placebo) and diarrhea (6 versus 4% in placebo). Of note, it is thought that the low placebo rate in this study is due to the much stricter standards for determining whether a patient is classified as a responder. In addition, the lower dose (8 µg) was chosen based on previous dose-ranging studies and may reflect the fact that patients with IBS often respond to medications at lower doses than other patients.

Patients who demonstrated > 70% study drug compliance during the 12-week blinded trial were invited to participate in a 36-week open-label extension study [40]. The primary end point was the same as used in the Phase III trials.

Table 4. Definition of a responder in the Phase III irritable bowel syndrome with constipation trials.

Responder question
"How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits and other IBS symptoms) over the past week compared to how you felt before you entered the study?"
Response choices (7-point balanced scale)
Significantly relieved
Moderately relieved
A little bit relieved
No change
A little bit worse
Moderately worse
Significantly worse
Monthly responder: A response of "Moderately relieved" or better in 4 out of 4 weeks
Or
A response of "Significantly relieved" in 2 out of 4 weeks
And
The percent of days of rescue medication use does not increase during the month as compared to baseline
And
Lubiprostone is not discontinued during the month due to lack of efficacy
And
There are no ratings during the month of "Moderately worse" or "Significantly worse"
Overall responder: A monthly responder for at least 2 out of the 3 months of the trial

IBS: Irritable bowel syndrome.

A total of 476 patients received 8 µg b.i.d. lubiprostone during the extension trial. Patients initially treated with placebo noted an increase in response from 8 to 31%, whereas those treated with lubiprostone noted a further increase in response from 15 to 37%. No serious adverse events were recorded, although nausea (3.5%) and diarrhea (4.8%) were the most common reported adverse events. Further trials are planned to assess the long-term benefits of lubiprostone in patients who have IBS with constipation.

7. Adverse effects and safety

A study of 26 healthy volunteers was designed to evaluate the safety and tolerability of lubiprostone [41]. Subjects in each group received either placebo or one of three doses of lubiprostone (72, 90 or 108 µg divided into three daily doses). The subjects were monitored closely for 7 days without any changes in ECGs, laboratory testing or vital signs. There were no serious adverse events. Two subjects who withdrew from the study did so voluntarily and had no adverse events. Almost all of the adverse events consisted of GI symptoms including vomiting, nausea and abdominal cramping. As expected, subjects receiving lubiprostone experienced more diarrhea than those on placebo. The effect did not seem to be dose-dependent.

Pooled data from previously mentioned studies, including 258 patients from two blinded studies and 858 patients from three open-label trials, were reviewed for a change in serum electrolytes due to lubiprostone (24 µg b.i.d.) [42]. In the blinded and open-label trials, 10.5 and 18.6% of patients, respectively, were 65 years of age or greater. There were no changes in electrolytes observed over the treatment period, which ranged from 12 to 48 weeks.

ECG changes due to lubiprostone were evaluated in 177 patients with chronic constipation and 68 healthy male and female volunteers (age was not reported) [43]. ECGs before and after a single dose of 24 µg lubiprostone or a supratherapeutic dose of 144 µg did not show any changes.

Analysis of post-marketing data found that some patients taking Amitiza experienced dyspnea within an hour of the first dose. This generally resolved spontaneously in 2 – 3 h, without any long term adverse effects. Patients should be cautioned to stop lubiprostone if this occurs and not restart it until evaluated by a knowledgeable health care provider. The exact mechanism by which lubiprostone causes dyspnea is not known at present.

In summary, lubiprostone seems to be safe with few serious adverse events. As previously noted, the most common adverse events are nausea, headache and diarrhea. Nausea and diarrhea seem to be dose-dependent. We do not recommend using lubiprostone during pregnancy due to the lack of human reproductive data, and the manufacturers have recommended using lubiprostone during pregnancy only if the benefits significantly outweigh potential risks. Before initiating therapy, a pregnancy test should be checked in all women of child-bearing age not using a reliable form of birth control. As noted above, lubiprostone is pregnancy category "C." Given the limited data available, we also do not recommend using lubiprostone in women who are breastfeeding (**Table 5**).

8. Future uses

8.1 Opioid-induced constipation

Constipation is a frequent side effect of opioid use. Studies to evaluate the efficacy and safety of lubiprostone in opioid-induced constipation in humans have begun, although data are not yet available. Lubiprostone does seem to improve opioid-induced constipation in a mouse model, however [44].

Table 5. Key properties of lubiprostone.

Recommended dosage	24 µg twice-daily
Route of administration	Oral
Time to peak plasma concentration	Approximately 1.5 h
Estimated terminal half-life	Approximately 3 h
Bioavailability	< 1%
Metabolite	M3: partially active
Metabolism	Carbonyl reductase
Pregnancy category	C

8.2 Pediatrics

Constipation is a common problem in children, although therapeutic choices are hampered by a lack of data from well-designed clinical trials. Studies are now planned to assess the safety and efficacy of lubiprostone in the pediatric population.

9. Conclusion

It is important to note that lubiprostone is at present the only medication approved by the FDA for the treatment of women with IBS-C. Clinicians who practice medicine using an evidence-based approach should choose this as the first therapeutic agent for women who have IBS and constipation if they wish to treat the global symptoms of IBS. In a similar light, lubiprostone is one of only three agents approved by the FDA for the treatment of chronic constipation [16]. Owing to insurance regulations, clinicians are generally not allowed to treat chronic constipation patients with lubiprostone until they have failed lifestyle modifications and over-the-counter agents such as polyethylene glycol. Data supporting the use of lactulose as a first-line agent is considerably weaker than for lubiprostone and thus lactulose is not recommended as a first-line agent.

10. Expert Opinion

Lubiprostone's route to FDA approval has followed a pathway similar to other recent drug treatments for chronic constipation and IBS-C. A relatively small number of preclinical studies identified a plausible mechanistic explanation for the benefit of constipation-related complaints. This was followed by the requisite toxicology, pharmacokinetic and pharmacodynamic studies, culminating in large, randomized, placebo-controlled clinical trials. Based on the available evidence, it is reasonable to conclude that lubiprostone should be added to the short list of evidence-based pharmacotherapies for chronic constipation and IBS-C.

Although the evidence supports the efficacy of lubiprostone for some patients with chronic constipation and IBS-C, a full understanding of the mechanisms responsible for these benefits remains to be determined. Lubiprostone's prosecretory effects provide a plausible explanation for its beneficial effects on constipation-associated symptoms. However, the mechanistic explanation for lubiprostone's effect on abdominal pain/discomfort in patients with IBS-C remains unclear. The beneficial effects of lubiprostone on abdominal pain/discomfort are all the more intriguing given that the effective dose in IBS-C is one-third of the effective dose in chronic constipation. It is possible that the benefits for pain are simply a byproduct of improving constipation-associated symptoms such as stool frequency, stool consistency and straining. Alternatively, it is also possible that improvements in abdominal pain/discomfort could be the consequence of an effect on visceral sensation. Abnormalities in intestinal barrier function have been identified in some patients with IBS. A recent study in pigs found that lubiprostone accelerated recovery of mucosal barrier function after ischemic injury of the ileum [45]. It has been hypothesized that a beneficial effect of lubiprostone on intestinal barrier function may provide a mechanistic explanation for the improvement in abdominal pain in IBS-C patients. This interesting, but very preliminary, data requires confirmation and elaboration.

It is also intriguing to consider the potential consequences of the FDA's approval of a lower dose of lubiprostone for IBS-C than for chronic constipation. The availability of the 8 µg dose provides clinicians with an effective treatment for a subset of patients with IBS-C. In addition, the 8 µg dose may prove useful for patients with chronic constipation who cannot tolerate the 24 µg dose because of nausea or diarrhea. Unfortunately, recommending and approving different doses of lubiprostone for chronic constipation and IBS-C will make it necessary for clinicians to distinguish between patients with chronic constipation and IBS-C. As longitudinal studies suggest that patients with functional disorders sometimes migrate between diagnoses, the recommendation of different doses of lubiprostone for these two conditions may cause confusion for clinicians. Given the overlap between chronic constipation and IBS-C, clinicians can consider two strategies when deciding on the initial dose of lubiprostone. Based on current product labeling, it is recommended that 8 µg b.i.d. be started in patients with IBS-C whereas 24 µg b.i.d. be used in those with chronic constipation. Alternatively, utilizing the minimum dose in all patients followed by dose escalation in nonresponders may decrease the chance of developing significant side effects with lubiprostone. Only further studies and clinical experience will settle this important question.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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CME

American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation

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Irritable bowel syndrome (IBS) and chronic idiopathic constipation ((CIC) also referred to as functional constipation) are two of the most common functional gastrointestinal disorders worldwide. IBS is a global problem, with anywhere from 5 to 15% of the general population experiencing symptoms that would satisfy a definition of IBS (1,2). In a systematic review on the global prevalence of IBS, Lovell and Ford (1) documented a pooled prevalence of 11% with all regions of the world suffering from this disorder at similar rates. Given its prevalence, the frequency of symptoms, and their associated debility for many patients and the fact that IBS typically occurs in younger adulthood, an important period for furthering education, embarking on careers, and/or raising families, the socioeconomic impact of IBS is considerable. These indirect medical costs are frequently compounded by the direct medical costs related to additional medical tests and the use of various medical and nonmedical remedies that may have limited impact. CIC is equally common; in another systematic review, Suares and Ford (3) reported a pooled prevalence of 14%, and also noted that constipation was more common in females, in older subjects, and those of lower socioeconomic status (3). Chronic constipation has also been linked to impaired quality of life (4), most notably among the elderly (5).

Neither IBS nor CIC are associated with abnormal radiologic or endoscopic abnormalities, nor are they associated with a reliable biomarker; diagnosis currently rests entirely, therefore, on clinical grounds. Although a number of clinical definitions of both IBS and CIC have been proposed, the criteria developed through the Rome process, currently in its third iteration, have been those most widely employed in clinical trials and, therefore, most relevant to any review of the literature on the management of these disorders.

According to Rome III, IBS is defined on the basis of *the presence of:*

Recurrent abdominal pain or discomfort at least 3 days/month in the past 3 months associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (6).

Rome III defines functional constipation as: the presence of two or more of the following:

- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week

Furthermore, loose stools are rarely present without the use of laxatives and there are insufficient criteria for IBS. Again, these criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis (6).

In Rome III, IBS is subtyped according to predominant bowel habit as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed type (IBS-M), and unclassified (IBS-U). The definition of

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bowel habit type is, in turn, based on the patient's description of stool form by referring to the Bristol Stool Scale (7). The recognition that IBS sufferers segregate into subtypes according to predominant bowel habit, together with research findings suggesting that IBS-C and IBS-D may be pathophysiologically distinct entities (8–10), led to the development of therapies specifically directed at each of these subtypes. Nonetheless, it is worth noting that symptoms may not be stable over a lifetime and individuals may exhibit one IBS subtype during a period, and then a different IBS subtype during another period in their lives.

However, although there is general awareness of the Rome criteria, they are infrequently employed in the assessment of IBS and CIC in clinical practice (11). To provide more "clinician friendly" definitions, as well as to permit inclusion of studies that predated the Rome process, American College of Gastroenterology Task Forces suggested the following definitions in prior systematic reviews:

IBS is defined by: *abdominal discomfort associated with altered bowel habits* (12).

Constipation is defined as: *a symptom-based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both.* Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool. CIC is defined as the presence of these symptoms for at least 3 months (13).

It is important to note that the Rome III criteria state that i ndividuals with chronic constipation do not fulfill criteria for IBS, with pain or discomfort being a major determinant in the latter. In practice, a clear separation between CIC and IBS with constipation may be challenging and studies have shown, not only considerable overlap between these entities (14–16), but also a significant tendency for patients to migrate between these diagnoses over time (15). It is appropriate therefore that in this update of prior American College of Gastroenterology monographs on IBS and CIC, these entities be addressed in the same exercise (12,13,17). The goal of this exercise, therefore, was to update the most recent systematic reviews commissioned by the American College of Gastroenterology on IBS from 2009 (17) and CIC from 2005 (13).

METHODS

We have conducted a series of systematic reviews on the efficacy of therapy in IBS and CIC. There have been several systematic reviews of therapy for IBS and CIC published in the past 5 years (18–22). There have been considerable data published in the intervening time, and hence we have, therefore, updated all these systematic reviews of IBS and CIC and synthesized the data, including the information from new trials, where appropriate.

The primary objective of this exercise was to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment. The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS with constipation, IBS with diarrhea, and mixed IBS), as well as assessing adverse events with therapies for both IBS and CIC.

Systematic review methodology

We evaluated manuscripts that studied adults (aged >16 years) using any definition of IBS or CIC. For IBS, this included a clinician-defined diagnosis, the Manning criteria (23), the Kruis score (24), or Rome I (25), II (26), or III (6) criteria. For CIC, this included symptoms diagnosed by any of the Rome criteria (6,25,26), as well as a clinician-defined diagnosis. We included only parallel-group randomized controlled trials (RCTs) comparing active intervention with either placebo or no therapy. Crossover trials were eligible for inclusion, provided extractable data were provided at the end of the first treatment period, before crossover.

For IBS, the following treatments were considered:

1. Diet and dietary manipulation
2. Fiber
3. Interventions that modify the microbiota: probiotics, prebiotics, antibiotics
4. Antispasmodics
5. Peppermint oil
6. Loperamide
7. Antidepressants
8. Psychological therapies, including hypnotherapy
9. Serotonergic agents
10. Prosecretory agents
11. Polyethylene glycol

For CIC, the following were considered:

1. Fiber
2. Osmotic and stimulant laxatives
3. 5-HT_4 agonists
4. Prosecretory agents
5. Biofeedback
6. Bile acid transporter inhibitors
7. Probiotics

Subjects needed to be followed up for at least 1 week. To be eligible, trials needed to include one or more of the following outcome measures:

(i) Global assessment of improvement in IBS or CIC symptoms
(ii) Improvement in abdominal pain for IBS
(iii) Global IBS symptom or abdominal pain scores for IBS
(iv) Mean number of stools per week during therapy for CIC

Search strategy for identification of studies

MEDLINE (1946 to October 2013), EMBASE and EMBASE Classic (1947 to October 2013), and the Cochrane central register of controlled trials were searched.

Studies on IBS were identified with the terms *irritable bowel syndrome* and *functional diseases*, *colon* (both as medical subject

headings (MeSH) and free text terms), and *IBS*, *spastic colon*, *irritable colon*, and *functional* adj5 *bowel* (as free text terms).

For RCTs of dietary manipulation, these were combined using the set operator AND with studies identified with the terms: *diet*, *fat-restricted*, *diet*, *protein-restricted*, *diet*, *carbohydrate-restricted*, *diet*, *gluten-free*, *diet*, *macrobiotic*, *diet*, *vegetarian*, *diet*, *Mediterranean*, *diet fads*, *gluten*, *fructose*, *lactose intolerance*, or *lactose* (both as MeSH and free text terms), or the following free text terms: *FODMAP$*, *glutens*, *food adj5 intolerance*, *food allergy*, or *food hypersensitivity*.

For RCTs of fiber, antispasmodics, and peppermint oil, these were combined using the set operator AND with studies identified with the terms: *dietary fiber*, *cereals*, *psyllium*, *methylcellulose*, *sterculia*, *karaya gum*, *parasympatholytics*, *hyoscyamine*, *scopolamine*, *trimebutine*, *muscarinic antagonists*, or *butylscopolammonium bromide* (both as MeSH and free text terms), or the following free text terms: *bulking agent*, *psyllium fiber*, *fiber*, *husk*, *bran*, *ispaghula*, *wheat bran*, *calcium polycarbophil*, *spasmolytics*, *spasmolytic agents*, *antispasmodics*, *mebeverine*, *alverine*, *pinaverium bromide*, *otilonium bromide*, *cimetropium bromide*, *hyoscine butyl bromide*, *butylscopolamine*, *peppermint oil*, or *colpermin*.

For RCTs of probiotics, these were combined using the set operator AND with studies identified with the terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*, or *probiotics* (both as MeSH and free text terms). For RCTs of prebiotics and synbiotics, these were combined using the set operator AND with studies identified with the term: *prebiotic* (both MeSH and free text terms) or *synbiotic* (both MeSH and free text terms). For RCTs of antibiotics, these were combined using the set operator AND with studies identified with the terms: *anti-bacterial agents*, *penicillins*, *cephalosporins*, *rifamycins*, *quinolones*, *nitroimidazoles*, *tetracycline*, *doxycycline*, *amoxicillin*, *ciprofloxacin*, *metronidazole*, or *tinidazole* (both as MeSH and free text terms), or the following free text terms: *antibiotic* or *rifamixin*.

For RCTs of loperamide, these were combined using the set operator AND with studies identified with the terms: *loperamide* or *antidiarrheals* (both as MeSH and free text terms), or the following free text terms: *imodium* or *lopex*.

For RCTs of antidepressants and psychological therapies, including hypnotherapy, these were combined using the set operator AND with studies identified with the terms: *psychotropic drugs*, *antidepressive agents*, *antidepressive agents (tricyclic)*, *desipramine*, *imipramine*, *trimipramine*, *doxepin*, *dothiepin*, *nortriptyline*, *amitriptyline*, *selective serotonin reuptake inhibitors*, *paroxetine*, *sertraline, fluoxetine*, *citalopram*, *venlafaxine*, *cognitive therapy*, *psychotherapy*, *behavior therapy*, *relaxation techniques*, or *hypnosis* (both as MeSH and free text terms), or the following free text terms: *behavioral therapy*, *relaxation therapy*, or *hypnotherapy*.

For RCTs of serotonergic agents, these were combined using the set operator AND with studies identified with the terms: *serotonin antagonists*, *serotonin agonists*, *cisapride*, *receptors* (*serotonin*, *5-HT$_3$*), or *receptors* (*serotonin*, *5-HT$_4$*) (both as MeSH and free text terms), or the following free text terms: *5-HT$_3$*, *5-HT$_4$*, *alosetron*, *cilansetron*, *ramosetron*, *prucalopride*, *mosapride*, or *renzapride*.

For RCTs of pro-secretory agents, these were combined using the set operator AND with studies identified with the following free text terms: *linaclotide* or *lubiprostone*.

For RCTs of polyethylene glycol (PEG), these were combined using the set operator AND with studies identified with the term *polyethylene glycol* (both as a MeSH and free text term).

Studies on CIC were identified with the terms *constipation* or *gastrointestinal transit* (both as MeSH and free text terms), or *functional constipation*, *idiopathic constipation*, *chronic constipation*, or *slow transit* (as free text terms). For the search involving biofeedback, the free text terms *dyssynergia*, *pelvic floor dysfunction*, *anismus*, and *outlet obstruction* were also added.

For RCTs of fiber, these were combined using the set operator AND with studies identified with the terms: *dietary fiber*, *cellulose*, *plant extracts*, *psyllium*, *cereals*, *plantago*, or *methylcellulose* (both as MeSH and free text terms), or the following free text terms: *fiber*, *soluble fiber*, *insoluble fiber*, *bran*, *ispaghula*, *metamucil*, *fybogel*, or *ispaghula*.

For RCTs of osmotic and stimulant laxatives, these were combined using the set operator AND with studies identified with the terms: *laxatives*, *cathartics*, *anthraquinones*, *phenolphthaleins*, *indoles*, *phenols*, *lactulose*, *polyethylene glycol*, *senna plant*, *senna extract*, *bisacodyl*, *phosphates*, *dioctyl sulfosuccinic acid*, *magnesium*, *magnesium hydroxide*, *sorbitol*, *poloxamer* (both as MeSH and free text terms), or the following free text terms: *sodium picosulphate*, *docusate*, *milk of magnesia*, *danthron*, *senna*, and *poloxalkol*.

For RCTs of 5-HT$_4$ agonists, these were combined using the set operator AND with studies identified with the terms: *serotonin agonists, receptors*, or *serotonin*, *5-HT$_4$* (both as MeSH and free text terms), or the following free text terms: *prucalopride*, *velusetrag*, or *naronapride*.

For RCTs of pro-secretory agents, these were combined using the set operator AND with studies identified with the following free text terms: *lubiprostone* or *linaclotide*.

For RCTs of biofeedback, these were combined using the set operator AND with studies identified with the MESH terms *biofeedback* and *psychology* and the following free text terms: *biofeedback* or *neuromuscular training*.

For RCTs of bile acid transporter inhibitors, these were combined using the set operator AND with studies identified with the following free text terms: *bile acid transporter*, *elobixibat*, or *A3309*.

For RCTs of probiotics, these were combined using the set operator AND with studies identified with the terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *E. coli*, or *probiotics* (both as MeSH and free text terms). For RCTs of prebiotics and synbiotics, these were combined using the set operator AND with studies identified with the term: *prebiotic* (both MESH and free text terms) or *synbiotic* (both MESH and free text terms).

The search was limited to humans. No restrictions were applied with regard to language of publication. A recursive search of the bibliography of relevant articles was also conducted. DDW (Digestive Diseases Week) and UEGW (United European

Gastroenterology Week) abstract books were hand searched between 2000 and 2013. Authors of trial reports that did not give enough detail for adequate data extraction were contacted and asked to contribute full data sets. Experts in the field were contacted for leads on unpublished studies.

Trials were assessed for risk of bias according to the methods described in the Cochrane handbook [27] using the following characteristics: method used to generate the randomization schedule, method used to conceal treatment allocation, implementation of masking, completeness of follow-up, and conduct of an intention-to-treat analysis.

Eligibility, quality, and outcome data were extracted by the lead reviewer (Alexander Ford) and by a masked second reviewer (Paul Moayyedi) on to specially developed forms. Any discrepancy was resolved by discussion between the two reviewers in order to reach a consensus. Data were extracted as intention-to-treat analyses, where all dropouts were assumed to be treatment failures, wherever trial reporting allowed this.

Data synthesis

For IBS, whenever possible, *any improvement of global IBS symptoms* as a binary outcome was taken as the primary outcome measure. If this was not available, *improvement in abdominal pain* was used. For CIC, *any improvement of global CIC symptoms* as a binary outcome was taken as the primary outcome measure. The impact of interventions was expressed as a relative risk (RR) of IBS or CIC symptoms not improving, together with 95% confidence intervals (CIs). If there were sufficient data, RRs were combined using the DerSimonian and Laird random effects model (28) to give a more conservative estimate of the efficacy of individual IBS therapies. For continuous data, such as global IBS symptom scores or individual IBS symptom scores, a standardized mean difference, with 95% CIs, was calculated. It should be noted that some treatments may be beneficial in IBS or CIC because of the effects on outcomes other than global symptoms or abdominal pain, but this was not evaluated and was outside of the scope of this review.

Tests of heterogeneity were reported (29). When the test of heterogeneity was significant ($P<0.10$ and/or $I^2>25\%$), the reasons for this were explored by evaluating differences in study population, study design, or study end points in subgroup analyses. Publication bias or other causes of small study effects were evaluated using tests for funnel plot asymmetry (30), where sufficient studies were identified (31).

The number needed to treat (NNT), which is the number of patients who would need to receive active therapy, over and above the control therapy, for one to experience an improvement in symptoms, and the number needed to harm (NNH), which is the number of patients who would need to receive active therapy, over and above the control therapy, for one to experience an adverse event were calculated as the inverse of the risk difference from the meta-analysis and checked using the formula: $\mathrm{NNT} = 100 / \mathrm{RRR} \times \mathrm{BR}$, where BR is baseline risk and RRR is relative risk reduction.

Box 1. Interpretation of the grading of the quality of evidence

Quality of evidence	Interpretation
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	The estimate of effect is very uncertain.

From: http://www.gradeworkinggroup.org.

Methodology for assessing levels of evidence and grading recommendations

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for grading the quality of evidence and strength of recommendation for each medical intervention (32). The system has been widely used in evidence-based guidelines and is endorsed by all major gastrointestinal societies (http://www.gradeworkinggroup.org). The quality of the evidence is based on the study design, as well as the extent of risk of bias, inconsistency, indirectness, imprecision, and publication bias that exists for the evidence supporting the intervention (33). Quality of evidence is described as high to very low, depending on the extent to which further evidence would change the estimate of treatment effect (**Box 1**). The grading scheme also classifies recommendations as strong or weak, according to the quality of the evidence, applicability to all patient groups, balance of benefits and risks, patient preferences, and cost. With this graded recommendation, the clinician receives guidance about whether or not recommendations should be applied to most patients, and whether or not recommendations are likely to change in the future after production of new evidence. "Strong" recommendations represent a "recommendation that can apply to most patients in most circumstances and *further evidence is unlikely to change our confidence in the estimate of treatment effect.*" The summary of the evidence for IBS is presented in **Table 1**, the reasons for the decision on the quality of that evidence in **Table 2**, and the reasons for the strength of recommendation in **Table 3**. Similarly, the summary of the evidence for CIC is presented in **Table 4**, the reasons for the decision on quality of the evidence in **Table 5**, and the reasons for the strength of recommendation in **Table 6**.

RESULTS

Irritable bowel syndrome

1. Diet and dietary manipulation in IBS

(a) Role of diet in IBS: Although food intake is one of the most common precipitants of symptoms in IBS (34), responses to food ingestion and interactions with components of the diet have not typically undergone rigorous evaluation in the context of a blinded trial. Based on their own experiences, IBS sufferers have generated their own theories to explain this phenomenon or seek guidance from other, usually unsupported, dietary remedies.

Table 1. Summary of results of monograph on interventions for IBS

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Specialized diets may improve symptoms in individual IBS patients.	3	230	NA	NA	Weak	Very low
Fiber provides overall symptom relief in IBS.	14	906	0.86 (0.80–0.94)	10 (6–33)	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	7	499	0.83 (0.73–0.94)	7 (4–25)	Weak	Moderate
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	2	198	NA	NA	Weak	Very low
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	23	2,575	0.79 (0.70–0.89)	7 (4–12.5)	Weak	Low
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	5	1,805	0.84 (0.78–0.90)	9 (6–12.5)	Weak	Moderate
Certain antispasmodics provide symptomatic short-term relief in IBS.	23	2,154	0.69 (0.59–0.81)	5 (4–9)	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms.	5	482	0.51 (0.33–0.79)	3 (2–4)	Weak	Moderate
There is insufficient evidence to recommend loperamide for use in IBS.	2	42	0.44 (0.14–1.42)	NA	Strong	Very low
As a class, antidepressants are effective in symptom relief in IBS.	17	1,084	0.67 (0.58–0.77)	4 (3–6)	Weak	High
A variety of psychological interventions are effective in improving IBS symptoms.	32	2,189	0.68 (0.61–0.76)	4 (3–5)	Weak	Very low
Alosteron is effective in females with IBS-D.	8	4,987	0.79 (0.69–0.90)	8 (5–17)	Weak	Moderate
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	9	2,905	0.96 (0.83–1.11)	NA	Strong	Low
Linaclotide is superior to placebo for the treatment of IBS-C.	3	2,028	0.80 (0.75–0.85)	6 (5–8)	Strong	High
Lubiprostone is superior to placebo for the treatment of IBS-C.	3	1,366	0.91 (0.87–0.95)	12.5 (8–25)	Strong	Moderate
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	2	166	NA	NA	Weak	Very low

CI, confidence interval; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NA, not available; NNT, number needed to treat; RR, relative risk.

Many IBS patients commonly believe that they have an allergy to certain foods, although true food allergies are uncommon in IBS (35). Thus, although the prevalence of true food allergies in Western societies is between 1 and 3% in adults, surveys of gastrointestinal clinic patients found that 30–50% believed that their symptoms represented food allergy or food intolerance (35–37). Most food-related IBS symptoms appear to represent food intolerance, although only 11–27% of patients can accurately identify the presumed offending food when re-challenged in a double-blind manner (38). Based on their own experiences with food, and despite a lack of objective evidence to incriminate a specific food, studies have shown that a majority of IBS patients institute dietary changes (39–41), sometimes to an extent that may compromise their nutrition (42).

(b) Role of dietary manipulation in IBS: Specialized diets may improve symptoms in individual IBS patients.
Recommendation: weak. Quality of evidence: very low.

We identified 12 RCTs that evaluated dietary intervention in IBS (43–54). Following exclusions due to nonextractable data (46,48,50,52–54), lack of relevant symptom data (45,49,51), and an intervention lasting <1 week (46), three evaluable RCTs involving 230 patients remained (43,44,47).

The first of these addressed the impact of gluten in IBS. In a double-blind, placebo-controlled trial, 34 patients with IBS were randomized to either remain on a gluten-free diet or to receive 16 g/day of gluten on completion of an open gluten-free run-in phase (44). In the gluten group, 68% (13/19) reported that their

Table 2. Reasons for quality of evidence of assessment for IBS data according to GRADE criteria

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Specialized diets may improve symptoms in individual IBS patients.	Very low	Only one low risk of bias trial	Each eligible RCT evaluated a different intervention	✓[a]	Only a small number of patients studied	Not evaluable
Fiber provides overall symptom relief in IBS.	Moderate	Only one low risk of bias trial and two high risk of bias	✓	✓	✓	✓
Psyllium, but not bran, provides overall symptom relief in IBS.	Moderate	Only one low risk of bias trial but this contributed to almost half the total number of patients and this trial mirrored the result of the meta-analysis	✓	Only one trial compared the two types of fibers. This trial confirmed the result of the systematic review at week 4 but not at week 12	✓	✓
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Very low	Only one synbiotic trial with dichotomous data. Overall result positive. Meta-analysis of continuous data from two trials showed no benefit	Differences in efficacy between the dichotomous and continuous data. Each trial evaluated a different preparation	✓	Only a small number of patients studied	Not evaluable
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	Low	✓	Significant heterogeneity between studies that was unexplained. Inconsistency considered very serious as most studies evaluated different probiotics	✓	✓	✓
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Moderate	✓	✓	✓	The impact of antibiotics on IBS symptoms was modest	✓
Certain antispasmodics provide symptomatic short-term relief in IBS.	Low	All trials unclear risk of bias and the effect on IBS symptoms was marked.	Significant heterogeneity between studies that was unexplained. Only a small number of studies evaluating each type of drug	✓	✓	There was funnel plot asymmetry suggesting reporting bias or other small study effects
Peppermint oil is superior to placebo in improving IBS symptoms.	Moderate	Only one low risk of bias trial and this study was the least positive (although still showing statistically significant benefit compared to placebo). Quality of evidence upgraded as effect on IBS symptoms marked	Significant heterogeneity between studies that was unexplained	✓	✓	Not evaluable
There is insufficient evidence to recommend loperamide for use in IBS.	Very low	Both trials have unclear risk of bias	Significant heterogeneity between studies that was unexplained	✓	Effect not significant and confidence intervals very wide	Not evaluable
As a class, antidepressants are effective in symptom relief in IBS.	High	Three low risk of bias trials. Meta-analysis of these showed statistically significant effect of antidepressants vs. placebo	✓	✓	✓	✓
A variety of psychological interventions are effective in improving IBS symptoms.	Very low	All trials high risk of bias	Significant heterogeneity between studies that was unexplained	Most RCTs did not have an adequate control group	✓	There was funnel plot asymmetry suggesting reporting bias or other small study effects
Alosteron is effective in females with IBS-D.	Moderate	Only one trial had low risk of bias but this trial was also positive and large	Significant heterogeneity between studies that was unexplained	✓	✓	✓

Table 2 continued on following page

Table 2. Continued

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Low	Only one trial was low risk of bias and this study was negative	Significant heterogeneity between studies that was unexplained	✓	✓	✓
Linaclotide is superior to placebo for the treatment of IBS-C.	High	✓	✓	✓	✓	Not evaluable
Lubiprostone is superior to placebo for the treatment of IBS-C.	Moderate	One other RCT performed but unable to obtain dichotomous data from the company or authors	✓	✓	Effect modest	✓
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Very low	Both trials are unclear risk of bias	RCTs cannot be combined as different populations studied	✓	No statistically significant effect on abdominal pain or overall symptoms. Overall number of patients studied was small	Not evaluable

GRADE, Grading of Recommendations Assessment, Development and Evaluation; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; RCT, randomized controlled trial.
[a]Check marks indicate that the criterion was fulfilled/not a concern.

symptoms were not adequately controlled as compared with 6/15 (40%) in the placebo group. Continuous symptom scores for abdominal pain, bloating, satisfaction with stool consistency, and tiredness were statistically significantly better in those who maintained a gluten-free diet.

The second of these studies examined the contribution of food allergy or hypersensitivity as assessed, not by immunoglobulin (Ig) E antibodies, but by IgG antibodies (43). In a double-blind, parallel-group trial, 150 IBS patients were randomized to either an exclusion diet based on the presence of IgG antibodies to various foods or a sham diet. Participants were followed for 12 weeks and symptoms assessed using a global impact score and the IBS severity score. Compared with 11/66 (17%) in the sham diet group ($P=0.14$), 28% (18/65) in the exclusion diet intervention arm noted a significant improvement in symptoms. The authors reported marginal statistical significance in those with high adherence to their diet.

The third study examined the role of FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). Forty-one IBS patients were randomized to a low-FODMAP diet or their regular (habitual) diet for 4 weeks (47). Of those randomized to the low-FODMAP diet, 68% (13/19) reported adequate control of their symptoms compared with 5/22 (23%) of the habitual diet group ($P=0.005$). Stool consistency did not differ between groups; stool frequency was less in the low-FODMAP diet group. A significant limitation of this study was the lack of blinding regarding the dietary intervention.

Summary: Belatedly perhaps, the role of dietary components in the precipitation of symptoms, or even in the basic pathogenesis of IBS, is now being addressed. To date, two mechanisms, intolerance and hypersensitivity, have been addressed in clinical trials, although it is highly plausible that other mechanisms (e.g., stimulation of gut hormones and interactions with the microbiota) may also be relevant to the effects of food or food components. While recognizing the challenges that any investigation of the role of an individual's diet or of a specific food component in IBS present, the current data provide limited guidance on the role of diet in the management of IBS. Gluten-free and low-FODMAP diets show promise but their precise role(s) in the management of IBS need to be defined.

2. Fiber in IBS

Fiber provides overall symptom relief in IBS.
Recommendation: weak. Quality of evidence: moderate.
Psyllium, but not bran, provides overall symptom relief in IBS.
Recommendation: weak. Quality of evidence: moderate.

Increased intake of dietary fiber is frequently recommended to improve bowel function for IBS, particularly for constipation-related symptoms. However, insoluble fibers frequently cause bloating and abdominal discomfort.

In updating our prior systematic review (18), we identified two additional studies for a total of 14 RCTs (55–69) involving 906 patients. All but five trials did not differentiate IBS by subtype and only two restricted recruitment to IBS-C (58,66).

Table 3. Reasons for strength of recommendation for IBS therapies according to GRADE criteria

Statement	Recommendation	Quality of evidence	All patient groups	Benefits vs. risks	Patient values	Cost[a]
Specialized diets may improve symptoms in individual IBS patients.	Weak	Very low	Likely to relate to only some IBS patients	Some diets are very stringent and difficult to follow	✓[b]	✓
Fiber provides overall symptom relief in IBS.	Weak	Moderate	May only relate to IBS-C, most trials did not state type of IBS patient	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
Psyllium, but not bran, provides overall symptom relief in IBS.	Weak	Moderate	May only relate to IBS-C, most trials did not state type of IBS patient	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Weak	Very low	Likely that only some patients will respond	✓	✓	Can be expensive to patients
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.	Weak	Low	Likely that only some patients will respond	✓	✓	Can be expensive to patients
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Weak	Moderate	Likely that only some patients will respond	Antibiotic resistance of GI flora a concern if use widespread. Long-term efficacy uncertain	✓	Can be expensive to patients
Certain antispasmodics provide symptomatic short-term relief in IBS.	Weak	Low	✓	✓	✓	✓
Peppermint oil is superior to placebo in improving IBS symptoms.	Weak	Moderate	✓	✓	✓	✓
There is insufficient evidence to recommend loperamide for use in IBS.	Strong	Very low	✓	✓	✓	✓
As a class, antidepressants are effective in symptom relief in IBS.	Weak	High	✓	Both TCA and SSRI associated with adverse events with an NNH of 9.	Some patients do not like the idea of taking antidepressants	SSRIs can be expensive. TCAs are inexpensive.
A variety of psychological interventions are effective in improving IBS symptoms.	Weak	Very low	✓	Can be time intensive for patients	Some patients do not like the concept of psychotherapy	Most psychotherapeutic interventions are expensive
Alosteron is effective in females with IBS-D.	Weak	Moderate	✓	Concerns regarding ischemic colitis	✓	Can be expensive and not freely available
Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Strong	Low	✓	✓	✓	✓
Linaclotide is superior to placebo for the treatment of IBS-C.	Strong	High	✓	✓	✓	Expensive
Lubiprostone is superior to placebo for the treatment of IBS-C.	Strong	Moderate	✓	✓	✓	Expensive
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Weak	Very low	Not clear whether this intervention is effective	Not clear whether this intervention is effective, and hence although adverse events are rare, cannot evaluate risks vs. benefits	✓	Can be moderately expensive for patients

GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; 5-HT_3, serotonin subtype 3; 5-HT_4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; NNH, number needed to harm; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]Cost was classified as expensive for the health service if the listed medication cost was >$5 per day. At this level, an economic analysis (289) has shown there is less certainty that the drug is cost effective, although it is important to emphasize that this will be cost effective for some patients but may not be for those with milder symptoms.

[b]Check marks indicate that the criterion was fulfilled/not a concern.

Table 4. Summary of results of monograph on interventions for CIC

Statement	No. of trials	No. of patients	RR symptoms (95% CI)	NNT (95% CI)	Recommendation	Quality of evidence
Some fiber supplements increase stool frequency in patients with CIC.	3	293	0.25 (0.16–0.37)	2 (1.6–3)	Strong	Low
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	4	573	0.52 (0.41–0.65)	3 (2–4)	Strong	High
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	2	148	0.48 (0.27–0.86)	4 (2–7)	Strong	Low
Sodium picosulfate and bisacodyl are effective in CIC.	2	735	0.54 (0.42–0.69)	3 (2–3.5)	Strong	Moderate
Prucalopride is more effective than placebo at improving symptoms of CIC.	8	3,140	0.81 (0.75–0.86)	5 (4–8)	Strong	Moderate
Linaclotide is effective in CIC.	3	1,582	0.84 (0.80–0.87)	6 (5–8)	Strong	High
Lubiprostone is effective in the treatment of CIC.	4	651	0.67 (0.58–0.77)	4 (3–6)	Strong	High
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	3	216	0.33 (0.22–0.50)	2 (1.6–4)	Weak	Low

CI, confidence interval; CIC, chronic idiopathic constipation; NNT, number needed to treat; PEG, polyethylene glycol; RR, relative risk.

Table 5. Reasons for quality of evidence of assessment of data on CIC according to GRADE criteria

Statement	Quality assessment	Study limitations	Inconsistency	Indirectness of evidence	Imprecision	Reporting bias
Some fiber supplements increase stool frequency in patients with CIC.	Low	All trials were unclear risk of bias but did show a marked effect	End points different even in the studies that could be combined	✓[a]	Only a small number of patients studied	Not evaluable
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	High	All RCTs low risk of bias and demonstrated strong treatment effect	Moderate heterogeneity between studies	✓	✓	Not evaluable
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	Low	Both trials at high risk of bias but there was a strong treatment effect	Moderate heterogeneity between studies	✓	Only a small number of patients studied with wide 95% CIs	Not evaluable
Sodium picosulfate and bisacodyl are effective in CIC.	Moderate	Both trials low risk of bias and strong treatment effect	Significant heterogeneity between studies	✓	Modest number of patients studied for each intervention	Not evaluable
Prucalopride is more effective than placebo at improving symptoms of CIC.	Moderate	5/8 Trials were low risk of bias and these studies were also positive	Significant heterogeneity between studies that was unexplained	✓	✓	✓
Linaclotide is effective in CIC.	High	✓	✓	✓	✓	✓
Lubiprostone is effective in the treatment of CIC.	High	Two trials low risk of bias, strong treatment effect	✓	✓	✓	Not evaluable
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	Low	All three trials were high risk of bias but the treatment effect was marked	End points different even in the studies that could be combined and intervention slightly different between studies	✓	Very modest number of patients studied.	Not evaluable

CI, confidence interval; CIC, chronic idiopathic constipation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PEG, polyethylene glycol; RCT, randomized controlled trial.
[a]Check marks indicate that the criterion was fulfilled/not a concern.

Table 6. Reasons for strength of recommendation for treatments of CIC according to GRADE criteria

Statement	Recommendation	Quality of evidence	All patient groups	Benefits vs. risks	Patient values	Cost[a]
Some fiber supplements increase stool frequency in patients with CIC.	Strong	Low	✓[b]	Fiber can cause bloating and abdominal discomfort	Some patients do not like taking fiber supplements	✓
PEG is effective in increasing stool frequency and improving stool consistency in CIC.	Strong	High	✓	✓	✓	Can be expensive to patients
Lactulose is effective in increasing stool frequency and improving stool consistency in CIC.	Strong	Low	✓	Lactulose can cause bloating	✓	✓
Sodium picosulfate and bisacodyl are effective in CIC.	Strong	Moderate	✓	✓	✓	✓
Prucalopride is more effective than placebo at improving symptoms of CIC.	Strong	Moderate	✓	✓	✓	Expensive
Linaclotide is effective in CIC.	Strong	High	✓	✓	✓	Expensive
Lubiprostone is effective in the treatment of CIC.	Strong	High	✓	✓	✓	Expensive
Biofeedback is effective in CIC patients with demonstrated evidence of pelvic floor dyssynergia.	Weak	Low	✓	✓	Some patients not receptive to the idea of biofeedback	Expensive

CIC, chronic idiopathic constipation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PEG, polyethylene glycol.
[a]Cost was classified as expensive for the health service if the listed medication cost was >$5 per day. At this level, an economic analysis (289) has shown there is less certainty that drug is cost effective, although it is important to emphasize that this will be cost effective for some patients but may not be for those with milder symptoms.
[b]Check marks indicate that the criterion was fulfilled/not a concern.

In the largest study to date, 275 patients, of whom 53–58% were IBS-C and 19–29% were IBS-D, were randomized to one of three arms: 10 g of the soluble fiber psyllium, 10 g of the insoluble fiber bran, or 10 g of a placebo once daily for 12 weeks (57). During the first month, a significantly greater proportion of patients receiving psyllium, but not bran, reported adequate symptom relief for at least 2 weeks compared with placebo (57% vs. 35% psyllium vs. placebo; RR 1.60, 95% CI 1.13–2.26). Bran was more effective than placebo during the third month of treatment only (57% vs. 32%; 1.70, 1.12–2.57). After 3 months of treatment, symptom severity in the psyllium group was reduced by 90 points compared with 49 points in the placebo group ($P=0.03$) and 58 points in the bran group ($P=0.61$ vs. placebo). No differences were found with respect to quality of life. Dropout was most common in the bran group; most commonly because of exacerbation in IBS.

Data on overall adverse events were only provided by six trials (57,58,60,64,65,69). These trials evaluated 566 patients, but as numbers of adverse events were so small in 5 of the trials, pooling of data was not carried out. A total of 130 (38.8%) of 335 patients receiving fiber reported adverse events compared with 63 (27.3%) of 231 in the placebo arms.

Summary: Although its use in the management of IBS is time honored, the status of fiber, in general, in IBS, is far from straightforward. Insoluble fibers may exacerbate symptoms and provide little relief; soluble fibers and psyllium, in particular, provide relief in IBS. These latter effects appear to transcend expected benefits in terms of relief of constipation.

3. Interventions that modify the microbiota: probiotics, prebiotics, and antibiotics

The suggestion that the gut bacteria could be relevant to IBS first came from the observation that a small, although definite, proportion of individuals who suffer an episode of bacterial gastroenteritis will go on to develop IBS *de novo*; postinfectious IBS (70). Although bacterial fermentation has been linked to bloating and flatulence and changes in the microbiota have been described in IBS, the contribution of the microbiota to these, or other symptoms in IBS, is unclear. Thus, although both small intestinal bacterial overgrowth (SIBO) (71) and quantitative and qualitative changes in the fecal microbiota (72) have also been linked to IBS (73), the overall contribution of SIBO to IBS remains controversial (74), and findings in relation to the microbiota require confirmation in larger patient populations. Prebiotics, probiotics, and prebiotic–probiotic preparations have been used for decades on an empirical basis by IBS sufferers; they have only recently been subjected to scrutiny in clinical trials. The interpretation of probiotic studies in IBS remains challenging as studies have employed different species, strains, preparations, and doses in various patient populations and often in substandard trials.

Although initial studies, employing the lactulose hydrogen breath test, suggested that more than "three quarters" of all IBS sufferers had SIBO (75), subsequent studies have, in general, failed to confirm such a high prevalence of SIBO in IBS (73,74). These divergent results may relate to problems inherent to the lactulose breath hydrogen test that may provide an overestimation of the true positive rate (73). Nevertheless, this finding provided a rationale for assessing antibiotics in IBS. Rifaximin, a nonabsorbable antibiotic, has demonstrated efficacy in clinical trials in IBS-D, and although statistically significant improvements were demonstrated over placebo in global IBS symptoms as well as in bloating, it is important to note that tests for SIBO were not performed in these pivotal trials, leaving the mechanism of action of rifaximin in IBS unclear (76).

(a) Prebiotics and synbiotics in IBS: There is insufficient evidence to recommend prebiotics or synbiotics in IBS.
Recommendation: weak. Quality of evidence: very low.

(b) Probiotics in IBS: Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS.
Recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient and conflicting data.
Recommendation: weak. Quality of evidence: low.

(c) Antibiotics in IBS: The poorly absorbable antibiotic rifaximin is effective at reducing total IBS symptoms and bloating in diarrhea-predominant IBS.
Recommendation: weak. Quality of evidence: moderate.

We identified one RCT that evaluated the *prebiotic* transgalactooligosaccharide in IBS (77); this study was excluded from further analysis as the data were not extractable. In relation to probiotics, it should be noted that changes in diet and intake of dietary fiber can exert prebiotic effects on gut microbiota; these are addressed in previous sections. We identified two trials assessing 198 IBS patients that evaluated *synbiotics* vs. control preparations. (78,79) Both studies evaluated different products. We excluded two other RCTs of synbiotics in IBS as data were not extractable in one case, (80) and in the second there was no control arm (81).

There was one study that assessed dichotomous outcomes in 68 patients (79). There were 7 (20.6%) of 34 patients assigned to synbiotics with persistent symptoms compared with 30 (88.2%) of 34 assigned to control therapy ($P < 0.01$). Both trials (78,79) assessed global IBS symptoms on a continuous scale in 185 patients; there was no statistically significant effect of synbiotics in reducing IBS symptom scores, even though both trials were individually positive, again because of significant heterogeneity.

We updated our previous systematic review and meta-analysis on *probiotics* in IBS (22,82), and identified a total of 20 new trials (83–102). However, one of these was a full publication of a trial previously included in the original meta-analysis in abstract form (89,103), and one trial in the original meta-analysis was pseudorandomized and included acupuncture in both study arms (104), and hence we excluded these two studies (103,104). Therefore, in total, there were 35 RCTs (83–102,105–119), involving 3,452 patients. Fourteen trials were at low risk of bias (87,89,91–93,97,99,101,105,109–111,118,119), with the remainder being unclear.

There were 23 RCTs involving 2,575 patients (as reported on **Table 1**) that gave outcomes as a dichotomous variable. Probiotics were statistically significantly better than placebo (RR of IBS not improving = 0.79, 95% CI 0.70–0.89), with the NNT of 7 (95% CI 4–12.5). There was statistically significant heterogeneity between studies. A further complicating factor in the assessment of probiotics was the use of a great variety of preparations. Combination probiotics, as well as formulations based on specific species (but widely variable strains); *Lactobacillus*, *Bifidobacterium*, *Escherichia*, and *Streptococcus*, were assessed in individual trials. Subanalysis only demonstrated a significant effect for combination probiotics, *Lactobacillus plantarum DSM* 9843 and *E. coli* DSM17252, but there was significant heterogeneity between studies for the first two and only one study for the third.

There were 24 trials, making 25 comparisons, and assessing 2001 patients who reported improvement in global IBS symptom scores or abdominal pain scores. There was a statistically significant effect of probiotics in reducing symptoms with no significant heterogeneity. Subanalysis, on this occasion, revealed significant effects for combinations of probiotics, but not for those containing *Lactobacillus* spp., *Bifidobacterium* spp., or *Saccharomyces* spp.

There were 17 separate trials, making 18 comparisons and containing 1,446 patients, that reported the effect of probiotics on bloating symptom scores. Overall, bloating scores were significantly reduced with probiotics, but with significant heterogeneity between individual study results.

In the 10 trials that assessed this outcome, flatulence scores were significantly lower with probiotics compared with placebo with no significant heterogeneity detected.

There was no apparent benefit detected for probiotics on urgency in the six trials that assessed this symptom.

Total adverse events were reported by 24 RCTs containing 2,407 patients. Overall, 201 (16.5%) of 1,215 patients allocated to probiotics experienced any adverse event compared with 164 (13.8%) of 1,192 assigned to placebo with the NNH of 35 (95% CI 16–362).

We identified 6 RCTs (120–124) involving 1,916 participants that evaluated *antibiotic* therapy in IBS patients. Two trials evaluating metronidazole (125) and rifaximin (126) were excluded as they did not provide extractable data. A further RCT (127) assessed *Helicobacter pylori* eradication therapy but was excluded as it assessed symptoms 2 years after a 1-week course of antibiotics. Overall, antibiotic therapy improved IBS symptoms compared with placebo, with no significant heterogeneity between studies. One trial (124) evaluated neomycin in 111 patients with a significant effect in favor of neomycin (RR = 0.73, 95% CI 0.56–0.96) with the NNT of 5 (95% CI 3–33). The remaining 5 trials (120–123) evaluated rifaximin in 1,805 IBS patients. There was a statistically significant benefit in favor of the anti-

biotic (RR = 0.84, 95% CI 0.78–0.90) with the NNT of 9 (95% CI 6–12.5). There were three (122,123) low risk of bias trials assessing 1,330 patients.

Three RCTs reported adverse events (121,122,124) in 1,456 patients. There was no difference in overall adverse events between the antibiotic and placebo groups (RR of adverse events = 0.70, 95% CI 0.42–1.16).

Summary: Although data accumulate to suggest a role for the microbiota in IBS, the primacy of any reported changes in enteric populations in the pathogenesis of IBS remains to be confirmed. Although, at this time there is insufficient evidence to permit a recommendation on the use of prebiotics or synbiotics in IBS, aggregated data do indicate a beneficial effect for probiotics, with bloating and flatulence appearing to be especially responsive. Though recognizing the intrinsic differences that exist between individual probiotic strains and the consumer's desire to obtain guidance on product selection, limitations intrinsic to available data, as well as a lack of comparative studies, severely limit one's ability to recommend a particular strain or product at this time. The antibiotic rifaximin, although not approved for this indication by the Food and Drug Administration, has shown modest but consistent efficacy in nonconstipated IBS and seems to be well tolerated and, despite concerns regarding the long-term or repeated use of an antibiotic, has proven safe at least over the time periods in which it has been evaluated.

4. Antispasmodics in IBS

Antispasmodics have been used for decades on an empirical basis in the treatment of IBS based on the assumption that gut, and especially colonic smooth muscle spasm, contributes to IBS symptoms and pain in particular; hence, the term *spastic colon*.

Certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.

Recommendation: weak. Quality of evidence: low.

We identified 23 RCTs (60,64,67,128–147) evaluating 2,154 patients with IBS. There was considerable variation between the studies concerning diagnostic and inclusion criteria, dosing schedule, and study end points. Only 3 studies used standardized diagnostic criteria (Rome I or II) (131,138,140), whereas all other 20 studies used author-defined IBS, reflecting the fact that most trials were conducted before Rome definitions were published. The majority of trials did not differentiate between the types of IBS patients recruited. Overall, the quality of trials was poor, with only 4 recruiting more than 100 patients. Only four trials (67,131,133,144) reported an adequate method of randomization and none reported on concealment of allocation, although all were double blind. Risk of bias was unclear in all of the trials. Of the drugs used in the various studies, only hyoscine (64,67,146) and dicyclomine (142) are available in the United States.

This review shows that as a class, antispasmodic therapy has a statistically significant effect in improving IBS symptoms with the NNT of 5 (95% CI 4–9). However, the effect of individual antispasmodics is variable and difficult to interpret, as there are only a small number of studies evaluating each of the 12 different drugs available for review.

With respect to individual agents, otilonium (128,129,131, 132,138), hyoscine bromide (64,67,146), cimetropium bromide (130,134,143), pinaverium bromide (133,139,147), and dicyclomine hydrochloride (142) showed beneficial effects with NNTs of 5, 3, 3, 3, and 4, respectively. However, some of these were evaluated in as few as just one study (142), and for those that were assessed in multiple studies, heterogeneity was a problem in some instances.

Mebeverine (one trial), trimebutine (three trials), pirenzipine (one trial), alverine (one trial), rociverine (one trial), prifinium (one trial), and propinox (one trial) did not have a statistically significant effect on IBS symptoms, although the numbers of patients studied were small.

Fifteen trials included in this review reported adverse events with either active drug or placebo. In total, 144 (16.3%) of 883 patients assigned to antispasmodics experienced adverse events compared with 92 (10.4%) of 882 allocated to placebo. When data were pooled, the incidence of adverse events was significantly higher among those taking antispasmodics as compared with placebo (RR of experiencing any adverse event = 1.61; 95% CI 1.08–2.39), with the NNH of 20 (95% CI 9.5–333). The most common adverse events were dry mouth, dizziness, and blurred vision, but there were no serious adverse events reported in either treatment arm in any of the trials.

Summary: Although many of the relevant clinical trials are old and far from ideal in terms of quality, antispasmodics, as a category, are effective in IBS, though their use may be limited by anticholinergic adverse events. However, not all antispasmodics have been shown to be effective, and studies on individual agents vary in quality and outcome measures. Furthermore, the availability of some of the more effective agents may be limited to certain regions.

5. Peppermint oil in IBS

Peppermint oil can be found in various preparations available through conventional or complementary venues. Limited experimental data suggest that it can relax smooth muscle, but it may also have effects via attenuation of visceral hypersensitivity and modulation of pain sensation, and hence its use for the treatment of IBS.

Peppermint oil is superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo.

Recommendation: weak. Quality of evidence: moderate.

We identified five RCTs (148–152) involving 482 patients. Most trials did not differentiate between the types of IBS patients recruited, with only one study providing data on this (148). There was only one RCT at low risk of bias (152), with the remainder being unclear. This RCT reported a less dramatic effect of peppermint oil on IBS symptoms compared with placebo, but this was

still statistically significant. Overall, there was a statistically significant effect in favor of peppermint oil compared with placebo with the NNT of 3 (95% CI 2–4). However, there was significant heterogeneity between results. In these studies, an enteric-coated preparation of peppermint oil was employed in doses ranging from 187 to 225 mg t.i.d.

When data were pooled, the incidence of adverse events was not significantly higher among those taking peppermint oil as compared with placebo (RR of experiencing any adverse event = 1.26, 95% CI 0.75–2.12).

Summary: In specific formulations, which may not be universally available, peppermint oil is effective in IBS.

6. Loperamide in IBS

There is insufficient evidence to recommend loperamide for use in IBS.

Recommendation: strong. Quality of evidence: very low.

There were two RCTs (153,154) involving 42 patients. There was no statistically significant effect in favor of loperamide compared with placebo. Both trials stated the type of IBS patients recruited, with one study recruiting only IBS-M patients (153) and the other only IBS-D (154).

Data on overall adverse events were provided in both trials. There were no adverse events in either arm in one trial (153) and four adverse events in each arm of the other study (154).

Summary: Although loperamide is an effective antidiarrheal, there is no evidence to support the use of loperamide for relief of global symptoms in IBS.

7. Antidepressants in IBS

Antidepressants were first introduced into the management of IBS based on the observation that depression and anxiety were frequent comorbidities among IBS subjects seen in secondary and tertiary care. Subsequent studies suggested that in subdepression doses these agents were effective in relieving pain of visceral origin.

Antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors) are effective in symptom relief in IBS.

Side effects are common and may limit patient tolerance.

Recommendation: weak. Quality of evidence: high.

We updated our previous systematic review and meta-analysis on antidepressants in IBS (20) and identified four further papers (155). Overall, there were 17 RCTs (64,156–171) evaluating 1,084 patients. The majority of trials did not differentiate between the type of IBS patients recruited, with seven studies providing data on this (159,161,162,164–166,170), one of which recruited only IBS-C patients (164) and another only IBS-D patients (165). Only three of the RCTs were at low risk of bias (167,169,170), with the remainder being unclear.

Antidepressants were effective in treating IBS symptoms with the NNT of 4 (95% CI 3–6). The effect of antidepressant therapy on abdominal pain was reported by 7 RCTs (158,159,161, 164–166,169), with 87 (46.7%) of 182 patients receiving antidepressants having persistent abdominal pain following treatment as compared with 123 (72.8%) of 169 subjects allocated to placebo, giving a RR of abdominal pain persisting of 0.62 (95% CI 0.43–0.88), but with considerable heterogeneity between studies ($I^2 = 72.4\%$, $P = 0.001$).

Tricyclic antidepressants were studied in 11 RCTs involving 744 patients (64,156–158,160,163,165–169), and active therapy was associated with a reduction in IBS symptoms compared with placebo with the NNT of 4. Selective serotonin reuptake inhibitors were studied in 7 RCTs involving 356 patients (159,161–164, 170,171), and active therapy was associated with a reduction in IBS symptoms compared with placebo with the NNT of 4.

Only seven trials reported on overall adverse events vs. placebo (157–160,162,166,168). In total, 65 (31.3%) of 208 patients assigned to antidepressants experienced adverse events as compared with 33 (16.5%) of 200 allocated to placebo. When data were pooled, the incidence of adverse events was significantly higher among those taking antidepressants as compared with placebo (RR of experiencing any adverse event = 1.63, 95% CI 1.18–2.25). The NNH was 9 (95% CI 5–111). Drowsiness and dry mouth were more common in patients taking tricyclic antidepressants than those on placebo.

Summary: Both tricyclic antidepressants and selective serotonin reuptake inhibitors are effective in providing global symptom relief and reducing pain in IBS. Adverse events and patient, as well as physician, acceptability have limited their use and influenced our recommendation. Available data, other than adverse event profile (e.g., constipating effects of tricyclic antidepressants), do not permit guidance on patient selection for antidepressant therapy.

8. Psychological therapies, including hypnotherapy, in IBS

A variety of psychological interventions are effective in improving IBS symptoms.

Recommendation: weak. Quality of evidence: very low.

We updated our previous systematic review and meta-analysis on psychological therapies in IBS (20,155), and identified a total of 10 new papers containing 11 separate RCTs, thereby providing in total 30 papers reporting 32 separate trials, involving 2,189 patients (167,172–200). The quality of these trials was generally poor, with only 8 having a sample size of more than 100 (167,174,175,178,18 1,189,191,194). Because of the nature of the intervention, double-blind studies would not have been possible, but only four papers reported that investigators were blinded (167,174,175,192). All of the trials were at high risk of bias.

There was a statistically significant effect in favor of psychological therapies with the NNT of 4 (95% CI 3–5), but with significant heterogeneity between studies.

In terms of the 10 different types of psychological therapies evaluated, the benefits were demonstrated for cognitive behavioral therapy (NNT of 3 (95% CI 2–6)), hypnotherapy (NNT of 4 (95% CI 3–8), multi-component psychological therapy (NNT of 4 (95% CI 3–7)), multi-component psychological therapy administered via the telephone (NNT of 5 (95% CI 3–17)), and

dynamic psychotherapy (NNT of 3.5 (95% CI 2–25)). No significant effects were evident for relaxation therapy, self-administered cognitive behavioral therapy, behavioral therapy delivered via the internet, stress management, or mindfulness meditation training. However, the latter three have only been tested in one or two RCTs, and therefore a definite lack of benefit cannot be assumed. Only four trials (172,178,184,187) used "sham" or "control" psychological interventions as a comparison.

Adverse events data were poorly reported by individual RCTs, precluding any meaningful analysis.

Summary: Although issues relating to blinding and choice of control intervention have complicated their evaluation, a variety of therapeutic approaches, loosely aggregated under the term "psychological therapies," have been shown to be effective in IBS. Availability of skilled therapists experienced in the management of IBS greatly limits their use.

9. Serotonergic agents

Serotonin (5-hydroxytryptamine (5-HT)) plays a critical role in gastrointestinal secretion, motility, and sensation (201), and a variety of 5-HT receptors have been targets for new drug development in functional gastrointestinal disorders (202). The serotonin subtype 3 (5-HT_3) receptors have been shown to play an important role in visceral pain, and 5-HT_3 antagonists decrease painful sensations from the gut and slow intestinal transit (203,204). Alosetron, a selective 5-HT_3 antagonist, was therefore evaluated in diarrhea-predominant IBS and, although it showed efficacy, instances of severe constipation and ischemic colitis (205) led, initially, to its withdrawal by the US Food and Drug Administration (FDA). It was subsequently reintroduced by the FDA in a restricted manner under a risk management plan for "women suffering with severe diarrhea-predominant IBS that is disabling" (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf; accessed June 10th 2014). The risk management plan was converted to a risk evaluation and mitigation strategy in 2010. Other 5-HT_3 antagonists such as cilansetron and ramosetron have never been introduced into clinical practice.

The serotonin subtype 4 (5-HT_4) receptors are distributed throughout the gastrointestinal tract and stimulation of these receptors enhances intestinal secretion, augments the peristaltic reflex, and increases gastrointestinal transit (206,207). Tegaserod is an aminoguanidine-indole categorized as a partial, selective 5-HT_4 agonist. The FDA granted approval for the use of tegaserod in women with IBS with constipation in July 2002. Because of possible cardiovascular adverse effects, tegaserod was withdrawn from the US market in March 2007. Tegaserod is the only 5-HT_4 partial agonist that has been evaluated in large, prospective, randomized controlled studies in IBS patients. As tegaserod is no longer available in the United States, an updated analysis of tegaserod efficacy and safety has not been performed. The interested reader is referred to the previous systematic review (19). A number of selective 5-HT_4 agonists have been developed and have shown efficacy in constipation (e.g., prucalopride that is available in Canada and the European Union) but no data are, as yet, available on the efficacy or safety of these agents for the treatment of IBS.

(a) 5-HT_3 antagonists in IBS: Alosteron is effective in females with diarrhea-predominant IBS.
Recommendation: weak. Quality of evidence: moderate.

We updated our previous systematic review and meta-analysis (19) and identified two new studies providing a total of 13 trials eligible containing 8,173 patients for inclusion (208–220). Only one trial was at low risk of bias (216), with the remainder unclear. All but one recruited nonconstipated IBS. Most trials recruited women only, or predominantly women, with the exception of two Japanese studies where men predominated (218,219), and a US-based trial that recruited only men (213).

Overall, there was a statistically significant effect in favor of 5-HT_3 antagonists with the NNT of 7 and significant heterogeneity.

There appeared to be no difference in efficacy between the three drugs alosetron (208,210–214,216), cilansetron (209,215,220), and ramosetron (218,219) within this class, all proving effective with NNTs of 8, 6, and 7, respectively.

There were 9 studies (208,210–214,216,218,219) evaluating 5,564 patients that provided total adverse event data. 5-HT_3 antagonists had statistically significantly more adverse events than placebo (RR of any adverse event = 1.17, 95% CI 1.08–1.25). The NNH was 11 (95% CI 8–17). The main adverse event that was more common with 5-HT_3 antagonists than with placebo was constipation. Ischemic colitis has been reported with alosetron, and it was withdrawn by the FDA in November 2001. In June 2002, the FDA announced the approval of a supplemental New Drug Application that allowed restricted marketing of alosetron to treat only women with severe diarrhea-predominant IBS. The approval includes a risk management program (termed a risk evaluation and mitigation strategy since 2010) to ensure patients and physicians are fully informed of the theoretical risks and possible benefits of alosetron (221).

(b) 5-HT4 agonists in IBS: No further analysis of these agents was performed as there were no new data and tegaserod has been withdrawn in most areas.

(c) Mixed 5-HT3 antagonists/5-HT4 agonists: Mixed 5-HT_4 agonists/5-HT_3 antagonists are not more effective than placebo at improving symptoms of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: low.

The complex physiology involved in the generation of IBS symptoms is thought to represent an intricate balance of 5-HT receptor agonism and antagonism (201,206,207). Several agents classified as mixed 5-HT_3 antagonists/5-HT_4 agonists have been developed for the treatment of IBS. These are collectively and individually reviewed below. It should be noted that cisapride has not been widely available since withdrawal from the US market in July 2000 and that this drug was shown to be not more effective than placebo in a recent meta-analysis (19).

A total of 9 double-blind, placebo-controlled trials involving 2,905 patients were eligible for inclusion (222–230). Four

studies each involved cisapride (223,225,227,228) or renzapride (222,224,226,229); one study involved mosapride (230). Eight trials recruited patients with constipation-predominant IBS (222–225,227–230) and one mixed IBS (226). The methodological quality of trials was low.

Analysis of all nine studies revealed no statistically significant differences between placebo and mixed 5-HT_3 antagonists/5-HT_4 agonists for the treatment of IBS and significant heterogeneity was identified between studies.

In terms of individual agents, neither renzapride (222,224,226, 229) in constipation-predominant or mixed IBS nor mosapride (230) showed significant benefit over placebo.

There was no statistically significant increase in adverse events with mixed 5-HT_3 antagonists/5-HT_4 agonists as compared with placebo.

Summary: Of the various agonists and antagonists to serotonergic receptors that have been developed and evaluated in IBS, only alosetron and ramosetron, both 5-HT_3 antagonists, are available (although in certain regions only) and supported by evidence of efficacy. Because of concerns regarding adverse events, the use of alosetron in the United States is limited to women with severe diarrhea-predominant IBS and can be prescribed only in the context of a carefully monitored program. Ramosetron is approved for the management of diarrhea-predominant IBS in Japan, Korea, and Thailand.

10. Prosecretory agents
(a) Linaclotide: Linaclotide is superior to placebo for the treatment of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: high.

Linaclotide is a 14-amino acid peptide structurally similar to hormones in the guanylin peptide family. Guanylin peptides are endogenous hormones that assist in the regulation of intestinal fluid and electrolyte homeostasis by binding to, and activating, guanylate cyclase-C receptors on the lumen of intestinal epithelium. Activation of guanylate cyclase-C results in an increase of cyclic guanosine monophosphate that triggers a series of events leading to the activation of the cystic fibrosis transmembrane conductance regulator that results in secretion of bicarbonate and chloride into the lumen, followed by sodium and water flux into the intestinal lumen, as well as modulation of pain afferent sensors (231).

Three randomized clinical trials in IBS patients were identified involving 2,028 combined patients (232–234). All trials were at low risk of bias, and there was no significant heterogeneity between individual trial results.

There was a statistically significant effect in favor of linaclotide compared with placebo with the NNT of 6 (95% CI 5–8), with no significant heterogeneity between studies. There was a statistically significant effect in favor of linaclotide compared with placebo on abdominal pain (NNT of 8), but with significant heterogeneity between individual trial results.

Data on overall adverse events were provided by two of the three trials (232,234). Overall, adverse event rates were not higher among those taking linaclotide compared with placebo (RR = 1.09, 95% CI 0.96–1.24). However, diarrhea, reported in all three trials, was significantly more likely with linaclotide as compared with placebo (RR = 6.62, 95% CI 4.39–9.96) with the NNH of 6 (95% CI 5.5–8). Flatulence, reported in two trials (232,234), was also significantly more common with active therapy (RR = 2.27, 95% CI 1.18–4.36), with the NNH of 50 (95% CI 23–167).

(b) Lubiprostone: Lubiprostone is superior to placebo for the treatment of constipation-predominant IBS.
Recommendation: strong. Quality of evidence: moderate.

Lubiprostone activates the chloride channel type 2 (CIC-2) on the apical surface of the intestinal epithelium. This results in chloride and water flux into the intestinal lumen, resulting in faster transit through the small and large intestines.

Four clinical trials of lubiprostone in IBS patients have been reported in three separate papers (235–237). However, one of these was a mixed population of IBS and CIC patients (236). Three studies reported dichotomous data in 1,366 IBS patients (235,237). All trials were at low risk of bias. There was a statistically significant effect in favor of lubiprostone as compared with placebo, with the NNT of 12.5 (95% CI 8–25), and no significant heterogeneity between the three individual trial results. The quality of evidence was graded as moderate according to GRADE criteria, as the effect on overall IBS symptoms was modest and the 95% CI for the RR was relatively close to a null effect. Furthermore, dichotomous data for IBS patients from one trial were not available (236).

Data on overall adverse events were reported in all three trials, but pooled for the two trials reported in a single paper (235). In the study by Johanson *et al.* (237), adverse events were reported by 66% of lubiprostone patients as compared with 58% of placebo, but this difference was not statistically significant. Nausea was also commoner (17% with lubiprostone compared with 4% with placebo), but again this was not statistically significant. The only adverse event occurring more frequently among those receiving lubiprostone was diarrhea (NNH = 10, 95% CI 5–25). In the two studies that pooled adverse events data (235), 50% and 51% of IBS patients receiving lubiprostone and placebo, respectively, reported at least one adverse event. Diarrhea occurred in 6% of lubiprostone-treated patients compared with 4% of those receiving placebo. Nausea was reported by 8% of those allocated to lubiprostone compared with 4% of those assigned to placebo.

Summary: The prosecretory agents linaclotide and lubiprostone are effective in constipation-predominant IBS. As both of these agents were evaluated in comparison with placebo rather than "standard therapy," their position in an IBS treatment algorithm (i.e., for those who have failed other treatments or as primary therapy) is difficult to define and complicated by lack of consensus on what "standard" therapy should be in IBS, given the limitations of data on other agents.

11. PEG in IBS
There is no evidence that PEG improves overall symptoms and pain in patients with IBS.
Recommendation: weak. Quality of evidence: very low.

PEG is a large polymer that behaves as an osmotic laxative, and although it is approved by the FDA for the treatment of occasional constipation, it has not been extensively studied in patients with IBS-C. One open-label study in 27 adolescents with IBS-C suggested that PEG improved stool frequency but not pain (238). We identified only two RCTs (239,240) of PEG in IBS. In one trial, there was no statistically significant effect on bowel movements or discomfort and pain (239). In the second trial (240), which recruited 139 patients with IBS with constipation, the mean increase in spontaneous bowel movements was significantly greater with PEG compared with placebo at 4 weeks, but there was no difference in effect on abdominal pain or discomfort. Response rates, defined as more than four spontaneous bowel movements per week with an increase of two or more from baseline and no worsening of abdominal pain or discomfort, were significantly higher with PEG (36.5% vs. 17.5% with placebo, $P<0.05$). However, there was no significant difference in the proportion of patients with a pain response, defined as a decrease by 10% or more from baseline (61.9% vs. 47.6%, $P>0.1$). Adverse event rates were higher with PEG (38.8% vs. 32.9%), but most of these were mild or moderate.

Summary: There is no evidence that PEG formulations alleviate pain or provide overall symptom relief in IBS.

Chronic idiopathic constipation

1. Fiber in CIC

Some medicinal and dietary fiber supplements increase stool frequency in patients with chronic idiopathic constipation.
Recommendation: strong. Quality of evidence: low.

Dietary fiber is defined as carbohydrate polymers that are incapable of being digested in the normal small intestine and are delivered to the colon. Fiber can be part of ingested food or purified and taken as a supplement ("medicinal fiber"). Fiber is classified as "soluble" or "insoluble" depending on its interaction with water. Psyllium is the archetypical soluble fiber; bran is insoluble.

Psyllium husk is the outer coat of the psyllium seed (known in India as ispaghula seed) from the plant *Plantago ovata*. It can undergo bacterial fermentation in the colon, thereby producing gas and bloating. Semisynthetic bulking agents less susceptible to fermentation include calcium polycarbophil and methylcellulose. Few studies have been done with bulking agents in CIC and the quality of evidence about the use of these agents is very low.

Six trials met the criteria for inclusion in this review (241–246), but a formal meta-analysis was only possible with three trials (243,245,246), and the remaining studies could not be analyzed because of crossover design (241,242) or a failure to provide dichotomous data for extraction (244) with uncertainty regarding whether the study was truly random. Four of the eligible trials used soluble fiber: three used psyllium (241,243,246) and the fourth used a combination of inulin and maltodextrose (245). Two used insoluble fiber: wheat bran in one study (242) and rye bread in the other (244).

Combined data from the three trials (243,245,246) suggested that fiber was beneficial compared with placebo with the NNT of 2 (95% CI 1.6–3) and no statistically significant heterogeneity between studies. Although these trials could be combined for analysis, the definitions of improvement were all different, and in one trial (245) not all patients enrolled in the trial had the outcome that was used to define treatment success present at baseline. The effect size given in this meta-analysis therefore needs to be treated with extreme caution.

In terms of individual formulations, among the three trials (241,243,246) that studied psyllium, including the largest identified RCT conducted by Fenn *et al.* (243), although outcomes varied between these RCTs, all reported significant benefits with psyllium.

Lopez Roman *et al.* (245) used 20 g of a soluble fiber mixture of inulin and maltodextrin, administered as a dairy preparation, and reported significant reductions in the proportion of patients with straining during defecation, sensation of incomplete evacuation, or sensation of obstruction with soluble fiber. In addition, the number of days between bowel movements was also significantly reduced.

Two trials reported on the efficacy of insoluble fiber in CIC (242,244). The 24 patients recruited were allocated to receive 20 g of bran per day or placebo. No significant benefits were noted with bran (242) but rye bread was effective (244).

No single study reported total adverse events. One trial reported the number of patients in each trial arm who dropped out because of adverse events (one with psyllium and two with placebo) (243). Ashraf *et al.* (241) recorded individual adverse events, with 18% of psyllium patients experiencing abdominal pain compared with 0% of placebo patients, but no differences in back pain, bloating, or cramping. Finally, there were higher combined symptom scores for gastrointestinal side effects such as abdominal pain, flatulence, borborygmi, and bloating with rye bread compared with low-fiber toast (244).

Summary: Fiber and soluble fiber, in particular, are effective in the management of chronic constipation. Adverse events and bloating, distension, flatulence, and cramping may limit the use of insoluble fiber, especially if increases in fiber intake are not introduced gradually.

2. Osmotic and stimulant laxatives in CIC

Osmotic laxatives contain poorly absorbed ions or molecules that retain water in the intestinal lumen. Osmotic agents used with some frequency include polyethylene glycol, lactulose, magnesium hydroxide, magnesium citrate, magnesium sulfate, and sodium phosphate.

(a) Osmotic laxatives in CIC: PEG is effective in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: high.
Lactulose is effective in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: low.

Five studies compared PEG with placebo (247–251); four reported dichotomous data in 573 patients (247–250) with the

NNT of 3 (95% CI 2–4). All trials were at low risk of bias and there was moderate heterogeneity between studies. Two studies (252,253) evaluated lactulose compared with placebo in 148 patients, with the NNT of 4 (95% CI 2–7). Both trials were at high risk of bias and there was moderate heterogeneity between studies.

Trials with osmotic laxatives did not report on the total number of adverse events. Where reported (247,248), the incidence of individual adverse events, including abdominal pain, or headache, did not differ between active agent and placebo.

(b) Stimulant laxatives in CIC: Sodium picosulfate and bisacodyl are effective in CIC.
Recommendation: strong. Quality of evidence: moderate.

Stimulant laxatives appear to induce fluid and electrolyte secretion by the colon or induce peristalsis in the colon, thereby producing a bowel movement. Stimulant laxatives include senna, bisacodyl, castor oil, cascara, rhubarb, and aloe.

Both trials of stimulant laxatives, containing 735 patients, reported dichotomous data and had a low risk of bias (254,255). In total, 42.1% of all patients randomized to stimulant laxatives failed to respond to therapy as compared with 78.0% of those receiving placebo, with the NNT of 3 (95% CI 2–3.5) and with statistically significant heterogeneity between studies.

Only one RCT reported total numbers of adverse events (254); the RR of experiencing any adverse event with laxatives was 1.94 (95% CI 1.52–2.47, NNH = 3, 95% CI 2–4). Diarrhea occurred significantly more frequently in the two trials (RR = 13.75, 95% CI 2.82–67.14, NNH = 3, 95% CI 2–6) (254,255).

Summary: Although supported by varying levels of evidence, the osmotic laxatives PEG and lactulose and the stimulant laxatives sodium picosulfate and bisacodyl have been shown to be effective in chronic constipation. Other stimulant laxatives, although commonly used by sufferers, have not been adequately studied and cannot be recommended at this time. Other laxatives have not been formally tested.

3. 5-HT_4 agonists in CIC
Prucalopride is more effective than placebo in improving symptoms of CIC.
Recommendation: strong. Quality of evidence: moderate.

Serotonin (5-HT) plays a critical role in the gastrointestinal tract and influences secretory, motor, and sensory functions (256). There are seven major classes of serotonin receptor subtypes (5-HT_{1-7}); stimulation of the 5-HT_4 receptor enhances intestinal secretion, augments the peristaltic reflex, and increases gastrointestinal transit (206,207). The 5-HT_4 receptor agonism has the potential to improve symptoms of CIC. The selective 5-HT_4 agonists prucalopride and velusetrag are reviewed below. Tegaserod, a selective, partial 5-HT_4 agonist, was removed from the US market in March 2007 because of possible adverse cardiovascular effects, and will not be discussed further.

Efficacy: We identified 9 randomized, placebo-controlled trials of 5-HT_4 agonists in CIC involving 3,441 patients (257–265). Eight of these trials involved prucalopride (257–259,261–265), whereas one trial involved velusetrag (260). Two studies investigated the effects of prucalopride in patients either resistant to, or dissatisfied with, laxatives (258,264). One study investigated the effects of prucalopride in patients aged 65 years and older (262). Doses ranged from 0.5 to 4 mg daily; studies lasted from 4 to 12 weeks. Five trials were considered to be at low risk of bias (257,260,262,263,265).

In an analysis of all 9 trials, 72.3% of patients (1,691/2,339) who received 5-HT_4 agonists failed to respond to therapy as compared with 88.1% (1,059/1,202) of those allocated to placebo, with the NNT of 6 (95% CI 5–8). Significant heterogeneity was noted between the studies.

Analysis of the 8 prucalopride trials revealed that 71.1% (1,454/2,045) of patients treated with prucalopride failed to respond to therapy as compared with 87.4% (957/1,095) of those randomized to placebo, with the NNT of 5 (95% CI 4–8). Significant heterogeneity was identified between studies. One study performed a subgroup analysis of those patients treated with prucalopride who had previously failed laxatives (264). The authors reported that the effects of prucalopride were similar in patients who had failed other laxatives compared with the overall population, although a better comparator would have contrasted those patients who did not use laxatives before being enrolled in the trial with those who did.

Analysis of the one velusetrag trial revealed that 80.6% (237/294) of patients treated with velusetrag failed to respond to therapy as compared with 95.3% (102/107) of those randomized to placebo; the NNT was 7 (95% CI 5–11).

Eight trials reported total numbers of adverse events (257–260, 262–265); these were more common in patients treated with 5-HT_4 agonists than with placebo (RR = 1.28, 95% CI 1.11–1.48, NNH = 8; 95% CI 5–16). Individual adverse events including headache, nausea, and diarrhea were all more common in patients who used 5-HT_4 agonists compared with placebo. Selective 5-HT_4 agonists were not associated with an increase in serious adverse event rates (RR = 0.84, 95% CI 0.57–1.25), and only 2 cardiovascular events were reported (supraventricular tachycardia in one patient and electrocardiogram signs of myocardial ischemia in the second) (257,265).

Summary: The 5-HT_4 agonists prucalopride and velusetrag are effective in CIC, with the former supported by considerably more data. To date, the cardiac adverse events that bedeviled prior 5-HT_4 agonists have not emerged as a significant issue; neither is available in the United States at this time.

4. Prosecretory agents in CIC
(a) Linaclotide: Linaclotide is effective in chronic idiopathic constipation. It is generally safe, with the main adverse event being diarrhea.
Recommendation: strong. Quality of evidence: high.

Review of the literature demonstrated no new randomized clinical trials since a previously published systematic review and meta-analysis (21). In total, three trials have been reported

in two separate publications (266,267) involving a total of 1,582 CIC patients. All three trials were at low risk of bias. Overall, 860 (79.0%) of 1,089 patients receiving linaclotide failed to respond to therapy as compared with 468 (94.9%) of 493 placebo patients, with the NNT of 6 (95% CI 5–8). No significant heterogeneity was observed between studies.

Two of the trials pooled adverse events data together (267), precluding meta-analysis. Overall, 58% of linaclotide patients experienced any adverse event compared with 52% of placebo patients. In the third trial, adverse event rates were very similar in number in both treatment arms (33.6% linaclotide vs. 31.9% placebo) (266). Separate adverse events data for diarrhea in each trial were obtained from the authors as part of the meta-analysis (21). Diarrhea was more common in patients receiving linaclotide compared with placebo (RR = 3.08, 95% CI 1.27–7.48, NNH = 12; 95% CI 7–38.5).

(b) Lubiprostone: Lubiprostone is effective in the treatment of chronic idiopathic constipation.
Recommendation: strong. Quality of evidence: high.

We updated a previous meta-analysis on lubiprostone in CIC (21) that had involved three trials of lubiprostone in CIC (268–270). We found two additional clinical trials of lubiprostone (236,271) but these two studies did not provide extractable dichotomous data. After contact with the authors, we obtained dichotomous data for one of these studies (271) but not the second (236), despite contacting both the original authors and the manufacturers. Therefore, this meta-analysis included four trials of lubiprostone in CIC involving 651 patients in total. Two trials were at low risk of bias (270,271).

Of the 364 patients receiving lubiprostone, 45.3% failed to respond to therapy compared with 66.9% of 287 placebo patients, with the NNT of 4 (95% CI 3–6) and no heterogeneity between studies.

Three trials reported adverse events data (268–270). Total numbers of adverse events were significantly higher with lubiprostone (RR = 1.79, 95% CI 1.21–2.65, NNH = 4, 95% CI 3–6). Diarrhea and nausea both occurred significantly more frequently with lubiprostone, but no significant difference in rates of abdominal pain or headache were detected.

Summary: The prosecretory agents linaclotide and lubiprostone are effective in CIC and are well tolerated. There have been no comparative studies. As both were evaluated in comparison with placebo rather than "standard therapy," a recommendation regarding their precise position in a CIC treatment algorithm (i.e., for those who have failed fiber, osmotic, or stimulant laxatives, or as primary therapy) cannot be made at this time.

5. Biofeedback in CIC

One of the potential causes of constipation is pelvic floor dysfunction or dyssynergia. Either alterations in pelvic floor anatomy or function can result in impaired ability to defecate effectively. Defecation requires coordinated activity that includes generation of intrarectal pressure, and relaxation of the internal and external anal sphincters, perineal muscles, as well as the levator ani including the puborectalis muscle (272). Incorrect technique, structural abnormalities (e.g., rectocele), and pudendal and perineal nerve damage can contribute to incomplete defecation (273). Symptoms and signs include straining, incomplete evacuation, and digital maneuvers. Complications can include rectal prolapse, rectocele, and anal fissures.

Typical features of pelvic floor dyssynergia include incomplete relaxation or paradoxical contraction of the anal canal, paradoxical contraction of the puborectalis muscle, or uncoordinated movement of the abdominal, rectal, and anal muscles. As such, the goals of biofeedback are to provide a tailored approach to correction of improper defecatory technique. Trained physical therapists use a variety of techniques and tools to assess and correct underlying technical abnormalities.

Biofeedback, performed by a trained and skilled therapist, is effective in relief of constipation symptoms in CIC patients with demonstrated evidence of pelvic floor dyssynergia.
Recommendation: weak. Quality of evidence: low.

A total of nine randomized clinical trials (274–282) of patients with CIC with pelvic floor dyssynergia were identified. Six were excluded because either they did not report a relevant outcome (277) or data were not extractable (278) or they compared biofeedback with balloon-assisted training or different forms of biofeedback (279–282), leaving three randomized clinical trials (274–276) that evaluated 216 patients that compared biofeedback to a sham therapy or PEG laxative. All trials were unclear or at high risk of bias because of inability to blind participants to the nature of the interventions, or a lack of reporting of methods used to generate the randomization schedule or conceal allocation. There was a statistically significant benefit of biofeedback (RR constipation not improved = 0.33, 95% CI 0.22–0.50) with the NNT of 2 (95% CI 1.6–4) and no statistically significant heterogeneity.

None of the eligible trials (274–276) reported on adverse events.

Summary: Although techniques may vary in precise methodological details, biofeedback administered by a skilled and experienced therapist is, in general, effective in the management of patients with CIC who have prominent features of pelvic floor dyssynergia. Access to such expertise limits the usefulness of this approach for many patients and their physicians.

6. Bile acid transporter inhibitors in CIC

The ileal bile acid transporter (IBAT) inhibitor A3309 is a promising new therapy for CIC.
Grading not appropriate as no implication for current CIC management.

The IBAT is the most important transporter of the bile acid reabsorption loop. IBAT inhibitors selectively inhibit the reuptake of bile acids in the ileum, resulting in increased secretion and motor activity in the colon. Recently, the IBAT inhibitor A3309 has been proposed as a potential treatment for CIC.

We identified 3 RCTs of the bile acid transporter inhibitor A3309 in CIC involving 256 patients (283–285). All three trials were at low risk of bias. Varying doses of A3309 were employed ranging from as low as 0.1 mg to as high as 20 mg. Responses were dose dependent. In the largest study to date (283), an increase of ≥1 complete spontaneous bowel movements per week over baseline for 4 of the 8 weeks of the study was reported for 58, 64, and 75% of those randomized to 5, 10, and 15 mg of A3309, respectively, compared with 33% for placebo.

Diarrhea was more common in the patients receiving A3309 compared with placebo (RR = 2.62, 95% CI 0.72–9.56).

7. Probiotics in CIC

There is insufficient evidence to recommend probiotics in CIC. Recommendation: weak. Quality of evidence: very low.

We identified three trials evaluating probiotics in 245 CIC patients (286–288). None of the eligible trials stated the method of randomization or concealment and one was an open design. In two trials (286,288), the risk of bias was deemed to be unclear and one (287) had a high risk of bias. There were two trials (286,287) that reported on improvement in constipation in 110 CIC patients. Although both trials were positive in favor of probiotics improving constipation, the pooled data were not statistically significant (RR = 0.29, 95% CI 0.07–1.12) in a random effects model as there was significant heterogeneity between the two trials. There were two trials (287,288) that reported on mean number of bowel movements per week in 165 patients. There was a significant improvement in the mean number of bowel movements per week (mean increase in bowel movements per week in the symbiotic group = 1.49, 95% CI 1.02–1.96).

CONFLICT OF INTEREST

Guarantor of the article: Eamonn M.M. Quigley, MD, FACG.

Specific author contributions: A.C. Ford and P. Moayyedi performed the meta-analyses and participated in writing and reviewing the manuscript; E.M.M. Quigley, B.E. Lacy, Y.A. Saito, L.R. Schiller, E.E. Soffer, B.M.R. Spiegel, and A.J. Lembo, together with P. Moayyedi, developed all grading and recommendations and contributed to writing the manuscript. All authors reviewed all drafts of the manuscript and agreed with the final version. A.C. Ford is first author on the monograph, but is not a member of the Task Force. *P. Moayyedi conducted systematic reviews with support of A.C. Ford, and carried out the technical analyses of the data independent of the Task Force.

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Potential competing interests: A.C. Ford has received grant/research support from Almirall and GE Healthcare, and is a consultant/speaker for Almirall, GE Healthcare, Mayoly Spindler, Merck Sharp & Dohme, and Shire Pharmaceuticals. B.E. Lacy has served on scientific advisory boards for Ironwood Pharmaceuticals, Takeda, Salix, and Prometheus, is a consultant to Furiex, and receives grant support from the NIH for the functional dyspepsia treatment trial. Y.A. Saito has received research funding from Pfizer and Ironwood Pharmaceuticals, and is on the advisory board of Salix. L.R. Schiller has served on the speakers' bureau for Forest Laboratories, Ironwood Pharmaceuticals, Abbott/Abbvie, Takeda, Salix, and Santarus Pharmaceuticals. E.E. Soffer has served as a consultant and shareholder for EndoStim. B.M.R. Spiegel has received grant support from Takeda, Ironwood Pharmaceuticals, Theravance, Amgen, Shire, and Nestlé Health Sciences, is an advisor to Astellas, and received consulting fees from Ironwood Pharmaceuticals and lecture fees from Takeda. E.M.M. Quigley has served as a consultant and/or on the advisory board for Salix, Almirall, Ironwood Pharmaceuticals, Forest Laboratories, Shire/Movetis, Janssen, Rhythm Pharmaceuticals, Vibrant, and Alimentary Health, has served as a speaker for Procter & Gamble, Almirall, Janssen, Alimentary Health, and Shire, has received research support from Rhythm, Alimentary Health, Vibrant Pharma, and Norgine, and has been a non-executive director, shareholder, and patent holder for Alimentary Health. P. Moayyedi has served as a speaker for AstraZeneca, Shire, and Forest Laboratories Canada, has served as consultant and/or on the advisory board for Forest Laboratories Canada, and his Chair at McMaster University is funded in part by an unrestricted donation from AstraZeneca to McMaster University. A.J. Lembo has served as a consultant and/or on the advisory board for Ironwood Pharmaceuticals, Forest Laboratories, Salix, Prometheus, AstraZeneca, and Furiex, and has received research support from Prometheus and Furiex.

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EXPERT OPINION

The use of psychotropic drugs in irritable bowel syndrome

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Introduction: Irritable bowel syndrome (IBS), the most common functional gastrointestinal disorder, is manifested by chronic abdominal pain associated with irregular bowel movements. Although not life threatening, IBS is associated with impaired quality of life that ranges from mild to severe.

Areas covered: The pathogenesis of IBS is not completely understood, but involves dysfunction of the "brain–gut axis" including peripheral visceral hypersensitivity and central maladaptive processing of visceral pain input. Stress and concomitant psychopathologies such as somatization, anxiety and depression are thought to play a major role in the development, clinical course and response to treatment. Psychopharmacological agents such as selective serotonin/serotonin-norepinephrine receptor antagonists, tricyclic antidepressants as well as other agents are commonly used in treating moderate to severe IBS. This review will provide the pathophysiological rationale for the use of psychopharmacological agents in IBS, review the main classes of drugs and evidence for their use in IBS and offer a practical approach to the use of these drugs.

Expert opinion: Psychotropic drugs can play a pivotal role in the treatment of IBS patients, so doctors should be familiar with their use. Further research with these drugs is needed to solidify our current knowledge and increase our therapeutic options.

Keywords: IBS, pain, pathogenesis, pharmacological therapy, treatment

Expert Opin. Investig. Drugs [Early Online]

1. Introduction

Most patients who present with gastrointestinal symptoms have no diagnostic structural abnormalities even after an extensive investigation, and are diagnosed with a functional gastrointestinal disorder (FGID); often considered a diagnosis of exclusion. However, FGIDs are recognized disorders that are diagnosed by their identifiable pattern of symptoms which are usually constant over time [1]. Among the FGIDs, irritable bowel syndrome (IBS) is the most common, affecting up to 15% of the general population [2]. The hallmark of IBS is chronic abdominal pain associated with irregular bowel movements. The pain can be mild and intermittent or severe, constant and debilitating. Although not a life threatening condition, IBS causes a considerable degree of impairment in patients' quality of life [3] and, because of its chronic nature, can lead to many years of suffering.

There is a common misconception among many doctors and patients that there is no effective treatment for IBS, or that treatment only has a transient effect and is limited in benefit. This may stem from the fact that many doctors are not familiar with the treatment modalities currently available for IBS (limited as they may be), nor are they knowledgeable of the value of centrally targeted medications, in particular antidepressants, which currently are used for painful medical disorders in addition to IBS. Importantly, few physicians are trained in the use of antidepressants in patient care. A study evaluating the usual care of IBS patients in the community found that only 12% of patients treated by primary care physicians were prescribed

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Article highlights.

- Central mechanisms of maladaptive pain dysinhibition and associated psychopathologies, are crucial for symptom generation and clinical presentation in moderate to severe IBS.
- An effective doctor-patient relationship, based on the bio-psycho-social model, is the corner stone for successful treatment in IBS.
- Psychotropic agents can have an important role in the treatment of moderate to severe IBS, therefore doctors should be familiar with their use.

This box summarizes key points contained in the article.

an antidepressant for IBS. However, this may be changing in gastroenterology. A higher rate of antidepressant prescribing, 23%, was reported in patients treated by gastroenterologists [4]. A review of the database of a large health maintenance organization found that 55% of patients diagnosed with IBS were treated with antidepressants [5]. Although this finding could support the contention that a change has taken place in the treatment of IBS, it is more likely that in most cases the drug was prescribed for associated psychopathology and not for IBS *per se*. Thus, it is not surprising that doctors and patients do not feel knowledgeable in the management of IBS symptoms [6]. The aim of this review is to provide a scientific background, as well as a practical approach, to the use of antidepressants in the treatment of IBS.

2. Irritable bowel syndrome and the "brain–gut axis"

IBS patients experience pain and bowel disturbances even with minimal physiological stimuli such as meals, everyday stress, or even just waking up in the morning. Symptoms may also occur without any apparent reason. Visceral hypersensitivity and visceral hypervigilance are key factors in understanding this process. Since first described in 1973, it has been consistently demonstrated that during rectal balloon inflation IBS patients report pain at lower inflation volumes compared with healthy controls either for normally low (allodynia) or higher threshold noxious (hyperalgesia) stimuli. This finding suggests that visceral hyperalgesia and allodynia play a role in explaining the discomfort and pain in IBS. Importantly, these phenomena are strongly mediated by factors that upregulate intestinal neural signaling as well as central pathways in the spinal cord and in the brain that can facilitate downregulation of incoming afferent signals from the gut. In IBS these pathways are dysregulated. The bilateral neural communication between the brain and the gut is called the "brain–gut axis" [7-9]. Since the brain can facilitate or inhibit visceral pain perception, symptoms are ultimately the summation of excitatory and inhibitory impulses along this axis. However, studies conducted over recent years have demonstrated repeatedly that only about 50 – 60% of IBS patients manifest visceral hypersensitivity [10,11]. Thus, this mechanism does not provide a full explanation for the symptom experience in IBS. In fact, data from some studies suggest that the experience of pain in IBS is related more to the tendency to report pain than to the degree of visceral hypersensitivity, a tendency that was correlated with psychological distress [12]. As a result, the mechanisms by which central mechanisms modulate hypersensitivity have drawn increased research interest [7,13]. It appears that the role of these central mechanisms in symptom generation is crucial.

Studies using advanced technologies such as functional MRI and voxel-based morphometry have shown that the brains of IBS patients differ from healthy controls in terms of both function and morphology. The supragenual anterior cingulate cortex (sACC) and other structures in the limbic or medial brain system, which are responsible for descending pain inhibition, are less active in IBS patients. This same phenomenon is found in other chronic pain syndromes such as fibromyalgia [14-16]. In contrast, the medial cingulate cortex (MCC), which is associated with the feeling of unpleasantness and fear, becomes overactive in response to rectal distension. Therefore, in IBS patients the normal adaptive inhibitory response to painful visceral stimuli is diminished and replaced by a maladaptive, presumably even aggravating, response [14,15,17]. The factors that ultimately lead to this shift into a maladaptive pattern are psychosocial in nature, namely, anxiety, depression, poor social support, and impaired coping skills [18]. One case report showed that these changes are potentially reversible with appropriate therapy [17].

Not only do IBS patients' brains function differently, but Seminowicz *et al.* also showed that they are different from controls in the density of gray matter in regions involved in cognitive and evaluative functions [19]. Other investigators have shown cortical thickening and increased hypothalamic gray matter density suggesting a possible connection with the hypothalamic–pituitary–adrenal axis response to stress, which is believed to be of importance in IBS [20]. Similar findings were also recently described in fibromyalgia [21] This may not be surprising in that many experts believe that functional pain syndromes share a common impairment of central processing [22].

Finally, psychological comorbidities are frequently seen in IBS and become more frequent as disease severity increases. The prevalence of a psychiatric disorder ranges from 40 to 60% or above among patients with IBS and other FGIDs in tertiary care centers. These disorders correlate with the severity of IBS and influence the clinical course and outcome [2]. Comorbid psychopathology is associated with a more severe presentation, greater impairment in quality of life, higher utilization of healthcare resources, and a poorer response to therapy. Moreover, psychological comorbidity plays a role not only via central mechanisms but also via peripheral mechanisms. Psychological stress has been shown to induce visceral hypersensitivity in animal models by promoting an immune-mediated inflammatory response predominantly through mast cells [23,24].

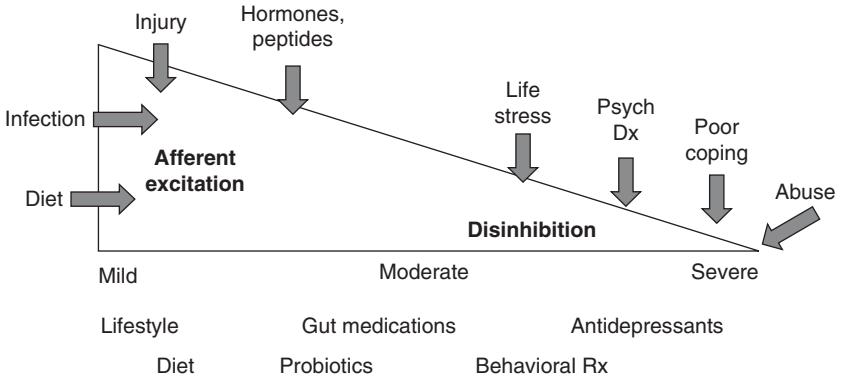

Figure 1. IBS – brain-gut influences on severity and treatment.

Taken together these data suggest that central mechanisms are crucial for symptom development and perception in IBS. In clinical practice this translates to the bio-psycho-social model [25]. The approach to the patient should be based on the bio-psycho-social model and address patient symptoms within their psychological and social context. Issues such as childhood trauma or abuse are important as predisposing factors and precipitating factors in IBS [26,27]. Specific stressors should be looked for (divorce, bereavement, financial difficulties, etc.) and concomitant anxiety or depression should be addressed. Without identifying and treating patients' feelings, emotions, cognitions and psychological status the treatment of IBS is unlikely to succeed. In clinical practice the more severe the clinical presentation is, the larger is the relative importance of central mechanisms. This translates to a higher rate of psychological comorbidity and psychological issues (such as trauma and abuse) in the more severe cases of IBS and other FGIDs (**Figure 1**).

Based on the above it is clear that pharmacological and non-pharmacological interventions directed at these central mechanisms are relevant to the treatment of moderate and severe IBS. While non-pharmacological treatment modalities such as cognitive behavioral therapy, psychotherapy, hypnosis, relaxation techniques and meditation have been tested and found to be helpful in IBS [28-33], this paper will focus on centrally acting drug treatment in IBS. **Table 1** summarizes the rationale for and some of the benefits of antidepressants in IBS.

3. Psychopharmacological agents in the treatment of IBS

3.1 Tricyclic antidepressants

TCAs are probably the most widely used psychotropic agents for the treatment of pain syndromes. They have been rigorously studied and have consistently demonstrated a good (although moderate) analgesic effect in different organic (e.g., post herpetic neuralgia, diabetic neuropathy) and functional pain syndromes (e.g., fibromyalgia) [34,35]. Their analgesic mechanism of action is complex and not fully understood, but evidence exists to suggest that their main mechanism is the inhibition of norepinephrine and serotonin reuptake in the synaptic space at both the spinal and supraspinal levels which allows for increased activity of these neurotransmitters in the synaptic cleft. Other putative mechanisms include blocking voltage-gated ion channels, increased GABAB receptor function, activation of opioid receptors and a decrease in inflammatory cytokine production [36]. This analgesic effect is probably unrelated to the antidepressant effect for several reasons. First, as mentioned above, these drugs are helpful in many organic pain syndromes in which the role of concomitant psychopathology is less prominent. Secondly, they are usually given in low ("non-psychiatric" doses). A study that assessed TCA blood levels in FGID patients found that the clinical response was not correlated with either the dose or the blood level of the drug [37]. Finally, a number of studies that directly addressed this question found that TCAs have an independent analgesic effect beyond their mood effect [38,39].

There are numerous published meta-analyses and systematic reviews that evaluated the efficacy of antidepressants and TCAs in IBS, the most recent of which is a Cochrane review from 2011 [40]. Nearly all of these reviews found that TCAs are helpful in relieving pain and reducing IBS symptoms and should be used in moderate to severe cases. For example, Ford *et al.* found, in a meta-analysis, that the relative risk for persistence of IBS symptoms in patients treated with TCAs was 0.66 and the number-needed-to-treat was 4 [41]. Rahimi *et al.* evaluated the use of TCAs (amitriptyline, imipramine, desipramine, doxepin and imipramine) in seven randomized placebo-controlled trials in IBS [42]. The pooled relative risk for clinical improvement with TCA therapy was 1.93 and the effect size vs placebo for mean change in abdominal pain score was -44%. In the biggest randomized controlled trial to date, Drossman *et al.* evaluated the efficacy of a 12-week treatment with desipramine in 431 women with moderate to severe IBS [43]. The primary intention-to-treat analysis showed no significant difference between the treatment and placebo groups. However, a per-protocol analysis did show a significant benefit in the desipramine-treated group (73% responder rate in the

Table 1. Rational for the use of antidepressants in irritable bowel syndrome.

Alterations in the brain-gut axis play a major role in IBS pathophysiology
Comorbid psychopathology is frequently seen in IBS
Antidepressants are helpful in similar mind-body conditions (e.g., fibromyalgia)
Some antidepressants have analgesic properties that are independent of their psychiatric effects
Antidepressants affect gastrointestinal motility
Antidepressants have a synergetic effect with other IBS treatment options (e.g., behavioral treatment, hypnosis)
Alterations in the brain–gut axis play a major role in IBS pathophysiology

desipramine group vs 49% in the placebo group, p = 0.01). The main reason for the difference between the intention-to-treat and the per-protocol analyses was a 20% dropout rate in the desipramine group due to side effects. This is a crucial point that emphasizes the difficulty of treating IBS patients. Strategies to enhance compliance with these drugs are discussed below. The most commonly used and investigated TCAs are amitriptyline, nortriptyline, and desipramine. The investigated daily dose was usually lower, at 25 – 50 mg, than the dose prescribed for depression. One exception was the Drossman study in which desipramine was prescribed at dosages up to 150 mg.

The most common side effects of TCAs are related to their anti-histaminic and anti-cholinergic effects. These include sedation or sometimes agitation, constipation, urinary retention, xerostomia and effects on sleep such as insomnia or nightmares. The fact that TCAs decrease colonic motility and are mildly constipating makes them suitable for IBS patients whose abdominal pain is associated with diarrhea.

3.2 Selective serotonin reuptake inhibitors

SSRIs are the most widely used drugs for the treatment of anxiety and depression. They increase specifically the synaptic concentration of serotonin by selectively inhibiting its reuptake from the synaptic space. They have a lesser analgesic effect than TCAs probably because they have no effect on synaptic levels of norepinephrine. The evidence supporting the use of SSRIs in non-gastrointestinal pain syndromes is not consistent. In diabetic neuropathy there is evidence from a single group, demonstrating that paroxetine and citalopram were superior to placebo. In contrast, another high-quality study that compared fluoxetine with placebo did not find any significant difference in their analgesic effect [44-46]. Interestingly, the latter study also found that TCAs were effective and suggested that their analgesic effect is probably related to norepinephrine rather than to serotonin. Moreover, no benefit over placebo was demonstrated in low back pain, rheumatoid arthritis, osteoarthritis, or tension-type headaches [47-49]. In fibromyalgia, a condition similar to IBS in many respects, fluoxetine and paroxetine improved overall fibromyalgia symptoms compared with placebo regardless of the degree of baseline level of depression and anxiety [50]. Seven randomized controlled trials evaluated the use of SSRIs in FGIDs. Three studies evaluated the use of paroxetine for 12 weeks vs placebo [51-53]. The study by Creed *et al.* demonstrated improvement in the physical component of the SF-36 quality of life questionnaire in the paroxetine group. However, only 50% of the recruited patients completed the study and a cost analysis showed no reduction in healthcare costs over a 1-year follow-up period. A study by Tabas *et al.* showed that patients treated with paroxetine reported an improvement in their overall well being, but not in pain, bloating or social functioning, compared to placebo. Masand *et al.* compared the use of controlled release paroxetine for 12 weeks to placebo in 72 IBS patients. They did not find a benefit for paroxetine over placebo in pain reduction. Kuiken *et al.* and Vahedi *et al.* conducted randomized control trials comparing fluoxetine with placebo in IBS. In the study by Kuiken *et al.* fluoxetine did not show any overall benefit over placebo. A sub-analysis demonstrated a decrease in abdominal pain in patients with visceral hypersensitivity on rectal balloon distention [54]. The second study evaluated the use of fluoxetine in constipation predominant IBS patients [55]. It was significantly more effective than placebo in decreasing abdominal discomfort, relieving the sensation of bloating, increasing the frequency of bowel movements, and improving the consistency of stool. Finally, two studies evaluated the use of citalopram in IBS. In one study treatment with citalopram for a period of 6 weeks significantly improved abdominal pain, bloating, the impact of symptoms on daily life, and overall well being compared with placebo in non-depressed IBS patients [56]. The other study failed to show any benefit for citalopram over placebo [57].

The side effects of SSRIs are usually mild and include nausea and diarrhea, sexual dysfunction with decreased libido and delayed orgasm, and neurologic/psychiatric symptoms such as anxiety, nervousness, tremor, insomnia, and nightmares. There is a black box FDA warning about an increased suicidal risk in adolescents and young adults with comorbid psychiatric conditions, such as depression, treated with SSRIs.

In all, SSRIs are probably less potent visceral analgesics than TCAs (or SNRIs reviewed below), but they have a modest but significant effect on global well being and anxiety-specific GI symptoms in IBS. Importantly, they have a substantial effect on psychopathology that is frequently associated with IBS, in particular anxiety and depression. They can be used to augment the analgesic effects of other drugs used in IBS such as TCAs. Thus, they represent a viable option in the treatment of IBS, mainly (but not exclusively) in constipated patients with prominent anxiety.

3.3 Serotonin-norepinephrine reuptake inhibitors

The main available SNRIs are duloxetine, venlafaxine, desvenlafaxine, and milnacipran. They have served as a focal

point in research on pain treatment distinct from treatment of depression over the last decade. In fact milnacipran is currently marketed in the United States as a pain medication rather than as an antidepressant. They are more potent analgesics than the SSRIs due to their noradrenergic effects and they do not have the same degree of sedation or anticholinergic side effects as TCAs. Duloxetine is indicated and approved for the treatment of diabetic neuropathic pain, chronic musculoskeletal pain, and fibromyalgia unrelated to depression, as well as for depression and anxiety. Their dual effect (analgesic and antidepressant) makes them an attractive choice in depressed patients with pain syndromes [58,59]. There are little data on their effectiveness in FGIDs, including IBS. In one small open-label study duloxetine was given to 15 non-depressed IBS patients for 12 weeks. Only eight patients completed the study; seven discontinued the medication due to side effects. In those who completed the study there was a significant reduction in pain and social dysfunction, and an increase in quality of life [60]. This preliminary study suggests a potential role for duloxetine in non-depressed IBS patients and once again highlights the central issue of adherence.

There is extensive research on the use of venlafaxine in pain syndromes. A Cochrane meta-analysis found venlafaxine to be as effective as TCAs in the treatment of neuropathic pain, with an NNT of 3.1 [61]. Data from healthy volunteers suggested that there are potential pathophysiological benefits for treatment with venlafaxine in IBS. In these individuals it altered colonic compliance and tone, and tended to reduce sensation during colonic distention [62]. Moreover, it increased the postprandial change in gastric volume suggesting a potential role in patients with functional dyspepsia. However, a randomized controlled trial failed to show any benefit for venlafaxine over placebo in patients with functional dyspepsia [63]. To date, there are no data regarding the use of venlafaxine in IBS. The usual daily starting dose is 37.5 – 75 mg with the highest psychiatric dose being 375 mg/day. Generally moderate to high dosages are needed (150 – 225 mg) in order to provide sufficient norepinephrine effect, i.e., analgesia. The side effect profile of SNRIs is generally similar to that for SSRIs, with the most common adverse effect being nausea and, in some cases, diarrhea.

3.4 Atypical antipsychotics

Atypical antipsychotics were initially approved for the treatment of schizophrenia, bipolar disorder and as an add-on to treat depression. More recently one of these agents quetiapine (Seroquel) was used in relatively low doses for the treatment of patients with non-psychiatric medical disorders accompanied by anxiety and other psychological comorbid symptoms. A small pilot study that was just recently published evaluated the use of quetiapine a mean dose of 132 mg as adjunct therapy in 51 refractory fibromyalgia patients [64]. This study found a significant positive effect on sleep, an unclear effect on fibromyalgia and mood symptoms, and no effect on pain. Its effect in fibromyalgia is currently being evaluated in a number of ongoing studies [65]. Quetiapine has the potential to benefit IBS patients by reducing anxiety, restoring normal sleep patterns, and possibly through a direct analgesic effect. One retrospective paper reported the use of quetiapine at low doses (50 – 200 mg) in patients with severe FGIDs, refractory to other treatment modalities including antidepressants. Ten of the 21 patients in the study discontinued the drug due to side effects or lack of efficacy, but of the 11 patients that stayed on the drug six reported improvement [66]. Although a small and uncontrolled study, these results can be considered encouraging since the participants suffered from extremely severe IBS. A larger, prospective, open-label study is currently underway. Olanzapine, another atypical antipsychotic, has also been evaluated in fibromyalgia and was found to decrease pain and improve quality of life [67]. To date, there are no studies evaluating its use in IBS or other FGIDs. Its primary value would appear to be as a means to augment the benefits of TCAs or SNRIs in patients who do not have an adequate pain response to other treatment modalities.

3.5 Miscellaneous agents

Mirtazapine is a tetracyclic antidepressant used primarily in the treatment of depression. It has antagonistic noradrenergic and serotonergic properties whose net effect is increased noradrenergic and 5-HT1A serotonergic activity [68]. In addition to its antidepressant effects it is also sometimes used as an hypnotic, antiemetic, and appetite stimulant, and for the treatment of anxiety. Animal data demonstrate that it ameliorates colonic hypersensitivity and improves gastric emptying, suggesting a potential role in IBS and functional dyspepsia [69]. However, a randomized controlled trial in healthy subjects failed to show any gastric pro-kinetic properties [70]. Data regarding its use in IBS are limited and more studies are needed to explore its potential [71,72]. Its main benefit in IBS may be related to the augmentation of the antidepressant and anti-anxiety properties of other agents (such as a TCAs or SNRIs) and in cases with prominent nausea and vomiting or low body weight (as may be seen in patients with a comorbid eating disorder).

Buspirone is a non-benzodiazepine, anti-anxiety agent that is used in psychiatry to augment the effect of antidepressants [73]. It also has a 5HT1 agonist effect, which may contribute to increased bowel compliance/relaxation as has been shown to occur in functional dyspepsia [74]. Therefore, it might be useful in patients with comorbid dyspeptic symptoms such as epigastric discomfort and early satiety. The results of a double-blind, placebo-controlled, crossover study on the use of buspiron in 17 patients with functional dyspepsia were recently published [75]. After 2 weeks of treatment with buspiron there was significant improvement in both gastric accommodation and dyspepsia symptoms compared with placebo. Although this study did not include IBS patients, many of the latter have comorbid dyspeptic symptoms and might benefit from this treatment.

Table 2. Common interventions used in IBS.

Drug	Drug (daily dose range [mg])	Comments
Tricyclic antidepressants (TCA)	Desipramine (25 – 150) Nortriptyline (25 – 150) Amitriptyline (25 – 150)	Begin with low dose and titrate by response Allow 4 – 8 weeks for maximal response
Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine (20 – 60) Escitalopram (10 – 20)	Begin with low dose and titrate by response
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine (25 – 300) Duloxetine (20 – 80)	Psychological and analgesic effects
Atypical antipsychotics	Quetiapine (25 – 100)	Preliminary reports
Tetracyclic antidepressant	Mirtazepine (15 – 45)	Anti-emetic properties
Azaspirodecanediones	Buspiron (10 – 60)	Improves gastric receptive relaxation

For optimal results these interventions can be used in combination ("augmentation" therapy). The use of more than one drug at a low dose can augment the therapeutic response and minimize the side effects.

4. Practical approach and key issues in treating IBS patients with psychotropic drugs

4.1 Before prescribing

Not all IBS patients require treatment with psychotropic drugs. Patients with mild or intermittent symptoms can usually be managed by reassurance, dietary modifications and peripheral symptomatic therapy such as bulking agents, laxatives, probiotics, and spasmolytics. The use of psychotropic drugs should be reserved for patients with a moderate to severe disorder, with or without psychological comorbidity.

As in almost any field of medicine, and especially when treating functional chronic painful conditions, it is of the utmost importance to establish a good doctor–patient relationship [25,76]. When a psychiatrist prescribes a psychotropic drug, the recommendation is perceived as relevant. However, when a gastroenterologist prescribes these drugs the patient may take this to mean that the doctor does not acknowledge their pain, does not believe them and thinks that they are "crazy." In such a scenario, the chances of adhering to the prescribed treatment are very low. Consequently, a thorough explanation about the nature of IBS, its pathophysiology and its relationship with psychological stress should be a first step. The initial explanation should include a description of the brain–gut axis, the principles of visceral hypersensitivity, and the fact that the gut is affected by stress. It should be emphasized that although no structural source for the pain could be identified, it is indeed real and manageable. It is also helpful to stress that while IBS is not a psychiatric condition, the hypersensitive gut is more prone to the effects of mental stress. Lastly, the doctor should explain the analgesic properties of antidepressants and reassure the patient that they are given in low, non-psychiatric doses as treatment for pain and not as a psychiatric agent.

Unfortunately, these initial explanations are often not enough in and of themselves. Adherence to treatment is a major obstacle and even in controlled trials drug discontinuation rates reach 50%. Frequently, the drugs are stopped early in the treatment due to side effects. Ironically, many of these "side effects" were actually present before the drug was started and are the result of stress and anxiety [77]. In our experience, the adherence rate increases if the physician is available, in real time, to address early adverse effects and other concerns that otherwise may lead the patient to discontinue therapy on their own. This can be achieved by establishing a practical means of communication (cell phone or e-mail), especially during the first week when most dropouts occur. Although this approach may seem to some doctors to be intrusive and time consuming, in our experience is that most patients do not abuse this privilege or use it inappropriately and most problems can be managed easily and quickly (by reassuring the patients about efficacy, side effects, and dosages).

4.2 The choice of psychotropic agent

The choice of psychotropic drug should be tailored to each specific patient. In general, in non-constipated IBS patients with pain as their predominant symptom, a low-dose TCA drug is a good choice. The usual starting dose is 25 – 50 mg and can be titrated up as needed. We usually use nortriptyline or desipramine because they have less antihistaminic and anticholinergic effects and are better tolerated then amitriptyline or imipramine. In constipated patients it may be more useful to start with an SNRI to avoid the sometimes constipating side effect of the TCAs and especially if there is evidence of comorbid psychopathology such as anxiety or depression. The SSRIs are less effective for pain, so they are not usually used as monotherapy but rather as an augmenting agent in combination with other drugs such as an SNRI or a TCA or when the patient has a high level of anxiety that is contributing directly to symptom exacerbation. The SSRIs and SNRIs have a more narrow therapeutic range. Starting doses are usually within the lower range of the psychiatric dose (e.g., citalopram 20 mg or duloxetine 30 mg) and titrated up as needed. For SNRIs, especially venlafaxine, the analgesic effect usually requires higher doses (225 mg and above). When nausea and weight loss are an issue, the addition of a low dose (15 – 30 mg) of mirtazepine can be helpful. We suggest reserving the use of quetiapine to patients with severe, refractory IBS who fail to respond to

combination therapy with an SSRI or SNRI together with a TCA. This drug is especially helpful if the patient has severe anxiety and sleep disturbances. We start at a low dose of 25 – 50 mg and titrate the dose up as required. High doses (> 200 – 250 mg) are rarely needed [78,79]. The different drugs and dosages are summarized in **Table 2**.

The concept of augmentation therapy refers to the use of a combination of drugs from different classes in low doses instead of one drug at a maximal dose. This approach allows us to obtain an optimal synergistic effect while minimizing dose-dependent side effects. This is a common approach in psychiatry that we find particularly helpful in the field of FIGDs, given the tendency of these patients to develop side effects and discontinue treatment. Examples of common combinations are adding a low-dose TCA with a low-dose SNRI or the addition of a low dose of an atypical antipsychotic to an SNRI or a TCA to augment their anxiolytic effects and treat associated psychopathology. In the same manner we commonly use mirtazapine or buspiron to alleviate dyspeptic symptoms such as early satiety, epigastric discomfort, or nausea and to reduce anxiety and depression [80].

4.2.1 *Reservations and safety issues*

Although antidepressants are used extensively in the treatment of FGIDs, they are still not uniformly endorsed by physicians and regulatory agencies and their use is considered "off label." The main reasons brought up by those who dispute their use are the absence of sufficient data to support a definitive recommendation, as well as safety concerns. For example, a recent study calculated not only the NNT for TCAs in IBS but also the "number needed to harm" (NNH), defined as the number of patients reporting side effects while using the drugs [81]. This study claimed that while the NNT in antidepressants was 8 the NNH was 18.3. This paper expresses the genuine concern of some authorities regarding treatment with antidepressants.

Undoubtedly these are important and valid issues. We believe that although the data in IBS are not robust, they are sufficient especially when taken together with evidence from other similar functional pain conditions (e.g., fibromyalgia) and the body of clinical experience that has accumulated among experts in the field. Moreover, we do not recommend the use of antidepressants for all IBS patients. They should be reserved for patients with moderate to severe disease severity, where impairment of quality of life is significant and other first-line treatments (dietary, spasmolytics, and fiber) have not provided satisfactory relief. One should keep in mind that although IBS is a benign functional condition, the impaired quality of life and increased extent of suffering may be greater than in organic conditions for some patients [82,83]. We agree that more high quality research is needed to substantiate and validate our recommendations and approach. However, this should not impede judicious, measured use of these agents in the interim.

The issue of safety may also be, to a great extent, "in the eye of the beholder." Those who oppose the use of antidepressants emphasize the benign nature of the condition. We empathize the disorder's significant effect on quality of life impairment and the lack of other effective therapeutic alternatives. Moreover, low doses of TCAs are rarely associated with severe or life-threatening side effects, most of which are minor and transient. The fear of dangerous cardiac arrhythmias may be the major safety concern in IBS. However, this is very rare in the low doses used in IBS. In fact, in the above-mentioned trial by Shah *et al.* the only cardiac side effects reported were tachycardia (that appeared at the same rate in the placebo group) and palpitations (reported by 9% of TCA group compared with 2% of the placebo group). Having said that, we recommend a baseline ECG or a cardiology consult in high-risk patients, such as elderly patients, patients with a history of cardiac disease, patients with a family history of arrhythmias or sudden death, and patients on other pro-arrhythmic drugs. SSRIs and SNRIs are generally considered safe and are widely prescribed by primary care physicians. We recommend caution especially in young teenage patients due to a possible increased risk of suicide in this age group. The treating physician should also be aware of signs and symptoms suggestive of the "serotonin syndrome," especially when using these drugs in high doses or in combination. These events are extremely rare. In general, physicians who are less experienced in the use of these drugs might consider a psychiatric consult before prescribing high doses or prescribing several psychotropic drugs in combination.

4.3 Summary and conclusion

IBS is the most frequent FGID and a major health problem. Its pathophysiology is complex and not sufficiently understood, but undoubtedly involves a dysfunctional brain–gut axis with a predominant component of central sensitization. Although not a psychiatric disorder *per se*, IBS is highly affected by stress and is frequently accompanied by comorbid psychopathology. The approach to the patient should be based on the bio-psycho-social model, where care is provided taking into consideration the patient's psychological and social background. Consequently, in addition to a therapeutic doctor–patient relationship, which is at the root of successful therapy, psychopharmacological agents that have a beneficial effect on motility and pain, as well as central effects, should be a cornerstone of treatment in moderate to severe IBS cases. It is important to remember that these drugs are not curative and that the "optimal" drug for IBS (assuming there is such a thing) has not yet been discovered.

5. Expert opinion

Abdominal pain is a hallmark of IBS and is essential for its diagnosis. In IBS, as in many other chronic pain syndromes, pain is a complex experience resulting from the interplay between peripheral (visceral) stimulation (enteric nervous system) and central modulation (central nervous system). The CNS can upregulate peripheral signals so that normal

physiological or mildly pathological input is perceived as an extremely painful event. Central factors such as anxiety, depression, somatization, and a past history of trauma or abuse are involved in this process. Evidence from advanced brain imaging studies demonstrated that the ACC and aMCC are key areas where a shift toward a maladaptive (augmenting) response to pain is taking place. Moreover, chronic pain conditions are also associated with structural changes in the brain, mainly reduced cortical density representing a process of neurodegeneration. As the perception of pain severity increases, central processing plays an increasingly important role compared to peripheral input. Once a pattern of central sensitization has taken hold, patients may even experience severe pain without any peripheral nociceptive stimulation. This is the case in extreme cases of functional gastrointestinal disorders.

In IBS, psychotropic medications (as well as other psychological interventions) can reduce noxious painful experiences via reduced signaling (with psychotropics) and enhanced downregulation at the level of the dorsal horn. These drugs are also useful in treating the commonly associated psychological comorbidity seen in IBS. Interestingly recent evidence suggests that they can also help reverse the neurodegenerative process in the brain. By "rebuilding the brain" psychotropics can help the brain regain a normal adaptive (inhibitory) response to pain as a substitute to its maladaptive (augmenting) response. But, however useful psychotropics are they are still underused in the field of IBS. This may relate to the perception of limited knowledge on the part of practitioners in using these agents or biases toward the patients. Moreover, prescribing these drugs requires effective communication skills and a good doctor–patient relationship. Establishing such a relationship is the cornerstone of treatment and the basis for all other interventions. Unfortunately, many physicians are under skilled or are not interested in investing the time and energy needed for creating and maintaining such a relationship. Consequently, a vicious cycle develops in which an ineffective doctor–patient relationship leads to clinical failure and subsequently to dissatisfaction and frustration that projects back on the relationship.

Although there is a large body of evidence about the use of psychotropics in IBS, there is still need for new high-quality data. Areas to be explored are the use of newer agents such as SNRIs and atypical psychotropics as well as the use of other agents such as mirtazepine or buspiron. SNRIs and atypical antipsychotics are probably the two classes of drugs that hold the most promise for the future in this field. Furthermore, studies evaluating the use of augmentation therapy with combinations of drugs, or combinations of drugs and other psychological interventions, are very much needed. Lastly, there is still a need for a better understanding of the exact mechanisms of pain processing in IBS and the effect of psychotropic drugs on these mechanisms. Brain imaging studies can help us understand the effects of centrally acting agents in IBS. In the future, these tests might serve as biomarkers for diagnosis or means to predict patient response to treatment.

By promoting research and education in the field of FGIDs, we will improve the quality of care and improve patients' quality of life. In order to reach this goal gastroenterologists and primary care physicians need to be better educated in brain–gut interactions, FGIDs, and the use of central treatments. Last but not least, doctors should be trained in communication skills in order to improve the quality of care and treatment satisfaction. Without doing so there is a risk of skyrocketing healthcare services cost. If clinicians are not able to reduce the burden of procedures in these patients by accepting the reality of FGIDs, it will be difficult to provide skilled patient-centered care. Ultimately doctors would shift to less demanding more profiting areas in gastroenterology (e.g., endoscopy), which can lead to a decrease in the number of physicians who treat patients with IBS and other FGIDs and increase the extent of care provided by physician extenders. One way to prevent this unfortunate scenario would be if reimbursement of services for "cognitive skills" were increased to provide appropriate compensation (compared to procedures) to clinicians providing proper patient care services.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Acupuncture for irritable bowel syndrome: systematic review and meta-analysis

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Abstract

Objective—Evidence-based treatment guidelines have been unable to provide evidence-based guidance on the effects of acupuncture for irritable bowel syndrome (IBS) because the only

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CONFLICT OF INTEREST/STUDY SUPPORT

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previous systematic review included only small, heterogeneous and methodologically unsound trials. We conducted a new systematic review and meta-analysis of randomized controlled trials (RCTs) to estimate the effects of acupuncture for treating IBS.

Methods—MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, Cumulative Index to Nursing and Allied Health, and the Chinese databases Sino-Med, CNKI, and VIP were searched through November 2011. Eligible RCTs compared acupuncture with sham acupuncture, other active treatments, or no (specific) treatment, and evaluated acupuncture as an adjuvant to another treatment. Our outcomes were overall IBS symptom severity and health-related quality of life. Dichotomous data were pooled to provide a relative risk (RR) of substantial improvement after treatment, and continuous data were pooled to provide a standardized mean difference (SMD) in post-treatment scores between groups.

Results—Seventeen RCTs (N=1806) were included. We found no evidence of an improvement with acupuncture relative to sham acupuncture on symptom severity (SMD = −0.11, 95% confidence interval: −0.35 to 0.13; 4 RCTs) or quality of life (SMD = −0.03, −0.27 to 0.22; 3 RCTs). Because of the homogeneity of the results of the sham-controlled trials, results were unaffected by restriction to the 4 sham-controlled RCTs that used adequate randomization, blinding, and had few withdrawals/drop-outs. Among RCTs that did not use a placebo control, acupuncture was more effective than pharmacological therapy (RR of symptom improvement=1.28, 1.12 to 1.45; 5 RCTs) and no (specific) treatment (RR = 2.11, 1.18 to 3.79; 2 RCTs). There was no difference between acupuncture and Bifidobacterium (RR = 1.07, 0.90 to 1.27; 2 RCTs) or between acupuncture and psychotherapy (RR=1.05, 0.87 to 1.26; 1 RCT). Acupuncture as an adjuvant to another Chinese medicine treatment was statistically significantly better than the other treatment alone, in trials with a high risk of bias (RR = 1.17, 1.02 to 1.33; 4 RCTs).

Conclusions—Sham-controlled RCTs have found no benefits of acupuncture relative to a credible sham acupuncture control on IBS symptom severity or IBS-related quality of life. In comparative effectiveness Chinese trials, patients reported greater benefits from acupuncture than from pharmacological therapies. Future trials may help clarify whether or not these reportedly greater benefits of acupuncture relative to pharmacological therapies are due entirely to patients' preferences for acupuncture or patients' greater expectations of improvement on acupuncture relative to drugs.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal condition characterized by altered bowel habits and abdominal pain and discomfort (1). A systematic review (2) has estimated that 10-15% of adults in North America have IBS, as diagnosed by either the Rome (3) or Manning (4) objective diagnostic criteria. IBS is associated with significant reductions in both health-related quality of life (5) and work productivity (1,6) and increased consumption of medical resources. Indeed, people with IBS consume over 50% more health care resources than age-matched controls without IBS (7,8). The combined direct and indirect costs associated with IBS patients in the United States in 2004 were estimated at over $1 billion (9).

Effective treatments for IBS are needed to relieve symptoms, improve quality of life, and to reduce healthcare utilization. In 2009, the American College of Gastroenterology Task Force conducted a series of systematic reviews to evaluate the efficacy of both pharmacological and non-pharmacological therapies for treating IBS (1). In terms of pharmacological treatments, the Task Force found "poor quality of evidence" for certain antispasmodics and "moderate quality of evidence" for tricyclic antidepressants, selective serotonin reuptake inhibitors, non-absorbable antibiotics (for diarrhea-predominant IBS), and C-2 chloride

channel activators (for constipation-predominant IBS). The Task Force found "good quality of evidence" for $5HT_3$ antagonists and $5HT_4$ agonists, but noted that these agents carry a possible risk of ischemic colitis and cardiovascular events, respectively, which may limit their utility. A subsequent systematic review showed that the benefits of these $5HT_3$ antagonists and $5HT_4$ agonists relative to placebo are "modest" (10). In terms of non-pharmacological therapies, the Task Force found "poor quality of evidence" for psyllium fiber and peppermint oil. The Task Force also noted that preliminary evidence suggested that some probiotics may be effective in reducing IBS symptoms (1). A subsequent systematic review (11) concluded that the specific probiotic B. infantis 35624 has shown repeated efficacy in well-designed randomized controlled trials (RCTs), and can be considered an effective treatment for IBS.

The Task Force was unable to make any recommendations either for or against acupuncture for treating IBS because the only available systematic review available at the time was a Cochrane review (12) which was inconclusive because it included only small, heterogeneous, and methodologically unsound trials. Given the safety of acupuncture (13-15) and the limited availability of other safe and effective treatments for IBS, the question of whether acupuncture is effective for treating IBS is highly relevant. Recently, several RCTs have been published which provide greater evidence to estimate the effects of acupuncture for treating IBS. We have therefore updated our previous Cochrane systematic review and meta-analysis of acupuncture for IBS (12) to assess whether the pooled effects of currently available trials show any benefit of acupuncture in improving symptoms or health-related quality of life in patients with IBS.

METHODS

Search strategy

We searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, the Cumulative Index to Nursing and Allied Health, and the Chinese databases Sino-Med (previously called the Chinese Biomedical Database), CNKI, and VIP (through November 2011). We considered all RCTs included in, or ongoing, at the time of the previous version of this review (12). To further avoid the risk of missing eligible trials (16), we also scanned bibliographies of included articles and systematic reviews for further references.

Study selection

We included randomized controlled trials, published in any language, as either full articles or abstracts. Because recent research indicates that a large proportion of Chinese-language RCT reports are of studies that are not truly randomized (17), an author interviewed the investigators of Chinese-language RCTs by telephone to determine whether they had used randomization. The interviews were conducted using questions adapted from the survey developed by Wu et al to verify the authenticity of "claimed" randomized trials (17). The same questions were asked of authors of English-language RCTs that did not include details about randomization methods in their published reports. Trials that were found to assign patients by alternation, rotation, or hospital record number were automatically excluded. Trials that used a random method of assignment, but with flaws or suspected flaws in the random assignment process were included, but with their limitations described.

We included trials evaluating traditional Chinese Medicine (TCM) acupuncture for the treatment of adults diagnosed with IBS. TCM acupuncture involves inserting needles into traditional meridian points, usually with the intention of influencing energy flow in the meridian. Needles may also be inserted at additional tender points and electrical stimulation

of the needles may be used. Since TCM acupuncture is often accompanied by moxibustion, we included trials using moxibustion as a co-intervention with acupuncture. We excluded trials of dry needling/trigger point therapy, a therapy which is based on principles of Western anatomy and physiology and rejects TCM concepts of energy and meridians. We also excluded RCTs of laser acupuncture, non-invasive electrostimulation (i.e., using electrodes on the skin rather than needles to stimulate acupuncture points (18)), and acupressure, to restrict our focus to the effects of traditional needle acupuncture. Finally, we excluded trials of micropuncture, a non-traditional acupuncture practice which is based on the principle that the ear (or nose, eye, etc.) is a microsystem of the entire body, and in which needles are only inserted on that microsystem.

We included trials comparing acupuncture to sham (placebo) acupuncture, other active non-TCM treatments, and no (specific) treatment, or evaluated acupuncture as an adjuvant to another treatment. We excluded RCTs in which one form of acupuncture was compared with another form of acupuncture or a different type of TCM (e.g., Chinese herbal medicine). Adjunctive treatments, either Western or TCM, were allowed as long as they had been given to both the acupuncture and control groups. Our primary outcomes were overall IBS symptom severity and IBS health-related quality of life. Studies that did not report at least one of these outcomes were excluded.

All records identified by searching were independently screened by at least one reviewer. The full text of potentially relevant reports was obtained and independently reviewed by two authors for eligibility. Disagreements between reviewers were resolved by discussion.

Outcome measures and data extraction

Two recent evaluations of symptom and quality of life measures in IBS concluded that the IBS Adequate Relief question (IBS-AR) (19) and the IBS Symptom Severity Scale (IBS-SSS) (20) possessed responsiveness, face and construct validity and were two of the most appropriate IBS symptom outcome measures, while the IBS Quality of Life measure (IBS-QoL) (21) was the most extensively validated quality of life scale (22,23). For overall symptom severity, we therefore gave preference to the IBS-AR for dichotomous outcomes and to the IBS-SSS for continuous outcomes, while for quality of life outcomes we gave preference to the IBS-QoL. In cases where dichotomous outcomes such as improvement in IBS symptoms were presented in the form of multiple strata, such that we had the option of choosing cutpoints for the dichotomous outcome, we followed the model of Ford et al. and created a dichotomous measure in which all positive outcomes were combined into a single positive category (i.e., improvement) and the remaining strata constituted the negative category (i.e., no improvement) (10,24). When investigators selected a cutpoint on a continuous scale to dichotomize between improvement and no improvement, we used the same cutpoint to define the dichotomous outcome (10).

We extracted outcome data for both short and long-term follow-up points. Short-term follow-up was defined as three months or less after randomization, and long-term follow-up was defined as closest to six months but more than three months after randomization. When we observed multiple short-term follow-up points, we chose to extract the data closest to eight weeks after randomization, which coincided with end of treatment. In cases where participants were lost to follow-up, and the RCT investigators conducted intention-to-treat (ITT) analyses using imputed values for the participants' missing data, we used these ITT results for our meta-analyses in preference to the available case analyses, if the ITT method for imputing data was described and if it was an appropriate method that would not bias the effect size calculation. If the method that the RCT investigators used for imputing missing data in their ITT analysis was not clearly described or not appropriate, we used the available case data instead (if available) for the primary analysis and the ITT data for a sensitivity

analysis. If either only the ITT data or only the available case data were reported, then those available data were used. (We did not impute missing data ourselves for the meta-analyses.) The potential impact of missing data (including missing data that were imputed using a method that was not clearly described) were considered in interpreting the results of the review, taking into account the degree of missing trial data across the treatment arms and the size of the effect estimate of the individual trial and the pooled effect estimate.

All study characteristics and outcome data were independently extracted by two authors, and disagreements were resolved by discussion. When reported data were incomplete or ambiguous, we requested additional information or clarification from the corresponding authors.

Assessment of acupuncture adequacy

Two acupuncturists (LL, XS) who have a combined acupuncture clinical experience of nearly fifty years in treating IBS, and who have previously worked on RCTs of acupuncture, assessed the adequacy of the acupuncture administered in the trials. Six aspects of the acupuncture intervention were assessed for adequacy: choice of acupuncture points; total number of sessions; treatment duration; treatment frequency; needling technique; and acupuncturist's experience (25-27). The likelihood of the sham intervention to have physiological activity was also assessed, using an open-ended question. The acupuncturist assessors were provided with only the part of the publications that described the acupuncture and sham procedures, so that their assessments could not be influenced by the results of the trials. To test the success of blinding the assessors to the study publication and results, we asked the assessors to guess the identity of each study being assessed. The acupuncturists assessed adequacy independently and achieved consensus by discussion.

Study risk of bias

For each included study, we assessed risk of bias using the Cochrane Collaboration's risk of bias tool (28), which is comprised of 6 domains that may increase the risk of over- or underestimating an intervention effect. We also evaluated 2 other risk of bias-related factors: baseline comparability and use of an intention to treat analysis.

In judging adequacy of blinding, which is one of the Cochrane risk of bias domains, we assigned sham-controlled trials a judgment of "Unclear" unless we felt certain that the sham control was sufficiently credible in fully blinding participants to the treatment being evaluated (26,27). We considered sham-controlled trials to have a low risk of bias for blinding if the trial either 1) evaluated the credibility of the sham and found the sham to be indistinguishable from true acupuncture or 2) used a penetrating needle or a previously validated sham needle (i.e., Streitberger needle (29)).

Two review authors independently judged whether each risk of bias criterion was adequately met. Any disagreement was resolved by discussion.

Data synthesis and statistical analysis

We only pooled data from trials that used similar control interventions (sham acupuncture, no treatment, or another active treatment), outcome measures (overall IBS symptom severity, IBS-related quality of life), and timing of outcome assessment (short-term, long-term). For pooled data, summary test statistics were calculated using the RevMan software version 5.1 (30) random effects model, to account for expected heterogeneity. We evaluated heterogeneity using the I^2 statistic (31), which indicates the proportion of variability across trials not explained by chance alone (32).

For the acupuncture versus sham comparison, data for the symptom severity outcome were presented in some studies as dichotomous data (e.g., adequate symptom relief) and in other studies as continuous data (e.g., symptom severity as measured by the IBS-SSS). We re-expressed odds ratios as standardized mean differences (SMDs), thereby allowing dichotomous and continuous data to be pooled together for this comparison/outcome (32), using the generic inverse variance method in RevMan. For the acupuncture versus sham comparison, all 3 studies that included the quality of life outcome reported continuous data (and 2 out of 3 did not also report dichotomous data), so we pooled these studies using the SMD. For all other comparisons/outcomes, all studies reported dichotomous outcome data (and some did not also report continuous data), so we pooled these studies as relative risks. For the Cochrane version of this review, all continuous and dichotomous data reported for all studies are presented in forest plots. There were no important differences between continuous and dichotomous results for any comparison/outcome.

RESULTS

Results of the search

Our searches identified 1421 citations of which 71 references, corresponding to 65 individual studies, were evaluated in full. Of these 65 studies, 48 were excluded, leaving 17 eligible randomized controlled trials (33-49), including a total of 1806 patients (see Supplementary Figure 1 online). Three of the studies included in our 2006 Cochrane review (50-52) were excluded from this update because either an adequate randomization process was not used (50,51) or the procedure could not be recalled by the author (52).

Table 1 includes a description of trial characteristics and acupuncture and control interventions. The Cochrane version of this review includes an additional figure for the flow of studies through the selection process, as well as the following additional tables: summary of findings table; list of studies that we excluded as well as the reasons for exclusion; full details of the characteristics of the included trials; full details of the risk of bias assessments for each trial; and assessments of adequacy of acupuncture and sham protocols.

Acupuncture adequacy

All trials included in this review were judged adequate on “Choice of acupoints”, except for the Lowe trial (42), which did not report the acupoints. The acupuncture frequency was judged adequate in all trials except for the Forbes and Reynolds trials (37,43). The acupuncture adequacy assessors were successfully blinded to the study publications and were unable to guess the identity or results of any of the studies they assessed.

Risk of bias in included studies

All sham-controlled trials reported adequate methods for sequence generation and allocation concealment. In 4 out of 5 of the sham-controlled trials (34,37,38,44) (i.e., all except for the Lowe trial (42)), we judged that the shams were likely to be indistinguishable from true acupuncture and that incomplete outcome data was adequately addressed. The Lowe trial was reported only as an abstract, and the completeness of outcome data ascertainment could not be assessed. In the one sham-controlled trial (37) that had a moderate total number of withdrawals (i.e., 8/59), the drop-outs were approximately evenly distributed across treatment groups, the withdrawals were unlikely to be related to knowledge of treatment assignment or effects of the treatment, and the degree of missing data would be unlikely to affect the estimate of the treatment effect in this individual trial or in the meta-analytic estimates.

In the trials comparing acupuncture with another active treatment (33,35,40,41,45,46,48,49), no (specific) treatment (38,43), or evaluating acupuncture as an adjuvant to another treatment received by all trial participants (36,39-41,47), blinding of participants was not possible, and this likely represents the major risk of bias in these trials. In these comparative effectiveness trials, there were also risks of bias associated with the randomization procedure and the follow-up of patients (see Risk of Bias table).

Acupuncture versus sham acupuncture

Five trials (34,37,38,42,44) compared the effects of acupuncture and sham acupuncture. The 5 individual sham-controlled RCTs, and also the pooled analysis, found no statistically significant differences between acupuncture and sham acupuncture, on the outcomes of symptom severity or quality of life. (One trial (44) did not measure the outcome of symptom severity and 2 trials (34,42) did not report quality of life.) For both outcomes, the results of all sham-controlled trials were homogeneous (I^2=0%) (see Figure 1). Only the Schneider et al trial (44) included a long-term follow-up time point, and this trial did not find a difference between acupuncture and sham in the quality of life outcome at six months (SMD 0.07, 95% CI −0.54 to 0.69).

Acupuncture versus other active treatments

The five trials (35,45,46,48,49) that compared acupuncture versus pharmacological therapies for IBS found that participants receiving acupuncture reported a greater improvement than participants receiving pharmacological therapies (see Figure 2).

Participants receiving acupuncture were not more likely to have responded to treatment than those treated with psychotherapy (40) or those treated with bifidobacterium (33,41).

Acupuncture as an adjuvant to other active treatments

Five trials (36,39-41,47) compared the combination of adjuvant acupuncture plus another IBS treatment received by all trial participants to the other IBS treatment alone. Pooled results showed that participants receiving adjuvant acupuncture were more likely to have reported improvement than those treated with another Chinese medicine treatment alone (although there was substantial heterogeneity of results and high risks of bias in these trials) (36,39,41,47), or those treated with psychotherapy alone (40).

Acupuncture versus no specific treatment

Two trials (38,43) compared the effects of acupuncture to no specific treatment. In both trials, all participants were allowed to continue receiving standard medical care for IBS, including prescribed medications, but control group participants were not assigned to any additional IBS treatment. Both of these trials showed a statistically significant benefit of acupuncture for improving IBS symptom severity, although there was substantial heterogeneity of results between the 2 trials (I^2 = 57%).

Subgroup and sensitivity analyses

For the sham-controlled trials, subgroup analyses on risk of bias or treatment adequacy-related variables would be uninformative because all sham-controlled trials had similar results and no combination of these trials resulted in a pooled statistically significant benefit, for either the symptom severity or quality of life outcome. For trials comparing acupuncture versus pharmacological therapies, restriction to the 4 trials that compared acupuncture versus evidence-based (53) antispasmodic pharmacological therapies (35,45,46,49) had similar results (RR 1.21, 95% CI 1.07 to 1.37, 249 participants, I^2=0). For the other comparisons, there were too few trials to attempt subgroup analyses (32).

For the Forbes et al trial (37), which reported both intent-to-treat (ITT) and available case data for the symptom severity outcome, a sensitivity analysis using ITT values instead of the available case values did not result in important differences in the SMDs for this trial.

Safety of acupuncture

Nine trials included descriptions of adverse events associated with acupuncture (33,34,36-38,41,43,45,46). For 8 of these 9 trials (33,34,36-38,41,43,46), no serious adverse events were reported, while the Shi et al trial (45) reported that 1 participant in the electro-acupuncture group withdrew because of syncope.

DISCUSSION

Summary of main results

Five sham-controlled RCTs have tested the effects of acupuncture for IBS, and 4 of these trials used adequate randomization, blinding, and had few withdrawals/drop-outs. None of these sham-controlled RCTs individually found a statistically significant benefit of acupuncture relative to sham acupuncture on the outcomes of symptom severity or quality of life. Similarly, pooling the data from these sham-controlled trials did not result in statistically significant benefits of acupuncture on either outcome. At the same time, 5 Chinese-language comparative effectiveness trials found that patients receiving acupuncture reported greater improvements in IBS symptoms compared to patients receiving pharmacological therapies for IBS.

How should physicians, researchers, and policy-makers interpret these seemingly contradictory trial findings in guiding treatment decisions and future trial design? First, both the comparative effectiveness trials and the sham-controlled trials have important limitations that complicate their interpretations. Namely, in the trials comparing acupuncture versus pharmacological therapy, in which the patients are not “blinded” to the treatment received, expectation effects (i.e., defined as “the impact of expectations on subjective outcomes” (54)), may differ between acupuncture and drugs (27,55,56). Such differences in expectations of benefits between acupuncture and drugs may contribute to different magnitudes of a placebo effect (i.e., a patient’s improvement in symptoms due to an inert treatment, or an inert component of a treatment). Because of the possibility of differential expectations of a benefit from acupuncture versus drugs in these trials (27,55,57), it cannot be determined whether any of the reported benefits of acupuncture are due to a larger biological effect of acupuncture needling relative to drugs, or rather due entirely to the impact of the study participants’ greater expectations of a benefit of acupuncture, on the subjective outcomes that they reported.

A limitation of the sham-controlled trial design is that the high placebo effects of sham acupuncture may preclude the detection of any small, true biological benefits of true acupuncture relative to sham, when patient-reported subjective outcome measures are used. Two “methodological” trials have evaluated the placebo effects of sham acupuncture, on both subjective and objective outcomes (56,58). One such methodological trial (56), designed to compare placebo effects of placebo pills and sham acupuncture, found that, relative to placebo pills, sham acupuncture was more credible as an authentic treatment and resulted in higher subjective patient reports of improvement. This trial also found that the placebo effect was confined to self-reported, subjective outcomes (e.g., pain) and that there was no placebo effect (i.e., no improvement from baseline) for either the placebo acupuncture or placebo pill on the objective outcome that they measured (i.e., grip strength). Another recent methodological trial (58) compared albuterol (i.e., a proven asthma drug) versus sham acupuncture for asthma patients, and found that while only the albuterol had a

biological effect on the objective outcome of airway flow, both the sham acupuncture and albuterol groups had dramatic and comparable improvements from baseline on the subjective outcome of patient self-reports of improvement, such that the albuterol showed no benefit relative to the sham acupuncture on self-reported improvement.

These methodological trials suggest that relying exclusively on subjective patient reports, such as those used as outcomes in IBS trials, may result in a failure to detect small biological effects of an active treatment (i.e., true acupuncture) relative to a highly credible, but physiologically inert, sham acupuncture control. Thus, while the high placebo effects among IBS patients (59) make it difficult to show that any pharmacological treatment is superior to an inert placebo pill, demonstrating such an effect may be even more difficult when the placebo control is sham acupuncture.

Overall completeness and applicability of evidence

How externally valid are the results of this review? Namely, do the types of interventions investigated in these studies represent current best practice of acupuncture for IBS? Assessing adequacy of the acupuncture treatment procedure is important because, for instance, basing conclusions about acupuncture efficacy on a suboptimal procedure is "analogous to a pharmaceutical trial formulating conclusions about the efficacy of a drug based on an inadequate dose" (60). For the sham-controlled trials, it might be argued that a possible reason for the lack of benefit might be explained by the fact that there were too few treatment sessions, an inadequate treatment frequency, or an insufficient duration of treatment. All sham-controlled trials were judged by our acupuncture adequacy assessors to have used an adequate number of sessions and duration of treatment. Only the Forbes sham-controlled trial (37) was judged to use an inadequate treatment frequency because this trial involved only 1 acupuncture session per week (for 13 weeks), which even though judged inadequate, probably still well reflects clinical practice. The other sham-controlled trials all used 2 sessions per week, which was judged by the acupuncture adequacy assessors as an adequate treatment frequency, so it seems unlikely that an inadequate frequency of treatment explains the lack of benefit. Although the acupuncture assessors judged the treatment frequency of the sham-controlled trials to be largely adequate, the Chinese language comparative effectiveness trials used a much greater treatment frequency, with daily acupuncture treatments used in 9 out of 11 of these comparative effectiveness trials, and all 5 of these trials that compared acupuncture versus drugs. The higher acupuncture treatment frequency in the Chinese comparative effectiveness trials, relative to the sham-controlled trials, might also help explain the different benefits of acupuncture relative to the controls in these 2 subsets of trials.

Quality of the evidence

Four out of the 5 sham-controlled trials in this review (34,37,38,44) did not have limitations related to a risk of bias criterion. Only the trial by Lowe (42) used a sham control that might not have been sufficiently credible to blind participants to whether they were receiving a true or sham treatment; however, any unblinding to the treatment received in this trial would likely only overestimate the effect of acupuncture (28).

It might be argued that one potential methodological limitation is that 2 of the 5 sham-controlled RCTs (34,37) used a sham control that involved skin penetrating needles inserted at non-acupuncture points that the acupuncture assessors in our review judged to have potential weak physiological activity that might influence the outcome, and which might therefore have biased these 2 RCTs to the null. However, we would not expect this to explain the lack of benefit of acupuncture relative to sham, both because these 2 shams were judged to have potential for only weak physiological activity and also because the other 3

sham-controlled RCTs used shams that were judged unlikely to have physiological effects, and these 3 RCTs also found no benefit of acupuncture relative to sham.

The quality of the evidence is also limited by the fact that all sham-controlled trials except the Lembo trial (38) had small sample sizes and were each underpowered to detect a small benefit of the acupuncture protocol evaluated. Although these trials may have been adequately powered to detect a moderate to large benefit of acupuncture relative to sham, an effect size of this magnitude may have been unreasonable to expect, considering that even specific $5HT_4$ agonists (i.e., tegaserod) and $5HT_3$ antagonists (i.e., alosetron and cilansetron), which are the only treatments with "good quality of evidence" for treating IBS (1) have only a modest efficacy. Although a meta-analysis of the 5 sham-controlled trials increases the statistical power to detect an effect, a limitation of pooling trials with different acupuncture protocols is that we cannot rule out the possibility that larger trials or meta-analyses focusing on one of these protocols might show a benefit of treatment. In addition, although the meta-analysis point estimates suggest no effects, the meta-analysis confidence intervals include the possibility that there could be small benefits which could be important to patients. A final limitation of the sham-controlled trial evidence base, related to the small sample sizes, and also the heterogeneity of participants, is that these trials did not restrict eligibility to specific subtypes of IBS patients, and the proportions of patients with different IBS subtypes differed across trials. An individual patient data (IPD) meta-analysis would be necessary to address whether acupuncture has different effects on different subtypes of IBS patients, although the relatively small numbers of patients would be unlikely to provide a confident answer to this question.

In the Chinese language comparative effectiveness trials, in addition to the primary risk of bias associated with the absence of patient blinding, there were also risks of bias associated with the randomization procedure and the follow-up of patients. Notably, for 5 of these trials (36,39-41,48), there were equal sized treatment groups, and the trial investigators could not adequately explain during our telephone surveys how this was achieved. This raises the possibility that the randomization might not have been adequately generated or concealed (61). The notion that randomized trials should have equal numbers in each treatment group has been shown to commonly lead clinical trial investigators to force equality by unscientific means (61). Indeed, previous methodological reviews of this issue have found that over one-half of trials using simple, unrestricted randomization schemes report equal numbers in each group (61,62), and 88% of reported randomized trials have been shown to exclude some randomized participants from their analysis (62). The Chinese trials with high risks of bias associated with the randomization and/or the accounting of randomized patients in the outcomes assessments evaluated acupuncture as an adjuvant to either another Chinese medicine treatment or psychotherapy, or compared acupuncture versus psychotherapy, probiotics, or a drug not indicated or commonly used for IBS (i.e., sulfasalazine (48)). Therefore, the findings from these comparisons should be considered only hypothesis generating, and are not included in our overall conclusions. In contrast, there was an overall low risk of bias in the 4 comparative effectiveness trials that found acupuncture more effective than 2 antispasmodic pharmacological therapies shown to be effective for IBS (53,63) (i.e., pinaverium bromide (35,45,46) and Trimebutine maleate (49)).

Authors' conclusions

Implications for practice—People with IBS have few treatment options available. Pharmacological therapies have modest benefits (24), can have high costs, and some of the newer drugs have been withdrawn from the market because of side effects (64,65). Safe, non-pharmacological therapies that may allow patients to feel more empowered and more in control of their symptoms should be evaluated for effectiveness. However, evaluating such

complex non-pharmacological therapies for IBS (e.g., mindfulness meditation (66), hypnotherapy (67)) poses challenges, particularly in regards to selecting a placebo control or a credible alternative treatment control.

While acupuncture can theoretically be compared with a sham acupuncture "placebo" control, a fundamental challenge has been developing a sham acupuncture control that is sufficiently believable to patients as to be indistinguishable from true acupuncture, and yet at the same time not so similar to true acupuncture that the sham has a therapeutic effect of its own and is therefore not an inert placebo. The sham acupuncture controls used in 4 of the 5 sham-controlled trials in this review appeared to be believable as authentic treatments, but 2 of the 5 sham-controlled trials used sham controls that might have had weak physiological activity, and therefore these shams may not have been completely inert placebos. While none of the sham-controlled trials showed a benefit of acupuncture relative to sham acupuncture, it is still not clear whether these findings are because acupuncture has no true biological effect above and beyond a placebo, or whether instead acupuncture has small biological effects, but the small sample sizes and heterogeneity of participants and interventions in these trials precluded detecting a statistically significant pooled benefit of acupuncture over sham, or whether any biological effects of true acupuncture cannot be detected because they are overridden and obscured by the large placebo effects of the sham control (56,58). Evidence from 4 Chinese language comparative effectiveness trials (35,45,46,49) showed acupuncture to be superior to 2 antispasmodic drugs, both of which have consistently been shown to be effective in high quality trials (53,63), although neither is approved for treatment of IBS in the United States (63). Patient preferences and expectations may partly explain the positive findings of these trials comparing acupuncture to drugs. That is, if the trial participants have pretreatment preferences for acupuncture over drugs, these preferences may have influenced the participants' later assessments of their subjective states, as reported on the patient-reported outcome measures used (27,55,57,68).

In addition to efficacy, safety and costs are other considerations. Safety is best determined with large prospective surveys of practitioners and 3 such surveys (13-15) show that serious adverse events after acupuncture are rare. There was 1 adverse event associated with acupuncture in the 9 trials that reported this outcome (33,34,36-38,41,43,45,46), although relatively small sample sizes limit the usefulness of this safety data. Finally, patients would also need to consider costs because acupuncture treatment often needs to be paid for out of pocket, at least in part.

Implications for research—Considering that our meta-analysis found no differences between acupuncture and sham, and also considering that there are limited resources available to conduct trials of acupuncture, a non-proprietary therapy, additional sham-controlled trials of acupuncture among IBS patients should not be a high priority in acupuncture research, at least until the large, ongoing sham-controlled trial, which is expected to complete data collection in March 2013, is published (Principal Investigator: Anastasi; n=171). This trial compares a sham control with 2 different acupuncture test treatment groups, one test group using a fixed formula and the other test group using an individualized treatment approach, for patients with diarrhea-predominant IBS. If this trial shows no benefit of acupuncture relative to the sham, then the need for additional sham-controlled trials would seem questionable. However, if this ongoing sham-controlled trial shows a benefit, then future sham-controlled trials building upon the results of this trial (e.g., restriction to diarrhea predominant IBS patients; using the same acupoints as used in this trial) would certainly be warranted. Such future sham-controlled trials should use non-penetrating, but demonstrably credible, shams to control for placebo effects, and ideally these sham needles should be placed far away from the true acupuncture points.

Because of the difficulties of controlling for placebo effects in acupuncture for IBS trials, which typically evaluate strictly subjective, patient-reported outcomes (e.g., symptom severity, quality of life), another approach forward for research is the evaluation of objective or semi-objective outcomes in IBS patients, using pragmatic and cost-effectiveness trials. Indeed, a recently completed trial (n=220) (Principal Investigator: MacPherson), compared the effectiveness and cost-effectiveness of acupuncture plus usual general practitioner (GP) care versus usual GP care alone, on the semi-objective outcomes of medication use, health service use, and days lost from work (69). Although this trial does not include a placebo control, because the outcome measures being assessed in this trial are semi-objective, its results will be less influenced by expectation effects (70-72), than trials that assess only strictly subjective outcomes (i.e., patient reports of symptom improvement). Indeed, the Rome criteria for design of IBS treatment trials note that placebo effects "are especially a problem where end points are subjective." (23) If this recently completed cost-effectiveness trial shows that acupuncture reduces healthcare utilization, then whether the resulting cost-savings are due to a specific effect of acupuncture needling or non-specific effects (e.g., greater autonomy and empowerment of patients, positive patient-practitioner relationship) seems of secondary importance.

However, it must be borne in mind that the patient population who elected to participate in this acupuncture trial may have stronger *a priori* beliefs about the benefits of acupuncture, than does the average population of IBS patients. As a result, the non-specific effects experienced by the patients in this unblinded trial may not be generalizable to the average population of IBS patients. However, because this pragmatic trial was designed to test whether acupuncture may be helpful as an additional option to standard GP care alone, its results may be generalizable to the subset of IBS patients in general practice who would elect to receive acupuncture, who may also have *a priori* expectations for acupuncture to be beneficial. To produce results generalizable to the average population of IBS patients, investigators of future pragmatic trials might minimize the recruitment of participants with a preference for acupuncture by not specifying, in the recruitment of patients, that acupuncture is one of the treatment options being investigated.

Future comparative effectiveness trials would also be helpful to validate and extend the preliminary evidence in this review, which suggests that acupuncture is associated with greater improvements in subjective patient self-assessments than pharmacological therapies. As previously mentioned, a limitation of the acupuncture versus pharmacological therapy trials in this review is that they did not use a design that controlled for the effects of patients' expectations for improvement, patient preferences, and non-specific therapeutic factors. Indeed, in the Chinese trials included in this review, the patients may well have had pre-treatment preferences for acupuncture, considering that these trials were conducted at hospitals of traditional Chinese medicine. Because acupuncture may elicit a greater expectation effect than pharmacological therapies or other active treatments (27,55,56), particularly among participants who have a preference for acupuncture, investigators conducting future trials that compare acupuncture with other active therapies should consider asking participants about their preferences and expectations (before and after the intervention), and studying the potential effects of pre-treatment preferences on study outcomes. Such trials should also include a credibility questionnaire to establish that the treatments being compared are perceived by the patients as equally credible treatments for IBS symptoms (66). Future comparative effectiveness trials in the West should also consider using a daily frequency of acupuncture, as was used in the Chinese trials in this review. However, even with additional well-designed trials, the truth about the effects of acupuncture for IBS will likely always be difficult to assess because the complexities and potential biases inherent to both the comparative effectiveness and sham acupuncture control

designs makes it difficult to evaluate the subjective, patient-reported outcomes typically used in IBS trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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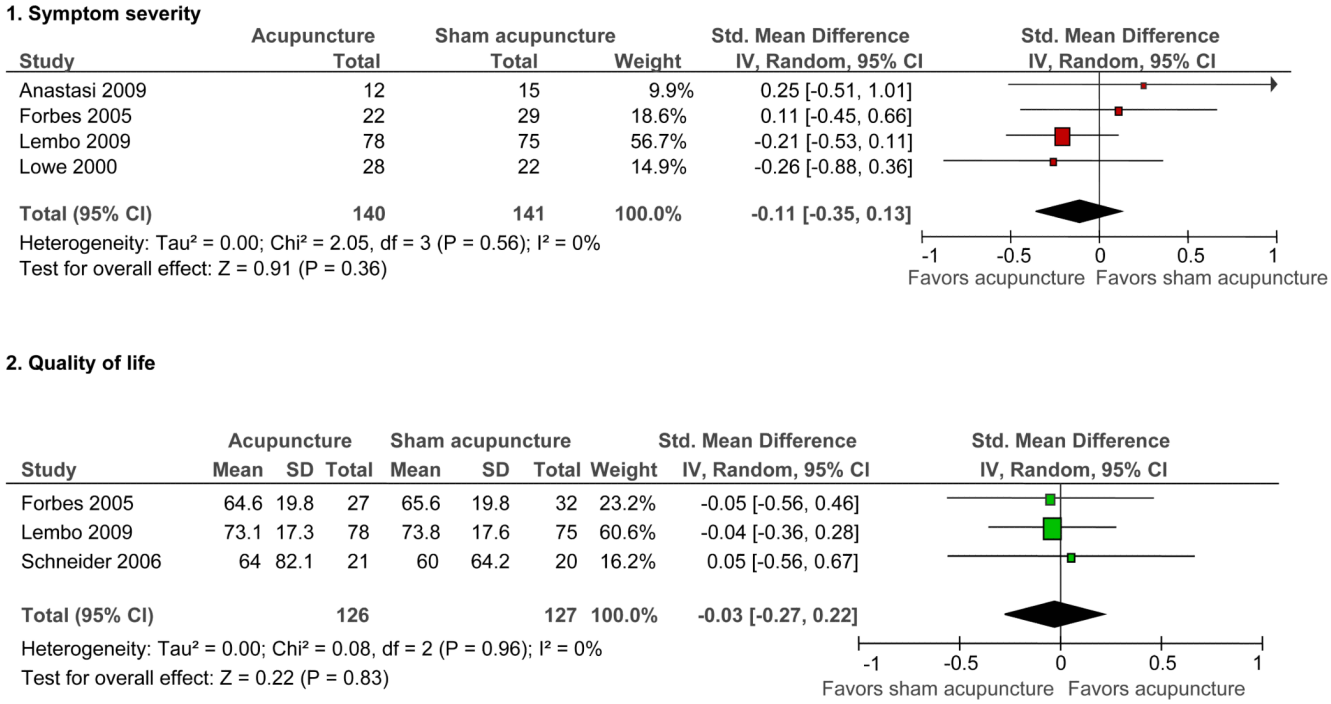

Figure 1.

Acupuncture versus sham acupuncture: Symptom severity and quality of life

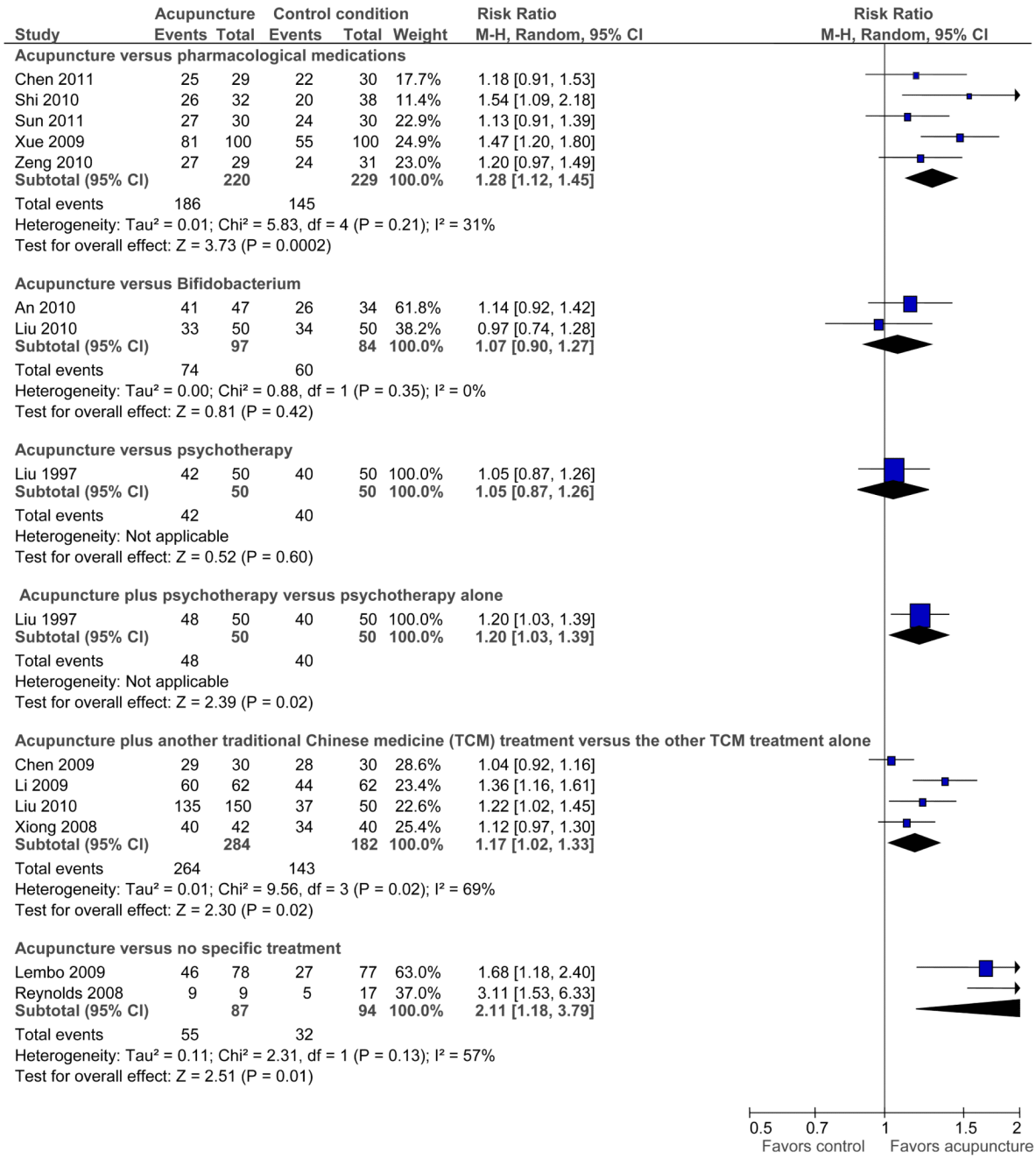

Figure 2.

Acupuncture versus another active treatment, as adjuvant to another active treatment, or compared to no specific treatment: Symptom severity

Table 1

Characteristics of randomized controlled trials of acupuncture in irritable bowel syndrome (IBS)

Study	N [a]	Country	Diagnostic criteria used for IBS	Criteria for improvement in overall IBS symptoms	Criteria for improvement in IBS-related quality of life	Time point for outcome assess-ment [b]	Acupuncture treatment	Control treatment(s)
An 2010 (33)	81 [c]	China	Rome II	Categorical [d]	- [e]	4 wks EoT)	Fixed formula with moxibustion at 2 fixed points; 24 sessions over 4 wks	Combined Bifidobacterium, lactobacillus and Enterococcus faecium capsules (2 pills, 3×/d)
Anastasi 1999 (34)	29	USA	Rome II/III	CGI	-	4 wks (EoT)	Flexible formula with moxibustion at all points; 8 sessions over 4 wks	Sham acupuncture -- superficial needling 2-3 cm from true acupoints
Chen 2009 (36)	60 [c]	China	Rome II	Categorical	FDG QoL scale	4 wks (EoT)	Flexible formula with moxibustion at 4 fixed pts; 12 sessions over 4 wks + Chinese herbal formula	Chinese herbal formula alone (3 pills, 3×/d)
Chen 2011 (35)	60	China	Rome III – IBS-D	Categorical	-	3 wks (EoT)	Flexible formula with moxibustion at 3-5 pts; 15 sessions over 3 wks	Montmorillonite (1 bag, 2×/day) + loperamide (4mg, 3×/day) + pinaverium bromide (50mg, 3×/d) [f]
Forbes 2005 (37)	59	UK	Rome I and Manning	Global symptom score based on patient diary [g]	EuroQol	13 wks (EoT)	Individualized; 10 sessions over 10 wks	Sham acupuncture -- penetrating needles at non-acupoints
Lembo 2009 (38) *h*	230	USA	Rome II	IBS-AR and IBS-SSS	IBS-QoL	3 wks (EoT)	Flexible formula; 6 sessions over 3 wks	**1** Sham acupuncture – validated Streitberger placebo needles placed at non-acupoints in general vicinity of the true acupoints **2** Wait list with continuation of usual care
Li 2009 (39)	186	China	Rome III	Categorical	-	10 wks (EoT)	Flexible formula with moxibustion at all points; 60 sessions over 10 wks + Tuina spinal massage	Tuina spinal massage alone (60 sessions over 10 wks)
Liu 1997 (40)	150	China	Not specified	Categorical	-	3-21 wks (EoT)	Flexible formula with moxibustion at 1 acupoint; 10-60 sessions over 20-120 days + psychotherapy	**1** Acupuncture alone **2** Psychotherapy alone
Liu 2010 (41)	300	China	Rome III – IBS-D	Categorical	-	4 wks (EoT)	Fixed formula EA; 28 sessions over 4 wks + Chinese herbal formula	**1** EA alone **2** Chinese herbal formula alone (150ml, 2×/d) **3** Bifidobacterim longum alone (1 pill, 2×/d)

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Study	N [a]	Country	Diagnostic criteria used for IBS	Criteria for improvement in overall IBS symptoms	Criteria for improvement in IBS-related quality of life	Time point for outcome assess-ment [b]	Acupuncture treatment	Control treatment(s)
Lowe 2000 (42)	50	Canada	Rome (version not stated)	Dichotomous measure of symptom relief	IBS-36	4 wks (Eot)	Fixed formula; 8 sessions over 4 wks	Sham acupuncture -- tapping blunt needle on the skin and then taping the needle in place
Reynolds 2008 (43)	30	UK	Rome II	IBS-SSS	-	3 mos (EoT)	Flexible formula; 8 sessions over 3 mos	Usual care
Schneider 2006 (44)	43	Germany	Rome II	Not measured	FDDQL	5 wks (EoT)	Fixed formula; 10 sessions over 5 wks	Sham acupuncture -- validated Streitberger placebo needles placed 2 cm from true acupoints
Shi 2010 (45)	70	China	Rome III – IBS-D	Categorical	-	5 wks (1 wk after (EoT)[i]	Flexible formula EA; 28 sessions over 4 wks	Pinaverium bromide (50mg, 3×/d)
Sun 2011 (46)	63	China	Rome III – IBS-D	Categorical	-	4 wks (EoT)	Fixed formula; 20 sessions over 4 wks	Pinaverium bromide (50mg, 3×/d)
Xiong 2008 (47)	120	China	Rome II	Categorical	-	4 wks (EoT)	Fixed formula with moxibustion at 2 pts; 28 sessions over 4 wks + Chinese herbal formula	Chinese herbal formula alone
Xue 2009 (48)	210	China	Rome II	Categorical	-	3-7 weeks (EoT)	Fixed formula with moxibustion at 1 point; 20-40 sessions over 3-7 wks	Sulfasalazine (10 mg, 1×/d)
Zeng 2010 (49)	65	China	Rome III – IBS-D	Categorical	-	30 d (EoT)	Flexible formula with moxibustion at 6 points; 30 sessions over 30 d	Trimebutine maleate (100mg, 3×/d)

IBS, irritable bowel syndrome; EoT, end of treatment; wks, weeks; d, day; CGI, Clinical Global Impression Scale (73); acupoints, acupuncture points; FDG QoL, Functional Digestive Diseases Quality of Life Scale, an IBS quality of life questionnaire which had been used in previous Chinese studies but that has not been validated; IBS-D, study restricted eligibility to IBS-D (IBS with diarrhea) subtype patients; EuroQol, EuroQol Group's rating scale (74); IBS-AR, IBS-Adequate Relief question (19); IBS-SSS, IBS Severity Scoring System (20); IBS-QoL, IBS Quality of Life Measure (22); EA, electroacupuncture; IBS-36 (75); FDDQL, Functional Digestive Diseases Quality of Life Questionnaire (76).

[a] Number randomized.

[b] The time point listed is the number of weeks after randomization.

[c] For these 2 trials, the author did not record nor recall the numbers randomized, nor the numbers of dropouts, and the numbers analyzed are reported here.

[d] For all 11 trials conducted in China, a symptom scale was used to assess the severity of the patients' overall IBS-related symptoms (e.g., abdominal pain, defecation difficulties, diarrhea) both at baseline and after treatment. For 8 of these trials (33,35,36,41,45-47,49), a percentage improvement from baseline scores was then calculated (i.e., (baseline symptom score – symptom score after treatment)/ baseline symptom score), and this percentage change from baseline was then grouped into 2 (45), 3 (33,49), or 4 (35,36,41,46,47) categories, which were then converted into 2 categories for the meta-analysis, as described in the Methods section. For the other 3 trials (39,40,48), it was not clear how the symptom scale scores were converted into the categorical data. For these 11 trials, the criteria for improvement is listed as "Categorical" in this table.

[e] A dash (-) indicates that the outcome not measured.

[f] The Montmorillonite was given to all patients and the loperamide and pinaverium bromide was added if the diarrhea did not stop.

[g] This symptom diary is based on the Bristol scale (77).

[h] In this trial, patients were randomized to five arms. The first arm was a wait-list control. Participants in the remaining 4 arms were randomized to sham or true acupuncture, with or without an augmented practitioner-patient interaction. There was no main effect of practitioner-patient interaction; therefore we combined the two acupuncture groups (augmented and limited encounter) and the two sham acupuncture groups (augmented and limited encounter) in order to compare the effects of acupuncture and sham acupuncture.

[i] This trial also included an EoT measurement point, for which the results were very similar to the 1 wk post EoT measurement point.

Table 2

Risk of bias summary*

	Adequate sequence generation	Allocation concealment	Patient blinding	Incomplete outcome data addressed	Free of selective reporting	Baseline compara-bility [a]	ITT [b]
An (2010) (33)	Yes	[Yes]	No	[Unclear][C]	Yes	Unclear	No
Anastasi (1999) (34)	[Yes]	[Yes]	Yes [d]	Yes	Yes	Yes	No
Chen (2009) (36)	[No] [e]	[No]	No	[Unclear][f]	Yes	Yes	No
Chen (2011) (35)	Yes	[Yes]	No	[Yes]	Yes	Yes	No
Forbes (2005) (37)	Yes	[Yes]	Yes [g]	Yes	Yes	Yes	Yes
Lembo (2009) (38)	Yes	Yes	Yes [h]	Yes	Yes	Yes	Yes
Li (2009) (39)	[No] [e]	[No]	No	[Unclear][C]	Yes	Yes	No
Liu (1997) (40)	[Unclear][i]	[Unclear]	No	[Unclear][C]	Yes	Unclear	No
Liu (2010) (41)	[Unclear][i]	[No]	No	[Unclear][j]	Yes	Unclear	No
Lowe (2000) (42)	[Yes]	[Yes]	Unclear[k]	Unclear[C]	Yes	Yes	Unclear
Reynolds (2008) (43)	[Yes]	[Yes]	No	Yes	No	Yes	Yes
Schneider (2006) (44)	[Yes]	Yes	Yes [h]	Yes	Yes	Yes	No
Shi (2010) (45)	[Yes]	[Yes]	No	Yes	Yes	Yes	Yes
Sun (2011) (46)	[Yes]	[No]	No	Yes	Yes	Yes	No
Xiong (2008) (47)	[Yes]	[No]	No	[Unclear][C]	Yes	Unclear	No
Xue (2009) (48)	[Unclear][i]	[Unclear]	No	Yes	Yes	Yes	No
Zeng (2010) (49)	Yes	[Yes]	No	Yes	Yes	Yes	No

*We followed the Cochrane Handbook criteria (28) for making judgments about the risk of bias for each of the 6 domains in the Cochrane Risk of Bias tool. Additional data obtained from RCT authors is enclosed in brackets to allow such data to be differentiated from the data included only in the publications.

[a]For the baseline comparability criterion to score "Yes", a comparison of the symptom scores between the treatment and control group(s) at baseline needed to be reported.

[b]For the ITT criterion to score "Yes", an intention-to-treat analysis needed to be reported.

[c] In these trials, the authors did not report the numbers of drop-outs in their publication, and did not have records of the numbers of drop-outs to provide during the telephone interviews.

[d] For the sham control, penetrating needles were superficially inserted at nonpoints which were 2-3 cm away from the true points, and placebo moxibustion was performed above the same sham points without generating a heat sensation.

[e] The authors of these trials confirmed in telephone interviews that a few patients were non-randomly assigned to achieve identical sized treatment groups.

[f] For this trial, the authors endeavored to maintain equal group sizes, by eliminating participants who withdrew during the trial and replacing them with new patients, and the number of such replacements was not recorded by the author.

[g] For the sham control, acupuncture needles were inserted at areas on the body that do not correspond to acupuncture points and are deemed to have no therapeutic value. The points and needling technique were varied somewhat each week, as was also done in the true acupuncture group, who received individualized point selection.

[h] For the sham control in these trials, the Streitberger placebo needle was used, which has been previously validated as a sufficiently credible sham (29). The Streitberger needles were placed close to the genuine acupuncture points in both trials. In both trials, the participants were acupuncture naïve.

[i] This criterion was scored as “Unclear” because the authors of these 3 trials were unable to explain how equal sample sizes were achieved.

[j] For this trial, the authors reported no drop-outs, which would be unusual in a 4 week trial of 300 participants.

[k] The sham control used in this trial was judged to have been potentially detectable as a fake treatment by the trial participants. The sham procedure involved tapping a blunt needle on the skin and then taping the needle in place. Although this procedure was described as “validated”, we are unaware of a validation study for this procedure. Also, in the trial report there was no description of whether or not the patients were required to have never previously used acupuncture, and there were no reported tests for checking the success of the blinding.

CME

REVIEW

The Efficacy and Safety of Rifaximin for the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis

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OBJECTIVES: **Irritable bowel syndrome (IBS) affects 10–15% of the population, and treatment options are limited. Rifaximin is a minimally absorbed antibiotic that has shown efficacy in IBS patients. The objective of our study was to perform a meta-analysis and systematic review of available randomized, placebo controlled trials evaluating the efficacy and tolerability of rifaximin in patients with IBS.**

METHODS: **We performed a systematic literature search of multiple online electronic databases regardless of language. Inclusion criteria entailed randomized, placebo controlled trials and IBS defined by accepted symptom-based criteria. Meta-analysis was conducted to evaluate the summary odds ratios (ORs) and 95% confidence intervals (CIs) of combined studies for the primary and secondary outcomes using a random-effects model based on the DerSimonian and Laird method to reflect both within- and between study variability. We assessed heterogeneity using χ^2 test and the inconsistency index statistic (I^2). Significant heterogeneity was defined as $I^2 \geq 25\%$. Meta-regression was performed using generalized linear mixed-effects model and study as random effects to estimate the summary OR adjusting for covariate differences across studies and treatment group. Publication bias was assessed by funnel plot analysis.**

RESULTS: **Systematic review identified 13,700 citations. Eighteen were deemed to be potentially relevant, of which five articles met eligibility. Meta-analysis found rifaximin to be more efficacious than placebo for global IBS symptom improvement (OR=1.57; 95% CI=1.22, 2.01; therapeutic gain=9.8%; number needed to treat (NNT)=10.2), with mild heterogeneity (P=0.25, I^2=26%). For the key secondary outcome of bloating, raw data were available for four studies. Rifaximin was significantly more likely to improve bloating than placebo (OR=1.55; 95% CI=1.23–1.96; therapeutic gain=9.9%; NNT=10.1), with no significant heterogeneity (P=0.27, I^2=23%). We found that studies with older patients and more females demonstrated higher response rates, which was consistent regardless of treatment group. In addition, studies with higher cumulative dose tended to report a higher response rate. Of the covariates evaluated, we found age to be most predictive of response, with a correlation coefficient of 0.97 between aggregate response rate and mean age in the placebo groups. Although studies with higher cumulative dose tended to show increased response rates, this was also seen consistently in both the treated and placebo groups. Adverse effects were similar among patients receiving rifaximin or placebo in all studies. The most common adverse events (AEs) (≤10%) with rifaximin were headache, upper respiratory infection, nausea, nasopharyngitis, diarrhea, and abdominal pain. Serious AEs were rare (<1%) and similar with rifaximin and placebo.**

CONCLUSIONS: **Rifaximin proved more effective than placebo for global symptoms and bloating in IBS patients. The modest therapeutic gain was similar to that yielded by other currently available therapies for IBS. AEs were similar between rifaximin and placebo.**

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INTRODUCTION

The irritable bowel syndrome (IBS) is a common gastrointestinal disorder, which is defined by recurrent episodes of abdominal pain/discomfort and disordered bowel habits (1). In all, 10–15% of the general population endorses symptoms compatible with the diagnosis of IBS (2–6). IBS leads to significant reductions in quality of life and work productivity (7–10). IBS accounts for significant health resource utilization with billions of dollars in direct and indirect costs (11–13).

Patients with IBS are subgrouped on the basis of their main bowel symptoms; IBS with constipation (IBS-C), IBS with diarrhea

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(IBS-D), and IBS with a mixture of constipation and diarrhea-related complaints (IBS-M). Such subgrouping has an important role in the selection of diagnostic tests and treatments in IBS patients.

The pathophysiology of IBS remains incompletely defined. Several potential mechanisms have been proposed, implicating genetic and environmental factors, altered motility, visceral hypersensitivity, altered brain–gut interactions, autonomic dysfunction, immune activation, altered mucosal permeability, and psychosocial distress (14–29). Recent work has suggested quantitative and qualitative differences in the gut microbiota between IBS patients and controls (30–37). Treatments aimed at altering or modifying the gut microbiota including diet, probiotics and antibiotics have been the focus of a large number of recent studies (38–43). Rifaximin is a semi-synthetic derivative of rifamycin, with an additional benzimidazole ring that prevents its systemic absorption (0.4% after oral administration) (44,45). The drug has *in-vitro* activity against Gram-positive, Gram-negative, and anaerobic bacteria and has been approved by the Food and Drug Administration (FDA) for traveler's diarrhea and minimal hepatic encephalopathy. A number of recent clinical trials have evaluated the efficacy and safety of rifaximin in IBS patients (41–43,46). Though the results of the available clinical trials have been generally favorable, given the variability in the methodology, a number of important questions about dose and, duration of therapy remain. The aim of this study was to conduct a systematic review and meta-analysis to estimate the efficacy and safety of rifaximin for IBS.

METHODS

Study protocol

We developed and adhered to a standard protocol for study identification, inclusion, and data abstraction in the conduct of this meta-analysis. We performed a systematic literature search of the following electronic databases: Medline (1950–May 2011), EMBASE (1947–May 2011), Cochrane library (1993–May 2011), Web of Science (1900–May 2011), and PubMed (1950–May 2011). Bibliographies from relevant gastrointestinal meetings including Digestive Diseases Week, The Annual Meeting of the American College of Gastroenterology, and United European Gastroenterology Week from years 2000–2011 were manually searched for relevant studies. Medical subject headings for our literature review included "IBS," "irritable bowel syndrome," "rifaximin," "xifaxan," "bloating," and "flatulence." Citations from identified articles were then cross-reference for completeness.

Study selection and data abstraction

Inclusion criteria included double-blind, randomized trials that compared the efficacy of rifaximin vs. placebo in patients with IBS as defined by accepted symptom-based criteria including Manning, Kruis, Rome I, Rome II, or Rome III. The primary outcome of improvement in global IBS symptoms was required for inclusion. Treatment duration and dosing for the trials were not pre-specified, all were included. Study references and citations were collected in EndNotex4 software application (Thomson Reuters, New York, NY) Two double-blind investigators (S.B.M. and M.M.) reviewed all titles, and those that appeared qualified were reviewed to assess eligibility. For manuscripts and abstracts that met our eligibility criteria, two investigators independently abstracted data using a standardized form developed for this study. Information collected included study design, diagnostic criteria for IBS, IBS subtypes, number of patients enrolled, rifaximin dose, treatment duration, length of follow-up after therapy, primary and secondary study outcomes, and adverse events (AEs). Discordant results were adjudicated by the senior author (W.D.C.). The paired agreement among the authors (S.B.M. and M.M.) was 0.97. The methodological quality of each trial was graded with the Cochrane Collaboration tool, which assessed the following: adequate sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, complete outcome data addressed, selective outcome reporting, and other sources of bias.

Data synthesis and analysis

We explored heterogeneity using χ^2 test and the inconsistency index statistic (I^2). Heterogeneity was defined as $I^2 \geq 25\%$. Although heterogeneity was not statistically significant, because the odds ratios (ORs) across the different studies varied substantially, data were pooled using a random-effects model based on the DerSimonian and Laird (47) method to reflect both within- and between-study variability. Summary OR and 95% confidence intervals (CIs) were reported for both the primary outcome of global improvement assessed 10–14 days after completion, and the secondary outcome of bloating assessed 10–14 days after completion of therapy. Distribution of patient characteristics were evaluated for their relationship to response rates as well as treatment groups. Patient characteristics uniformly available across all studies included mean age, percent female, and dose. To assess the effect of cumulative dose, rifaximin dosing was categorized into four groups based on the product of daily dose by duration of treatment. Despite the small total number of included studies, we expanded the data to patient level and performed a meta-regression using generalized linear mixed-effects model with logit link and study as random effects to estimate the summary OR adjusting for covariate differences across studies and treatment group. Publication bias was assessed by funnel plot analysis. Analyses were done using Stata 10.2, Rev Manager 5.0 (Oxfordshire, UK) and SAS 9.2 (Cary, NC).

RESULTS

Our systematic review identified a total of 13,700 citations. After cross-referencing the index terms, titles, and abstracts, potentially relevant citations were manually evaluated for potential inclusion (**Figure 1**). Ultimately, 18 full manuscripts and abstracts were reviewed in detail of which five studies ($N = 1,803$) fulfilled inclusion criteria and were included in the meta-analysis. Details regarding the study populations enrolled, sample size, rifaximin dose and duration, and length of follow-up after the completion of rifaximin therapy can be found in **Table 1**.

Figure 2 summarizes the risk of bias across studies utilizing the Cochrane Collaboration tool. Low risk of bias was seen for all

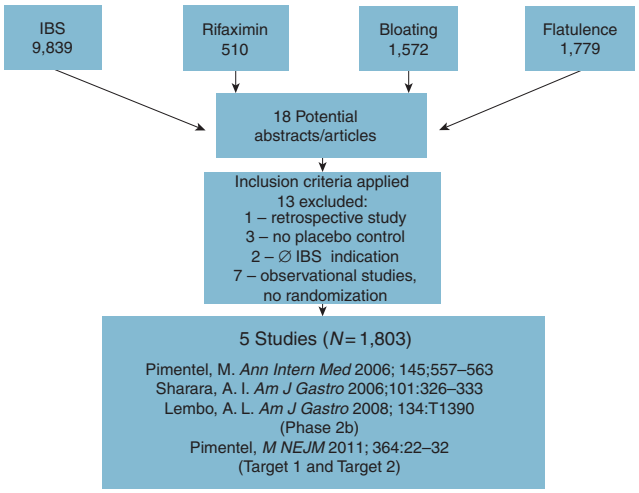

Figure 1. Flowchart of study eligibility and classification. IBS, irritable bowel syndrome.

papers in the following domains: (i) sequence generation; (ii) allocation concealment; (iii) blinding of participants, personnel and outcome assessors; and (iv) incomplete outcome data. High risk of bias was noted in the Sharara *et al.* (43) study for the "selective outcome reporting" domain. The primary concern stemmed from the data reported for IBS patients as defined by Rome II criteria, which was not a pre-specified outcome. For the last domain, "other potential threats to validity," the initial Pimentel study reported a baseline imbalance in abdominal pain severity score between the placebo and rifaximin groups, which was considered a high risk factor (46).

Primary outcome: global improvement

Overall, rifaximin was associated with improvement of global IBS symptoms compared with placebo (summary OR = 1.57 (95% CI = 1.22–2.01), $P < 0.001$ from random effects) (**Figure 3**). For the rifaximin group, 42.2% reported global improvement compared with 32.4% in the placebo group (therapeutic gain = 9.8% with an number needed to treat (NNT) = 10.2) (**Table 2**). Mild heterogeneity was identified across the studies ($P = 0.25$) with an I^2 statistic of 26%. Importantly, all studies gave ORs larger than 1, demonstrating that rifaximin improves global IBS symptoms. Funnel plot analysis revealed no evidence of asymmetry (Begg test $P = 0.46$) (**Figure 4**).

Despite mild statistical evidence for heterogeneity, as the ORs varied widely (ranging from 1.39 to 4.83) and the relatively small number of included studies, distribution of patient and study characteristics were evaluated for their relationship to response rates as well as to treatment groups. We did not find significant differences in mean age or percent females between rifaximin vs. placebo groups within each study. However, we found studies with older patients, and studies with more females showed higher response rates. This was consistent regardless of treatment group. In addition, studies with higher cumulative dose tended to report a higher response rate. Of the covariates evaluated, we found age to be most predictive of response, with a correlation coefficient of 0.97 between aggregate response rate and mean age in the placebo groups. Although studies with higher cumulative dose tended to show increased response rates, this was also seen consistently in both the rifaximin and placebo groups. Because dose is relevant only to the rifaximin group, placebo group patients in studies with higher dose showing higher response rates suggest that variation in response rate may be from the underlying differences in patient characteristics such as age or gender, or other study characteristics such as variation in outcome measures, duration of follow-up, or compliance rather than the cumulative dose. The summary OR after adjusting for the mean age difference was 1.60 (95% CI = 1.31, 1.94). Age was also a significant predictor of improvement in symptoms in this model (OR = 1.16; 95% CI = 1.07–1.25), but percent of females was found not to be significantly associated with improvement after adjusting for age. We note, however, that percent of females and the mean age of the study participants were positively correlated ($r = 0.65$).

Secondary outcomes

For our key secondary analysis of bloating, four of the five studies provided the data necessary to perform a meta-analysis. Overall, rifaximin was associated with an improvement in bloating compared with placebo (OR = 1.55; 95% CI = 1.23, 1.96; $P < 0.001$) (**Figure 5**). At 10–14 days post-treatment, 41.6% of subjects randomized to rifaximin reported improvement of bloating compared with 31.7% of subjects randomized to placebo (therapeutic gain = 9.9%; NNT = 10.1) (**Table 3**). No significant heterogeneity was identified across the studies (P value = 0.27, I^2 statistic = 22.9%). Funnel plot analysis demonstrate no asymmetry, suggesting no publication bias (Begg test $P = 0.73$) (**Figure 6**).

For the outcome of improvement of abdominal pain, raw data were not available for meta-analysis. Sharara *et al.* did not assess change in abdominal pain as an outcome. Pimentel *et al.* and Lembo *et al.* did not demonstrate a significant difference in improvement of abdominal pain with rifaximin or placebo. However, both Target 1 and Target 2 demonstrated an improvement in abdominal pain with a combined P value = 0.003.

Data addressing stool consistency were available as an outcome in three studies; Lembo *et al.*, Target 1 and Target 2. Lembo *et al.* showed no difference between rifaximin and placebo in improving stool consistency. However, Target 1 and Target 2 demonstrated improvement in stool consistency with the use of rifaximin compared with placebo (P value < 0.001).

AEs and discontinuation rates

AE data were available for four studies. Overall, the percentage of study participants reporting AEs was similar between the rifaximin and placebo groups. The most frequent AEs (all ≤6%) included headache, upper respiratory infection, nausea, nasopharygitis, diarrhea, and abdominal pain. Serious AEs (SAEs) were rare (< 1%), and only reported in Lembo *et al.*, Target 1 and Target 2. In Lembo *et al.*, two patients in the rifaximin group suffered eight SAEs (confusional state, disorientation on two occasions, dehydration, hypoxia, respiratory acidosis, hypotension, and Crohn's disease). Three patients in the placebo group suffered six SAEs events (spinal fracture, bronchitis, dyspnea, hyperhidrosis, dizziness, and chest pain). Pooled data from Target 1 and Target 2 had the

Table 1. Characteristics of included studies

Author	Criteria	Study population	IBS subtypes	Primary outcome	Secondary outcomes	*N* (rifaximin vs. placebo)	Dose	Treatment duration	Length of follow-up
Sharara *et al.*	Rome II	Single center	All subtypes 20% IBS-D 38.3% IBS-C 41.7% IBS-M	Global symptom improvement: (yes or no). Do you consider that your symptoms have improved since starting the study drug?	1. Changes in LHBT 2. Changes in the composite 10-day symptoms score	37 vs. 33	400 mg b.i.d.	10 Days	10 Days
Pimentel *et al.*	Rome I	Two centers	All subtypes (% of subtypes not available)	Global IBS: Patients were asked to provide a % of global improvement from 0 to 100%	1. Bloating 2. Abdominal pain 3. Diarrhea 4. Constipation	43 vs. 44	400 mg t.i.d.	10 Days	10 Weeks
Lembo *et al.*	Rome II	Multi-center	IBS-D	1. Global IBS: Adequate relief (yes or no) for at least >2 of the final 3 weeks of treatment phase 2. IBS-related bloating: Adequate relief (yes or no) for at least >2 of the final 3 weeks of treatment phase	1. Adequate relief of both IBS symptoms and IBS-related bloating 2. Change from baseline to week 4 for the following: -Normal BM -Hard and lumpy BM -Loose or watery BM -Loose or watery BM with urgency -Bothersomeness of abdominal pain/discomfort -Bothersomeness of IBS-related bloating	191 vs. 197	550 mg b.i.d.	14 Days	12 Weeks
Target 1 Pimentel *et al.*	Rome II	Multi-center	Non-C	Global IBS: Adequate relief (yes or No) for at least 2 of the 4 weeks	1. Adequate relief of IBS-related bloating. 2. Daily assessment for IBS symptoms 3. Daily assessment for bloating 4. Daily assessment for abdominal pain 5. Daily assessment of abdominal pain plus loose or watery stools.	309 vs. 314	550 mg t.i.d.	14 Days	10 Weeks
Target 2 Pimentel *et al.*	Rome II	Multi-center	Non-C	Global IBS: Adequate relief (yes or no) for at least 2 of the 4 weeks	1. Adequate relief of IBS-related bloating. 2. Daily assessment for IBS symptoms 3. Daily assessment for bloating 4. Daily assessment for abdominal pain 5. Daily assessment of abdominal pain plus loose or watery stools	315 vs. 320	550 mg t.i.d.	14 Days	10 Weeks

BM, bowel movement; IBS, irritable bowel syndrome; LHBT, lactulose hydrogen breath test.

following SAEs: chest pain, cholecystitis, and breast cancer. None of the serious AEs was considered by the investigators to be attributed to study medication. Additionally, there were no reported cases of *Clostridium difficile*-associated diarrhea. Discontinuation rates were similar between the rifaximin and placebo groups and accounted for 1.6% (28/1,803) of the study population.

DISCUSSION

We performed a series of meta-analyses to evaluate the efficacy and safety of rifaximin as compared with placebo in patients with IBS. Overall, we found that rifaximin led to statistically significant improvements in global IBS symptoms (OR = 1.57) and bloating (OR = 1.55) as compared with placebo. We did not find evidence of publication bias. Further, the incidence of AEs was similar between rifaximin and placebo.

The clinical benefits of rifaximin for global IBS symptoms and bloating were modest with therapeutic gains over placebo of ~10% and NNTs of 10. That being said, the therapeutic gain and NNT offered by rifaximin is similar to that reported for other drugs such as including tegaserod, lubiprostone, and alosetron, which have been tested in high-quality randomized, controlled trials and

deemed effective for IBS (3). At present, treatment of IBS is largely empiric, based upon a patient's predominant symptoms rather than underlying physiology. It is likely that the inherently heterogeneous pathogenesis of IBS accounts for the modest clinical benefit of rifaximin and other currently available medical therapies for IBS. These observations underscore the need for the identification of reliable biomarkers, which will allow IBS patients to be subgrouped on the basis of physiology rather than only symptoms.

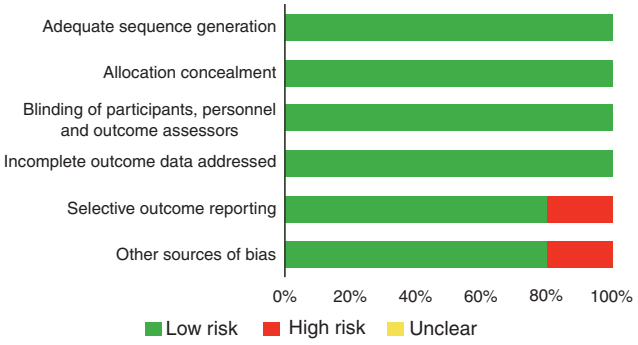

Figure 2. Risk of bias assessment.

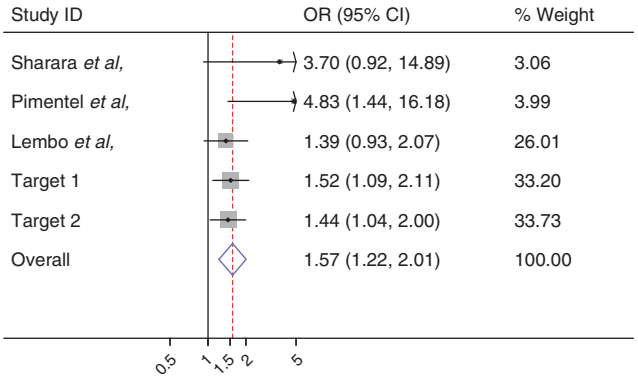

Figure 3. Forest plot of primary outcome, global improvement of irritable bowel syndrome (IBS) with weights from random-effects analysis; heterogeneity $\chi^2=5.38$ (df=4), $P=0.25$; $I^2=26\%$; test of odds ratio (OR)=1: $z=3.56$, $P<0.001$. CI, confidence interval.

The precise mechanisms by which rifaximin improves IBS symptoms remains incompletely defined. It has been argued that rifaximin's benefits in IBS patients are at least in part due to alteration of the quantity, location, or quality of the hosts' intestinal microbiota. The primary support for this suggestion comes from studies that have found an increased prevalence of abnormal surrogate tests for small intestinal bacterial overgrowth, including lactulose or glucose breath testing, in IBS patients compared with controls (30,48). Further, Pimentel has reported that normalization of breath test results after oral antibiotic therapy correlates with an improvement in IBS symptoms (43,49). It is plausible to hypothesize that these effects might derive from several pathways including a reduction in the release of bacterial products that otherwise produce untoward effects on the host and/or alteration of the host's immune response by reducing local mucosal engagement with gut microorganisms (41). Given that the results from the various studies have not been entirely consistent and the intrinsic deficiencies of breath tests as a surrogate means of identifying small intestinal bacterial overgrowth (SIBO), it is important to consider other possible mechanisms by which rifaximin might improve IBS symptoms. For example, it is also possible, though entirely unproven, that the benefits of rifaximin might in part be the consequence of effects on colonic bacterial populations and

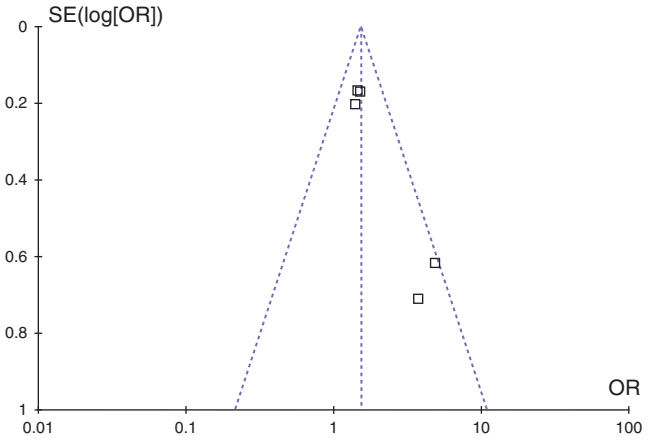

Figure 4. Funnel plot analysis of global improvement of irritable bowel syndrome (IBS) (Begg test $P=0.46$). OR, odds ratio.

Table 2. Primary outcome: global improvement of IBS symptoms, rifaximin vs. placebo

Study	Dose duration	Response rate, % (response/*N*)		Therapeutic Gain, %	NNT	OR
		Rifaximin	Placebo			
Sharara *et al.*	400 mg b.i.d., 10 days	27.0 (10/37)	9.1 (3/33)	17.9	5.6	3.70
Pimentel *et al.*	400 mg t.i.d., 10 days	32.6 (14/43)	9.1 (4/44)	23.5	4.3	4.83
Lembo *et al.*	550 mg b.i.d., 14 days	52.3 (100/191)	44.2 (87/197)	8.1	12.3	1.39
Target 1	550 mg t.i.d., 14 days	40.8 (126/309)	31.2 (98/314)	9.6	10.4	1.52
Target 2	550 mg t.i.d., 14 days	40.6 (128/315)	32.2 (103/320)	8.4	11.9	1.44
Pooled OR	—	42.2 (378/895)	32.4 (295/908)	9.8	10.2	1.57

IBS, irritable bowel syndrome; NNT, number needed to treat; OR, odds ratio.

hence, fermentation (48,50,51). There are also little data on whether rifaximin exerts direct effects on gastrointestinal or colonic motility or sensation, which could also impact of IBS symptoms (52,53).

Statistical evidence for mild heterogeneity was found for the primary outcome and inspection of the summary statistics from each study suggested potential heterogeneity. This may be due to different inclusion criteria utilized by each study. However, additional covariate analysis of our primary outcome demonstrated that age was predictive of response rates regardless of treatment group where studies with older patients had higher rates of improvement in global IBS symptoms. Similarly, studies with greater percentages of females showed higher response rates, regardless of treatment group. We also found studies with older participants tended to have more female participants, as reflected by a correlation coefficient of 0.65 between mean age and percent females across the 10 study by treatment subgroups. This makes it difficult to determine the independent effect of either patient characteristic on IBS symptom improvement, especially given the small number of studies. Gender differences in response to therapy have been observed in the psychiatric and IBS literature but we did not find evidence of differential treatment effect for either mean age or percent of females in this study (54). The summary OR from the five studies remained similar after adjusting for mean age of the study participants in each treatment group where odds of global improvement in IBS symptoms was 1.6 times higher in treated group compared with placebo group (OR = 1.60; 95% CI = 1.31, 1.94).

The ORs were consistent in direction across the different studies and only differed in their magnitudes despite the heterogeneity in both response rates and in ORs seen across studies (though not statistically significant). Additionally, the differences in the OR's were associated with different base response rates, where studies with higher response rates in the untreated group were associated with lower ORs. Consistent with this, studies with higher placebo response rates showed lower therapeutic gain and higher NNT. Although we cannot determine which patient characteristics contributed to the variation in base response rates, increasing mean age and percent of females were each associated with higher base response rates. Limitations of these covariate adjustments include relatively small number of studies and not being able to adjust for individual patient level covariates.

In short-term studies, rifaximin was well tolerated with a similar AE profile and discontinuation rate to placebo. This is likely secondary to the near absence of systemic absorption of rifaximin. Diarrhea was one of the more common side effects with rifaximin; however, there was no increase over placebo and there were no reported cases of *C. difficile*-associated diarrhea. Rifaximin has high activity against *C. difficile in vitro*, and is now used as an adjunct treatment for recurrent *C. difficile* (55–58). Though the poor systemic absorption of rifaximin should minimize the risk

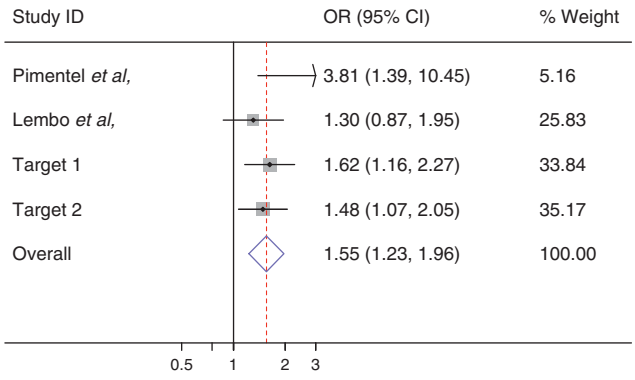

Figure 5. Forest plot of secondary outcome, bloating; heterogeneity $\chi^2 = 3.89$ (df = 3), $P = 0.27$; $I^2 = 22.9\%$; test of odds ratio (OR) = 1: $z = 3.67$, $P < 0.001$. CI, confidence interval.

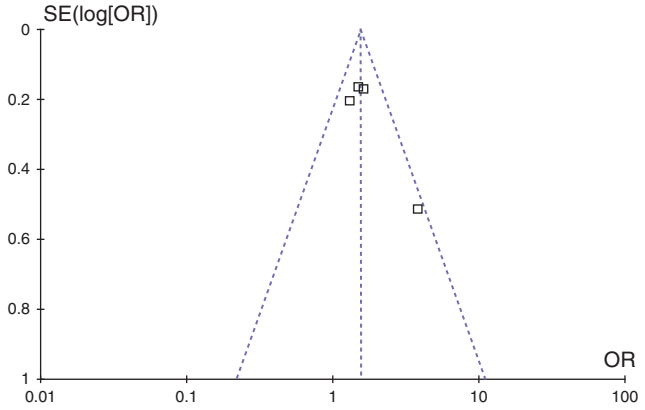

Figure 6. Funnel plot analysis of improvement of bloating (Begg test $P = 0.73$). OR, odds ratio.

Table 3. Secondary outcome: improvement of bloating, rifaximin vs. placebo

Study	Response rate, % (response /N)		Therapeutic Gain, %	NNT	OR
	Rifaximin	Placebo			
Pimentel *et al.*	41.9 (18/43)	15.9 (7/44)	26	3.8	3.81
Lembo *et al.*	46.1 (88/191)	39.6 (78/197)	6.5	15.4	1.33
Target 1	39.5 (122/309)	28.7 (90/314)	10.8	9.3	1.62
Target 2	41.0 (129/315)	31.9 (102/320)	9.1	11	1.48
Pooled OR	41.6 (357/858)	31.7 (277/875)	9.9	10.1	1.55

NNT, number needed to treat; OR, odds ratio.

of developing rifaximin resistance outside of the gastrointestinal tract, the possible development of rifaximin-resistant gut bacteria remains an as yet uninvestigated concern (59). Further study of this area is encouraged.

The main limitation of our analysis extend from the various forms of potential bias within each individual study. Overall, there was a low risk of bias in this analysis; however, we did find two areas of potential bias. In the Sharara *et al.* study, the assessment of global improvement in patients with IBS was a *post-hoc*, subgroup analysis. Also, Pimentel *et al.* had a higher prevalence of baseline abdominal pain in the rifaximin group compared with placebo, although it did not affect the global improvement outcome in their analysis but may have impacted their secondary outcome of abdominal pain. As discussed above, using average patient characteristics such as mean age rather than individual age may have led to spurious results from aggregation bias, and a small number of the included studies limit statistical power to adjust for additional covariates and does not allow any sensitivity analysis. For the same reasons, we were not able to make confident statements about optimal dose and duration of rifaximin for IBS. Other sources of variation such as level of patient compliance or other patient characteristics were also not available across the studies and hence could not be adjusted for. In assessing publication bias, the power of our analysis is modest with only five studies included. With this small number of studies, there could be publication bias or other small study effects, which could be missed by this type of analysis. Additionally, the number of subjects enrolled in the different studies was not evenly distributed. The Target 1 and Target 2 studies contributed the largest proportion of subjects (35.1% and 37.0% of the total population included in this analysis). It is also notable that the included studies did not address the natural history of IBS symptoms beyond 16 weeks of follow-up. As such, we cannot make any statements about the likelihood and timing of IBS symptoms recurrence nor are we able to discuss the optimal means by which patients with recurrent symptoms should be managed. Finally, due to the inherent differences in the design of the included studies, we are unable to combine them to address long-term efficacy. The Sharara study did not collect extended data on symptom response. Raw data from the original Pimentel and Lembo studies suggest improvement over a follow-up period of 10 and 12 weeks, respectively. Data from the Target 1 and 2 studies reported statistically significant benefits for rifaximin over placebo for all but the last of 10 weeks follow-up.

In summary, our results show that rifaximin is more effective than placebo at improving global symptoms and bloating in patients with IBS. Though therapeutic gain offered by rifaximin is modest, it is similar to that yielded by other currently available therapies for IBS. Studies with older patients and more females yielded higher response rates. Rifaximin has been well tolerated in short-term trials although efficacy and safety data beyond 16 weeks of therapy has not been established.

CONFLICT OF INTEREST

Guarantor of the article: William D. Chey, MD, AGAF, FACG, FACP.

Specific author contributions: S.B.M., M.M., and W.D.C. conceived and drafted the study. S.B.M. and M.M. collected all data. S.B.M., M.M., W.D.C., and H.M.K. analyzed and interpreted data. H.M.K. provided statistical advice and support. S.B.M. drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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Systematic review: complementary and alternative medicine in the irritable bowel syndrome

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Summary

Background Complementary and alternative medical therapies and practices are widely employed in the treatment of the irritable bowel syndrome.

Aim To review the usage of complementary and alternative medicine in the irritable bowel syndrome, and to assess critically the basis and evidence for its use.

Methods A systematic review of complementary and alternative medical therapies and practices in the irritable bowel syndrome was performed based on literature obtained through a Medline search.

Results A wide variety of complementary and alternative medical practices and therapies are commonly employed by irritable bowel syndrome patients both in conjunction with and in lieu of conventional therapies. As many of these therapies have not been subjected to controlled clinical trials, some, at least, of their efficacy may reflect the high-placebo response rate that is characteristic of irritable bowel syndrome.

Of those that have been subjected to clinical trials most have involved small poor quality studies. There is, however, evidence to support efficacy for hypnotherapy, some forms of herbal therapy and certain probiotics in irritable bowel syndrome.

Conclusions Doctors caring for irritable bowel syndrome patients need to recognize the near ubiquity of complementary and alternative medical use among this population and the basis for its use. All complementary and alternative medicine is not the same and some, such as hypnotherapy, forms of herbal therapy, specific diets and probiotics, may well have efficacy in irritable bowel syndrome. Above all, we need more science and more controlled studies; the absence of truly randomized placebo-controlled trials for many of these therapies has limited meaningful progress in this area.

Introduction

Irritable bowel syndrome (IBS) is a common but potentially disabling disorder which may affect as many as 20% as the adult population in western Europe and North America[1] Typical symptoms include abdominal pain, bloating, abdominal distension and altered bowel habit. Until recently, therapy has focused on symptomatic relief and on pain, diarrhoea and constipation, in particular. However, evidence for long-term efficacy of any pharmacological agent employing this approach in IBS was lacking. While some new compounds have been developed which offer promise of greater efficacy, these are not widely available, as yet.[2] It should come as no surprise, therefore, given the frequency and disabling nature of IBS symptomatology, that recourse to complementary and alternative medical (CAM) remedies and therapies has long been common place among IBS sufferers. Interest in CAM is not unique to IBS; indeed, such therapies have attracted the attention of the mainstream literature in many areas of medicine of late.[3]

Our goal was to perform a systematic review of the use of CAM in IBS. To achieve this we performed a Medline search using ‘irritable bowel syndrome’ as one keyword linked (by ‘and’) to either ‘complementary’, ‘alternative’, ‘herbal’, ‘mind–body’,

'hypnotherapy', 'probiotic', or other CAM modalities. Review articles were also searched for additional references. Emphasis was placed on controlled trials.

Complementary and alternative medicine

CAM is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as medical practices that are not currently considered to be a part of conventional medicine.[4] It must be stressed at the outset that this definition is somewhat arbitrary and cultural, ethnic, social, religious, educational, economic and other factors, as well as the prevailing attitude of the local medical profession will influence what is and what is not regarded as CAM.

Complementary medicines or medical practices are, by definition, taken or used in conjunction with conventional medicines; as illustrated, for example, by the use of aromatherapy as an aid to pharmacological analgesia in the post-operative patient. Alternative medicines or medical practices, in contrast, are taken or used in place of conventional medicines or practices; an example here would be choosing a special diet rather than surgery, radiation therapy or chemotherapy in the management of cancer. The term integrative medicine refers to an approach to patient care that combines 'mainstream' and CAM practices and/or therapies; some high quality evidence already exists for the safety and efficacy of this method in several areas.[5, 6]

CAM practices may be conveniently divided into five main categories.[4]

1 Manipulative and body-based methods: These therapies such as massage, chiropractice and osteopathic manipulation are based on the application of manipulation, pressure or movement to one or more parts of the body.

2 Mind–body interventions: This form of CAM involves a variety of techniques such as meditation, hypnosis, cognitive therapy, patient support groups and prayer, which are designed to enhance the capacity of the mind to influence or control bodily functions and relieve symptoms.

3 Biologically based therapies: These CAM therapies employ substances such as herbal products, dietary constituents or additives that are found in nature, so-called 'natural' products, to achieve relief.

4 Energy healing therapies: There are two forms of CAM therapy that employ some form of energy.

a Biofield therapies that are intended to affect the energy field that surrounds and penetrates the human body. Examples of this approach include Qi gong, acupuncture, reiki and therapeutic touch methods.

b The second form of energy therapy involves the use of bio-electromagnetic fields and includes such methods as pulsed field therapy, magnetic field therapy and the application of direct or alternating current fields.

5 Alternative medical systems: These systems such as homeopathy, or traditional Chinese medicine (TCM), involve an all-encompassing theory and practice of medicine and may include several different therapeutic approaches.

The use of CAM has increased dramatically in many countries in recent decades. In one survey performed in the United States the use of some type of CAM product or practice for medical benefit or general well being had increased from 25% to 42% of the entire population between 1990 and 1997.[7] In the same survey the number of visits to CAM practitioners actually exceeded those to traditional primary care doctors during 1997 and the annual cost of professional services related to the delivery CAM had increased to 21 billion US dollars,[7] by 1997. Furthermore, patients expressed equal confidence in CAM and conventional medical practitioners.[7, 8]

It is clear that the public and the medical profession have markedly differing views on CAM. Consumers, on the one hand, find CAM attractive as they perceive many modalities to be based on what they regard to be a more holistic approach, which allows patients to feel they are more actively participating in their own health care. In addition, they believe that natural therapies will be safer and more effective than synthetic pharmaceuticals.[8] On the other hand, allopathic practitioners often dismiss CAM, based on what they believe to be a lack of sufficient scientific evidence to support their effectiveness, and attribute their perceived efficacy, by patients, to the high-placebo response rates associated with many of the disorders for which CAM is most commonly employed. The fact that few CAM therapies have been submitted to scientific study in the form of a randomized-controlled trial[9] and that many of those that have been so evaluated were concluded in a manner that would be regarded as of low quality,[10] has not helped to increase acceptance of CAM among the medical profession. In one review of over 5000 trials of CAM only 258 met generally accepted standards for the conduct of a randomized-controlled clinical trial. Over 90% were neither truly randomized nor blinded. The mean score for trial quality for the 258 that were acceptable was only 44.7 (s.d.: ±14.3) on a 100-point scale.[11] The interpretation of CAM data are further complicated by the observation that most clinical trials performed in Asia and eastern Europe from where many trials in CAM emanate provide a favourable response.[12]

CAM in irritable bowel syndrome

Public awareness and usage of CAM in IBS and other functional disorders have also increased in the developed world in recent years. In one survey, performed on a total of 1409 subjects at a local supermarket, the incidence of CAM use was 49.5% for subjects with inflammatory bowel disease, 50.9% for those with IBS and 20% among those with other gastrointestinal diseases.[13]

Koloski *et al*. tried to define the predictors of conventional and alternative care seeking for IBS.[14] Two hundred and seven community-based patients were included in the study. One hundred and three (49.9%) patients had sought conventional care for IBS in the last 12 months. Only 43 (20.8%) pursued an alternative medicine pathway and the rest of the patients did not seek any care. Frequent abdominal pain and greater satisfaction with the doctor–patient relationship were identified as independent predictors of conventional healthcare use. Being a female, independently predicted alternative healthcare use.

Is, as some will assert, CAM no more than a placebo in IBS? This is an important issue given the high prevalence of a placebo response in clinical trials in IBS; this averages 47% for all trials and approximately 38%, if Rome I or II criteria were used to define IBS prior to entry into the study.[15] Pitz *et al*. sought to determine the components of IBS clinical trials that correlated with higher levels of placebo response.[16] Placebo responses for global symptom improvement and for decreased abdominal pain were assessed. Higher rates of global improvement correlated with frequency of administration of study intervention, duration of the study and overall treatment effect of the active agent being studied. Higher rates of decreased abdominal pain correlated with the frequency of intervention and overall treatment effect. On multivariate analysis, global improvement in the placebo group was associated with intervention frequency and overall treatment response. Decreased abdominal pain was associated with frequency of intervention and overall treatment response. They suggested that in designing IBS trials, it may be possible to minimize the placebo response by less frequent dosing. Conversely, in treating patients with IBS, it may be possible to harness the placebo response and maximize therapeutic response rates by more frequent dosing. In CAM, many therapies are administered frequently and are often accompanied by significant contact with the therapist, another factor which may increase the placebo response.

Manipulative and body-based methods in IBS

A small number of studies have evaluated the role of reflexology in IBS management. One single-blinded trial was carried out on 34 Rome II-positive IBS patients in primary care. Participants were allocated to receive either a reflexology foot massage or a non-reflexology type of foot massage. No clinical benefit was found in relieving abdominal pain, constipation, diarrhoea or

abdominal distention.[17] In another study, Herbert Benson's relaxation response meditation (RRM) program was tested as a possible treatment for IBS. Sixteen adults were included; 13 participants completed the treatment programme. Patients were taught the mediation technique and asked to practice it twice a day for 15 min. At the end of the treatment period, significant within-subject improvements were noted for flatulence and bloating. At follow-up 3 months later, significant improvements in flatulence, belching, bloating and diarrhoea ($P = 0.03$) were revealed from evaluation of symptom diaries.[18] The same group of patients later participated in a 1-year follow-up study to determine whether the effects of RRM on IBS symptom reduction were maintained over the long-term. Ten of the 13 who completed the original protocol participated; significant reductions, from pre-treatment, were now noted for the symptoms of abdominal pain, diarrhoea, flatulence and bloating. Continued use of meditation appeared, therefore, to be particularly effective in reducing the symptoms of pain and bloating.[19]

Mind–body interventions in IBS

Of these approaches, hypnotherapy has been the most widely used in the treatment of IBS. In one study, 250 unselected IBS patients were treated with hypnotherapy. Patients underwent 12 sessions of hypnotherapy over a 3-month period. At the end of the study, marked improvements were seen in all symptom scores, as well as in quality of life, and scores for anxiety and depression. All subgroups of patients appeared to do equally well, with the notable exception of males with diarrhoea.[20]

In another study, a total of 78 IBS patients completed a validated symptom-scoring questionnaire, the Hospital Anxiety and Depression (HAD) Scale and the Cognitive Scale for Functional Bowel Disorders (FBDs), before and after 12 sessions of gut-focused hypnotherapy. Hypnotherapy resulted in significant improvements in symptoms, quality of life and scores for anxiety and depression. IBS-related cognitions also improved, with a reduction in the total cognitive score and all component themes related to bowel function. This study showed that symptom improvements, in IBS, in relation to hypnotherapy are associated with cognitive changes.[21]

Tan *et al*. reviewed a total of 14 published studies ($N = 644$) on the efficacy of hypnosis in treating IBS (eight with no control group and six with a control group). They concluded that hypnosis consistently produces significant results and improves the cardinal symptoms of IBS in the majority of patients, as well as positively affecting non-colonic symptoms. When evaluated according to the efficacy guidelines of the Clinical Psychology Division of the American Psychological Association, the use of hypnosis in IBS qualifies for the highest level of acceptance as being both efficacious and specific. With regard to putative mechanisms of action, evidence for both physiological and psychological effects exists.[22]

Biologically based therapies and alternative medicine

Herbal therapies have been commonly used for a variety of disorders since ancient times. A recent study of patients using CAM modalities for gastrointestinal disorders showed that 48% used some form of herbal therapy.[23]

Traditional Chinese medicine has long used combination herbal therapy, whereby TCM herbal formulae are individualized based upon a given patient's pattern of symptoms, rather than being generic for a specific disease process. Furthermore, formulae may be modified over time, as the pattern of symptoms changes. These factors render comparisons between studies nigh impossible and militate against blinded, placebo-controlled studies. Variations in quality between studies or, even from day-to-day, in the same centre, further complicate the interpretation of these studies.

Herbs that have been used in TCM formulae for IBS have included many common foods such as rhubarb, barley, tangerine peel, cardamom and liquorice; most formulae include five or more herbs. While these therapies have been used in China for thousands of years, there have been few studies of their efficacy in the western literature. That this can be achieved, despite all of the aforementioned obstacles, is illustrated by one well-designed trial in which 116 patients were randomized into three groups: placebo (an inert formula looking and smelling just like the herbal treatment), a formula individually formulated for each patient by a trained TCM practitioner, or a standardized formula developed for IBS.[9] About 42% of those patients who received either of the herbal treatments had a greater improvement in their symptoms than those taking the placebo (16%). No differences in improvement rates for symptoms were found between individualized and standardized Chinese herbal formulae at 16 weeks.

Peppermint oil is commonly used, as both a component of prescription medicines and as a constituent of several over-the-counter remedies, for the treatment of IBS.[24, 25] The most common and, potentially distressing, side-effect of peppermint oil treatment is heartburn. Earlier, several small trials showed that peppermint was variably superior to placebo in improving abdominal discomfort, bloating and overall IBS symptoms.[26–28] However, these trials were small in size, usually of short duration and would be regarded, nowadays, as substandard. Not surprisingly, therefore, a recent review and meta-analysis of all available trials using peppermint oil in IBS concluded that the data were insufficient to justify its use.[29]

Various dietary modifications and food supplements have been used in IBS. These have included elimination diets, fibre supplements and probiotics. As IBS patients commonly report the precipitation of their usual symptoms by various foods and

food constituents, it should come as no surprise that exclusion diets have been tested in IBS patients, although with varying results. The usual approach involves an initial limitation of diet to a very small number of specific foods followed by a gradual introduction of potentially implicated foods on a one-by-one basis. Response rates to elimination diets have varied markedly from as low as 6% to as high as 58% in various studies; as a consequence no generalized recommendations can be made with regard to the use of elimination diets in IBS.[30]

More recently, attempts have been made to define food sensitivities based on immunological studies. While tests involving immunoglobulin E (IgE) antibody titres have not proven predictive, two recent studies have demonstrated more promise for IgG-based antibodies. Zar *et al*. found high levels of IgG antibodies to milk, eggs, wheat, beef, pork and lamb among their IBS patients. Exclusion of these substances was associated with significant symptomatic improvement.[31] Whorwell and colleagues randomized 150 out-patients with IBS to receive, for 3 months, either a diet excluding all foods to which they had raised IgG antibodies or a sham diet excluding the same number of foods but not those to which they had antibodies. After 12 weeks, the exclusion diet based on the IgG test resulted in a 10% greater reduction in symptom score than the sham diet.[32]

Probiotics have several actions that could be of benefit in IBS. These include antibacterial, immune modulating and mucosal barrier protective effects.[33] Probiotics can also induce quantitative and qualitative changes in the gut flora and alter stool mucus and bile salt composition. Qualitative changes in the flora could, in turn, reduce the abnormal colonic fermentation that has been reported by some authors,[34] in IBS. Evidence now accumulates to suggest efficacy for certain probiotics, at least, in IBS. Nobaek *et al*. evaluated the response of symptoms and the colonic flora to supplementation, for 4 weeks, with a rose-hip drink containing 5×10^7 cfu/mL of *Lactobacillus plantarum* (DSM 9843) and 0.01 g/mL oat flour.[35] When evaluated 1 year later and when compared with a placebo-treated group, the probiotic group experienced a significant reduction in flatulence but not in abdominal pain or bloating. Kim *et al*. investigated the effects of 8 weeks of treatment with the probiotic cocktail, VSL#3, on gastrointestinal transit and symptoms in 25 patients with Rome II-positive IBS with predominant diarrhoea.[36] While treatment with VSL#3 resulted in a reduction in abdominal bloating scores, there were no effects on other IBS symptoms such as abdominal pain, gas and urgency. In a further trial, the same group found that VSL#3 reduced flatulence scores and retarded colonic transit but without altering bowel function among a group of patients with IBS and bloating.[37] In the most promising study to date, O'Mahony *et al*. compared the responses of symptoms and peripheral blood mononuclear cell cytokine ratios in IBS patients to ingestion of milk-based probiotic preparations containing either a *Lactobacillus* or a *Bifidobacterium* with a placebo in an 8-week study.[38] Patients who were randomized to *B. infantis* 35624 reported a greater reduction in symptom

scores; composite and individual scores for abdominal pain/discomfort, bloating/distention and bowel movement difficulty were significantly lower than for placebo for those randomized to *B. infantis* 35624 for most weeks of the treatment phase. No consistent benefits were associated with therapy with the *Lactobacillus*. Clues to the possible mode of action of the *Bifidobacterium* were provided by cytokine assays. At baseline, patients with IBS demonstrated an abnormal interleukin (IL)-10/IL-12 ratio, indicative of a proinflammatory Th-1, state; this was normalized in the *Bifidobacterium* group alone. If these results are replicated in larger studies and if probiotics can be delivered in an encapsulated, consistent and quality-controlled manner, these 'food supplements' may well move from the CAM category into that of mainstream pharmaceuticals.

Energy healing therapies

Acupuncture is another area that has been studied in IBS management. Acupuncture, originated from ancient Chinese medicine, is based on channels of energy (Qi), called meridians, which run through the body. On the meridians lie 360 acupuncture points. Although claims for efficacy for acupuncture in IBS exist, there is little data. One pilot study of just seven patients reported improvements in bloating and general well being.[39]

A prospective, blinded, sham-controlled trial of traditional Chinese acupuncture was conducted on 60 IBS patients at a single postgraduate teaching hospital in Europe.[40] The primary end point was a predefined fall in symptom score at 13 weeks. Patients in treated and sham groups improved significantly during the study, mean improvements in scores being equal (−1.9) and significant for both. There was a small numeric but non-significant difference between the response rates in patients receiving acupuncture (40.7%) and sham treatment (31.2%). Several secondary end points marginally favoured active treatment, but an improved symptom score occurred more often with sham therapy (65.6% vs. 59.2%).

Conclusions

It is abundantly clear that recourse to CAM is widespread among IBS patients; doctors must recognize this and attempt to understand this reliance on therapies which, in many instances, do not have a scientific basis. The high-placebo response rate in IBS renders studies difficult; it has indeed been suggested that CAM is the new placebo.[41] All CAM is not the same and some, such as hypnotherapy, forms of herbal therapy and probiotics, may well find a place in the armamentarium of the gastroenterologist and primary care doctor caring for IBS sufferers (Table 1). Above all, we need more science and more

controlled studies; the absence of truly randomized placebo-controlled trials for many of these therapies has limited meaningful progress in this area.

Table 1. Controlled trials of CAM in IBS

Intervention	*n*	Response	Reference
Reflexology	34	No advantage over placebo	17
Herbert Burns relaxation response meditation	16	Reduced flatulence and bloating. Sustained at 6 months	18, 19
Chinese herbs	116	Improvement in 42% vs. 16% for placebo	9
Exclusion diet based on IgG4 antibodies	25	Pain, bloating, bowel habit satisfaction improved at 3 months, sustained at 6 months	31
Exclusion diet based on IgG antibodies	150	Improvements in symptom score (10% over placebo) and global rating	32
Lactobacillus plantarum	60	Reduced flatulence	35
Probiotic cocktail VSL#3	25	Less bloating	36
Probiotic cocktail VSL#3	48	Less flatulence in bloated IBS	37
Lactobacillus salivarius and *Bifdobacterium infantis* 35624	77	Reduced pain, bloating, composite score with *Bifidobacterium*, not with *Lactobacillus*	38
Acupuncture	60	No benefit over sham	40

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Citing Literature

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DEPARTMENT OF HEALTH

Irritable Bowel Syndrome (IBS) Issue Brief

INCLUDING IBS AND IBS-D

OCTOBER 2022

Introduction

This briefing was prepared in response to petitions to consider adding irritable bowel syndrome (IBS) and irritable bowel syndrome with diarrhea (IBS-D) as new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used identify any ongoing or completed clinical trials.

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Symptom severity can range from debilitating to mild or moderate. Further, IBS is often associated with additional somatic comorbidities (conditions that affect the body), psychiatric conditions, and visceral sensitivity (Enck et al., 2016).

IBS is thought to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the gut. The associated problem between the brain and the gut leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both (Ford et al., 2020).

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes, IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools is loose, or watery and more than a quarter of a patient's stools are hard and lumpy (Chey et al., 2015).

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis is irritable bowel disease (IBD). Unlike IBS, which is characterized by a gut-brain disorder, IBD, which encompasses Crohn's disease (CD) and Ulcerative colitis (UC), is characterized by chronic relapsing inflammation and immune activity (Abdul Rani et al., 2016). However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological comorbidities, specifically depression and anxiety (Abdul Rani et al., 2016). Further, studies have found that depression can increase a patient's probability for developing increased inflammation (Fagundes et al., 2013, Johnson et al., 2002). Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development (Abdul Rani et al., 2013). However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent (Abdul et al., 2016). Finally, both IBD and IBS patients experience abnormal gut microbiota (Abdul et al., 2016). However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease (Abdul et al., 2016). Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks. Ultimately, more large-scale research is needed to define a clear connection.

Epidemiology

IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years (Chey et al., 2015). Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion (Chey et al., 2015). Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms (Chey et al., 2015).

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity (Chey et al., 2015).

Diagnosis

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or inflammatory bowel disease. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale (Chey et al., 2015).

Diagnostic Criteria for Irritable Bowel Syndrome (IBS) With Subtypes includes:

Recurrent abdominal pain or discomfort at least three days a month associated with two or more of the following: reduced abdominal pain with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (Chey et al., 2015).

IBS with constipation (IBS-C) is defined as hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements. IBS with diarrhea (IBS-D) is defined as loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements. Mixed IBS (IBS-M) is defined as hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements (Chey et al., 2015).

While diagnosis of IBS-D or IBS-C is relatively straightforward, the diagnosis of patients with IBS-M presents a unique challenge. Therefore, a detailed history of a patients mixed bowel patterns is required to better understand the underlying disease state (Chey et al., 2015). Further, the consideration of all prescription and over-the-counter medications is needed to determine how they might affect IBS symptoms (Chey et al., 2015).

In addition to the identification of symptom-based criteria, a detailed assessment to eliminate the potential for alternative disease is required to finalize the diagnosis. A patient with clear IBS symptoms combined with an absence of diagnostic markers indicative of other gastrointestinal related disorders, can be diagnosed as having IBS with some level of accuracy (Chey et al., 2015).

Current Therapies

Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates) (Chey et al., 2015). A meta-analysis of the low-FODMAP diet found

that the diet was effective at improving patient well-being and reducing symptoms (van Lanen et al., 2021). However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP (van Lanen et al., 2021). Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established (van Lanen et al., 2021).

Medications

A doctor may recommend medication to relive IBS symptoms dependent on the type of IBS a patient is suffering from.

Antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume (Chey et al., 2015). However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit of loperamide compared to the placebo group for the overall reduction of IBS symptoms (Chey et al., 2015). Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic (Chey et al., 2015).

Serotonin agents such as Alosetron, a 5-HT_3 antagonist has been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies (Chey et al., 2015). Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo.

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools (Chey et al., 2015). Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms (Chey et al., 2015). Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it has not been shown to improve abdominal pain or bloating (Chey et al., 2015). Stimulant laxatives have also been used as a therapy for IBS-C patients, but there have been few randomized controlled trials evaluating its efficacy (Chey et al., 2015).

Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel, and abdominal symptoms in IBS-C patients (Chey et al., 2015). Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls (Chey et al., 2015).

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity

compared to placebo controls (Chey et al., 2015). Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea (Lacy et al., 2009). As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximize effects are felt (Chey et al., 2015).

The use of probiotics and antibiotics has been explored as a treatment for IBS (Chey et al., 2015). Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence (Ford et al., 2014). However, there was some variability in the probiotics used and grouping methods employed that limited comparability (Ford et al., 2014). As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation regarding the use of specific probiotic preparations for IBS (Chey et al., 2015). Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients (Menee et al., 2012). However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms (Chey et al., 2015). Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern (Chey et al., 2015).

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain (Dekel et al., 2013). However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS (Chey et al., 2015). Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms (Ford et al., 2014). However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS (Hussain et al., 2006). However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture (Manheimer et al., 2012). Studies evaluating herbal remedies have yielded mixed results. There is a lack of an understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary interventions, medication, and behavioral strategies to maximize treatment of IBS (Chey et al., 2015).

Pre-clinical Research

Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the CB1 receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system (Hill et al., 2017, Brugnatelli et al., 2020). Pre-clinical studies have shown a direct connection

between the endocannabinoid system and regulation of gastrointestinal motility (Storr et al., 2008). In fact, activation of the cannabinoid 1 (CB1) and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility (Hasenoehrl et al., 2016). Additionally, research by Vianna et al., 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility. Despite the promising pathophysiologic mechanism, studies examining the impact of an endocannabinoid deficiency on IBS are limited.

Clinical Trials

A clinical trial by Wong et al. in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS (Wong et al., 2011). In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, Wong et al. attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial conducted by Wong et al. in 2012 failed to reproduce the findings seen in 2011 (Wong et al. 2012). In addition, a study by Klooker at al., 2011, showed that the cannabinoid receptor agonist delta-9-tetrahydrocannabinols (THC) had no effect on rectal distension or rectal sensitivity in healthy volunteers and IBS patients. Moreover, a placebo-controlled crossover study (a study where patients receive both the treatment and the placebo at different times during a study) reported no significant difference in IBS patient pain scores between CBD and placebo treatments. However, this study was small scale and only recruited women for the study (Anne-Claire B. et al., 2021). Finally, a small clinical trial investigating the impact of cannabidiol therapy on IBS patients found at the group level there was no difference in the pain score of those who received the cannabidiol therapy compared to those who did not receive the cannabidiol therapy (van Orten-Luiten et al., 2021). Overall, while some studies, such as the 2011, Wong et al. have shown the promising potential for dronabinol, several more recent studies have failed to reproduce these findings. Thus, more large-scale clinical trials are needed.

Ongoing Clinical Trials

A search for current ongoing clinical trials was conducted on clinicaltrials.gov. Search terms specific to cannabis and IBS were used to identify clinical trials. Search terms for IBS included Irritable Bowel Syndrome, IBS, IBS-D, IBS-C, and IBS-M. Search terms for Cannabis included cannabis, THC, marijuana, and dronabinol. Currently there are no ongoing clinical trials investigating the potential role of cannabis as a treatment for IBS.

Observational Studies

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS (Choi et al., 2022). The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis (Choi et al., 2022). When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users (Choi et al., 2022). However, Choi et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission (Choi et al. 2022). Therefore, the authors found that cannabis use had no impact on IBS-specific 30-day hospital readmission rates but did reduce total hospitalization cost and charges.

Adejumo et al. conducted a national survey, using the international classification of disease, 9th edition codes to identify individuals with Cannabis Use Disorder (CUD) and IBS. They found that patients with CUD were significantly more likely to have IBS compared to patients without CUD (Adejumo et al. 2019). These finding suggest that the abnormal use of cannabis may either contribute to the development or exacerbation of IBS and its symptoms. Adding to this, a study of 31,272 patients by Patel et al., 2020, found that patients with CUD had a higher odd for IBS hospitalization compared to patients without Cannabis Use Disorder (Patel et al. 2020). This suggests the use of cannabis among those with CUD may be associated with the development of IBS or exacerbation of IBS symptoms. Therefore, while there is a potential benefit associated with the use of cannabis, the improper use of cannabis poses some risk to the development and aggravation of IBS.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers), reported that cannabis use may decrease inpatient health-care utilization in IBS patients. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users (Desai et al., 2020). Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users (Desai et al., 2020, Choi et al., 2022). In contrast, a study by Adeyinka et al., 2019, reported a higher likelihood of hospitalization among people who use cannabis conflicting with prior reports of a shortened stay. This paper also noted that an elevated state of anxiety might countermand the effects of cannabis on the endocannabinoid system (Adeyika et al., 2019). In conclusion, while cannabis as a therapy for IBS shows promise, the data remains inconclusive and more large-scale clinical trial research is needed.

In contrast to IBS, IBD research suggests that the use of small doses of cannabis can help reduce inflammation and reduces the overall IBD symptomology (McCallum et al., 2014, Perisetti et al., 2020). However, consumption of cannabis at high levels can exacerbate IBD symptoms and increase a patient's likelihood to be hospitalized due to severe IBD (UC and CD) (McCallum et al., 2014, Perisetti et al., 2020). Therefore, extreme cause should be taken when using cannabis as a therapy for IBD.

National Medical Organization Recommendations

In 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

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4. **Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation**

Content for this section was borrowed heavily from the Minnesota Department of Health's Issue Brief on Irritable Bowel Syndrome, which was published in October 2022 in support of its decision to add Irritable Bowel Syndrome to the state's list of Qualifying Conditions for Medical Marijuana. For more information, we encourage you to contact the Minnesota Department of Health's Office of Medical Cannabis at:

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Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the cannabinoid 1 (CB1) receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system.[1] [2] Pre-clinical studies have shown a direct connection between the endocannabinoid system and regulation of gastrointestinal motility.[3] In fact, activation of the CB1 and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility.[4] Additionally, research in 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility.[5] While this pathophysiologic mechanism is promising, more studies examining the impact of an endocannabinoid deficiency on IBS are needed.

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A clinical trial in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS.[6] In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, several of the same researchers attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial failed to reproduce the findings seen in 2011, highlighting the need for more research.[7]

Overall, while some studies involving THC or synthetic THC, such as the 2011, Wong et al. study, have shown the promising potential for drugs like dronabinol, others have been inconclusive. Thus, more large-scale clinical trials are needed.

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS.[8] The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis.[9] When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users.[10] However, Choi

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et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission.[11] Therefore, the authors found that cannabis use reduced total hospitalization cost and charges.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers) ultimately concluded that cannabis use may decrease inpatient healthcare utilization in IBS patients, possibly through the effect of cannabis on the endocannabinoid system. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users.[12] Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users and ultimately incurred fewer total charges for services.[13]

Finally, in 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date, the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

Most states where medical marijuana is legal have added at least one bowel disorder as a qualifying condition. These include at least nine that specifically list Inflammatory Bowel Disease (Maine, Michigan, Minnesota, Missouri, New Jersey, Ohio, Pennsylvania, Tennessee, Virginia), thirty-two that specifically list Crohn's disease (Alabama, Arizona, Arkansas, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Louisiana, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, New Hampshire, New Jersey, New Mexico, North Dakota, Ohio, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia), twelve that specifically list Ulcerative Colitis (Arkansas, Connecticut, Illinois, Iowa, Michigan, Mississippi, New Hampshire, New Mexico, Ohio, South Carolina, Tennessee, Utah), and two that specifically list IBS (Illinois and Minnesota).[14] Further, many other states like Arkansas, California, Colorado, New York, Washington, Wisconsin, and Washington D.C. have open-ended

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Cannabis Use is Associated with Reduced 30-Day All-cause Readmission Among Hospitalized Patients with Irritable Bowel Syndrome: A Nationwide Analysis. *Journal of clinical gastroenterology*, *56*(3), 257–265. https://doi.org/10.1097/MCG.0000000000001498

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[14] List of Qualifying Conditions by State - https://www.compassionatecertificationcenters.com/news/list-of-qualifying-health-conditions-for-medical-marijuana-in-each-state/

qualifying conditions that allow doctors to recommend medical marijuana for IBS. Recent studies demonstrating promise in the use of cannabis to treat and alleviate symptoms related to IBS.[15]

The truth is that many would-be patients may already be using marijuana to treat symptoms related to IBS, and research is starting to show how medical marijuana may help with IBS symptom management in some patients, which is why the Minnesota Department of Health recently concluded that "Irritable bowel syndrome (IBS) is a disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating" and that "Research has shown that people who suffer from [IBS] can see benefits from using medical cannabis to treat their symptoms."[16]

[15] List of Qualifying Conditions by State - https://www.compassionatecertificationcenters.com/news/list-of-qualifying-health-conditions-for-medical-marijuana-in-each-state/

[16] MDH Press Release on New Qualifying Conditions - https://www.health.state.mn.us/news/pressrel/2022/cannabis113022.html

DEPARTMENT OF HEALTH

Irritable Bowel Syndrome (IBS) Issue Brief

INCLUDING IBS AND IBS-D

OCTOBER 2022

Introduction

This briefing was prepared in response to petitions to consider adding irritable bowel syndrome (IBS) and irritable bowel syndrome with diarrhea (IBS-D) as new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, members of the Medical Cannabis Review Panel, and interested members of the public, scientific studies of cannabis products as a therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) were included, especially if there are few clinical trials or observational studies. Interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses; however, surveys published in peer-reviewed journals were included for completeness. Published recommendations or opinions of national medical organizations were also included.

Searches for published clinical trials and observational studies of cannabis therapy were conducted using the National Library of Medicine's Medline using key word searches appropriate for the petitioned condition. Articles identified as clinical trials, observational studies, or review articles were collected and reviewed. References in the identified articles were examined to ensure all the articles associated with the petitioned condition were identified and included. Moreover, clinicaltrials.gov, a federal government-maintained website responsible for tracking current clinical trials funded, was used identify any ongoing or completed clinical trials.

Definition

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, and irregular bowel movements that can result in diarrhea, constipation, both diarrhea and constipation, or bloating. These symptoms can occur without any visible signs of damage or disease within the digestive tract. Symptom severity can range from debilitating to mild or moderate. Further, IBS is often associated with additional somatic comorbidities (conditions that affect the body), psychiatric conditions, and visceral sensitivity (Enck et al., 2016).

IBS is thought to be caused by a functional gastrointestinal disorder, resulting in disrupted interactions between the brain and the gut. The associated problem between the brain and the gut leads to increased sensitivity and changes in bowel muscle contractions. More sensitive bowels experience more bloating and pain, whereas irregular bowel muscle contractions result in diarrhea, constipation, or both (Ford et al., 2020).

A commonly used diagnostic tool for IBS (Rome IV criteria) categorizes IBS into three main subtypes, IBS-C, IBS-D, and IBS-M. IBS-C (constipation) occurs when more than a quarter of a patient's stools are hard and lumpy, while less than a quarter of their stools are loose or watery. IBS-D (diarrhea) occurs when more than a quarter of a patient's stools are loose or watery, while less than a quarter of stools are hard or lumpy. Lastly, IBS-M (mixed) occurs when more than a quarter of a patient's stools is loose, or watery and more than a quarter of a patient's stools are hard and lumpy (Chey et al., 2015).

Another common gastrointestinal (GI) disorder already approved as a condition for medical cannabis is irritable bowel disease (IBD). Unlike IBS, which is characterized by a gut-brain disorder, IBD, which encompasses Crohn's disease (CD) and Ulcerative colitis (UC), is characterized by chronic relapsing inflammation and immune activity (Abdul Rani et al., 2016). However, IBS and IBD have similarities. For example, both IBD and IBS patients are predisposed to psychological comorbidities, specifically depression and anxiety (Abdul Rani et al., 2016). Further, studies have found that depression can increase a patient's probability for developing increased inflammation (Fagundes et al., 2013, Johnson et al., 2002). Further, recent studies in the U.S., Sweden, and the U.K. noted that like IBD, IBS patients experience a genetic mutation in their immune activation markers, suggesting a similar pathway to disease development (Abdul Rani et al., 2013). However, the level of inflammation seen in IBD patients is markedly greater than that seen in IBS patients and inflammation seen in IBD patients is often ongoing and slow to resolve, while IBS inflammation is variable, or even absent (Abdul et al., 2016). Finally, both IBD and IBS patients experience abnormal gut microbiota (Abdul et al., 2016). However, unlike IBS, IBD is an organic disease evidenced by inflammation in the mucosal section of the stomach, whereas IBS is seen as a spectrum of functional disorder, with no evidence of organic disease (Abdul et al., 2016). Overall, evidence supports an intimate interlink between IBS and IBD, but with different presentations and outlooks. Ultimately, more large-scale research is needed to define a clear connection.

Epidemiology

IBS results in significant reductions in health-related quality of life and work productivity. Approximately 12% of people living in the United States have IBS. Women are two times more likely to develop IBS than men, and people younger than 50 years of age are at an increased risk of developing IBS compared to those over 50 years (Chey et al., 2015). Further, IBS is estimated to account for $3.1 million ambulatory care visits and 5.9 million prescriptions annually, with the total indirect and direct costs exceeding $20 billion (Chey et al., 2015). Over time, an estimated 2% to 18% of clinical-based IBS patients experience worsening symptoms; 30% to 50% patients remain unchanged; and 12% to 38% experience improved symptoms (Chey et al., 2015).

Factors that increase a person's likelihood of developing IBS include a family history of IBS, a history of stress, difficult/traumatic life events or abuse, severe digestive tract infection, small intestinal bacterial overgrowth, and food intolerance/sensitivity (Chey et al., 2015).

Diagnosis

IBS diagnosis is based on the presence of characteristic symptoms and exclusion of select diseases, including other gastroenterological disease such as colon cancer, celiac disease, or inflammatory bowel disease. The distinguishing features of IBS in accordance with current diagnostic standards, and Rome III criteria, include abdominal pain discomfort or altered bowel habits. Stool consistency is used to distinguish between the three subtypes of IBS, because it has been identified as a more consistent marker of disease compared to stool frequency as a marker. Stool consistency can be assessed using the Bristol Stool Form Scale (Chey et al., 2015).

Diagnostic Criteria for Irritable Bowel Syndrome (IBS) With Subtypes includes:

Recurrent abdominal pain or discomfort at least three days a month associated with two or more of the following: reduced abdominal pain with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool (Chey et al., 2015).

IBS with constipation (IBS-C) is defined as hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements. IBS with diarrhea (IBS-D) is defined as loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements. Mixed IBS (IBS-M) is defined as hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements (Chey et al., 2015).

While diagnosis of IBS-D or IBS-C is relatively straightforward, the diagnosis of patients with IBS-M presents a unique challenge. Therefore, a detailed history of a patients mixed bowel patterns is required to better understand the underlying disease state (Chey et al., 2015). Further, the consideration of all prescription and over-the-counter medications is needed to determine how they might affect IBS symptoms (Chey et al., 2015).

In addition to the identification of symptom-based criteria, a detailed assessment to eliminate the potential for alternative disease is required to finalize the diagnosis. A patient with clear IBS symptoms combined with an absence of diagnostic markers indicative of other gastrointestinal related disorders, can be diagnosed as having IBS with some level of accuracy (Chey et al., 2015).

Current Therapies

Treatment of IBS focuses on relieving symptoms so a patient can live a normal life. Mild signs and symptoms can often be controlled by reducing stress and by making changes in diet and lifestyle. Lifestyle changes include avoiding foods that trigger symptoms, eating high-fiber foods, drinking plenty of fluids, exercising regularly, and getting enough sleep. Patients may also need to eliminate high-gas foods, gluten, and consume a low-FODMAPS diet (a diet low in fermentable carbohydrates) (Chey et al., 2015). A meta-analysis of the low-FODMAP diet found

that the diet was effective at improving patient well-being and reducing symptoms (van Lanen et al., 2021). However, the impact the low-FODMAP diet might have on the gut microbiome community is still unknown, and more research needs to be conducted to determine the long-term effects of the low-FODMAP (van Lanen et al., 2021). Further, many studies included in the meta-analysis had large variation in control diets between studies, and the content of these controls have not been well established (van Lanen et al., 2021).

Medications

A doctor may recommend medication to relive IBS symptoms dependent on the type of IBS a patient is suffering from.

Antidiarrheal medication, such as loperamide, is often used as primary treatment for IBS-D. It can be used to inhibit peristalsis (involuntary, wave-like muscle contractions that push content forward), which prolongs gut transit and reduces fecal volume (Chey et al., 2015). However, two randomized controlled trials focusing on IBS-D and IBS-M patients found no benefit of loperamide compared to the placebo group for the overall reduction of IBS symptoms (Chey et al., 2015). Loperamide was able to reduce stool frequency, increase stool consistency and could be used as a diarrheal prophylactic (Chey et al., 2015).

Serotonin agents such as Alosetron, a 5-HT_3 antagonist has been approved for use in the United States for the treatment of women with severe, debilitating IBS-D when the patient has not responded well to traditional medical therapies (Chey et al., 2015). Alosetron has been found to improve IBS-D symptoms in women and men for up to a year, with patients receiving a 15% reduction in symptoms compared to the placebo.

Notably, the American College of Gastroenterology Functional Bowel Disorders Task Forces concluded that certain antispasmodics (otilonium, hyoscine, cimetropium, pinaverum, and dicyclomine) can provide short-term symptomatic relief to IBS patients. However, because some patients have an exaggerated gastrocolonic reflex, antispasmodics may function better as a treatment for upper abdominal pain after eating or loose stools (Chey et al., 2015). Dose-dependent adverse events, such as constipation, fatigue, dry mouth, dizziness, and blurred vision have been known to occur. Peppermint oil has been identified as a potential antispasmodic treatment in several small clinical trials. However, some patients may experience severe reflux symptoms (Chey et al., 2015). Laxatives, such as polyethylene glycol, are frequently recommended as a therapy for IBS-C, and clinical trials have demonstrated an improvement in stool frequency and consistency. However, it has not been shown to improve abdominal pain or bloating (Chey et al., 2015). Stimulant laxatives have also been used as a therapy for IBS-C patients, but there have been few randomized controlled trials evaluating its efficacy (Chey et al., 2015).

Certain agents, such as lubiprostone, can stimulate intestinal fluid secretion and improve global bowel, and abdominal symptoms in IBS-C patients (Chey et al., 2015). Two phase-three clinical trials found a significantly higher percentage in patients treated with lubiprostone compared to placebo controls (Chey et al., 2015).

Alternatively, a different agent, Linaclotide, has been identified as a treatment for IBS-C patients. Specifically, a 2013 meta-analysis found that Linaclotide reduced IBS-C severity

compared to placebo controls (Chey et al., 2015). Linaclotide was also found to be somewhat effective at reducing the likelihood of diarrhea (Lacy et al., 2009). As a result, Linaclotide treatment is most effective at improving stool frequency a week after treatment initiation, whereas abdominal pain and bloating may take 8 to 12 weeks before maximize effects are felt (Chey et al., 2015).

The use of probiotics and antibiotics has been explored as a treatment for IBS (Chey et al., 2015). Specifically, a meta-analysis of 35 randomized control trials found that probiotics improved overall IBS symptoms including abdominal pain, bloating, and flatulence (Ford et al., 2014). However, there was some variability in the probiotics used and grouping methods employed that limited comparability (Ford et al., 2014). As a result, higher-quality studies are needed, as the current literature does not allow for any recommendation regarding the use of specific probiotic preparations for IBS (Chey et al., 2015). Alternatively, antibiotics such as rifaximin, have been shown to demonstrate therapeutic gains of 9% to 10% for global symptoms in no constipated IBS patients (Menee et al., 2012). However, clinical studies suggest that many rifaximin responders will eventually develop recurrent IBS symptoms (Chey et al., 2015). Overall, the role of antibiotics such as rifaximin remains unknown, and antimicrobial resistance due to overuse remains a significant concern (Chey et al., 2015).

Recently, antidepressants have become a widespread treatment option for patients with moderate to severe IBS. A meta-analysis of 17 randomized controlled trials found that antidepressants were effective at reducing abdominal pain (Dekel et al., 2013). However, Tricyclic antidepressants were shown to cause dose-dependent constipation, whereas selective serotonin-reuptake inhibitors can cause diarrhea. Further, although selective norepinephrine-reuptake inhibitors offer benefits for anxiety, depression, and somatic pain, they have yet to be evaluated as an efficacious treatment for IBS (Chey et al., 2015). Psychological therapies have been identified as an alternative or adjunctive therapy for IBS patients. Specifically, a meta-analysis of 32 studies found that 10 different psychological therapies were effective at reducing IBS symptoms (Ford et al., 2014). However, despite these results, access to behavioral therapy remains limited.

Alternative medicines, such as acupuncture, have been considered as a therapy for treatment of IBS (Hussain et al., 2006). However, a meta-analysis of five studies found that acupuncture was no better at reducing IBS symptoms compared to those not receiving acupuncture (Manheimer et al., 2012). Studies evaluating herbal remedies have yielded mixed results. There is a lack of an understanding of active ingredients involved. And there is no clear standardized treatment. Overall, current therapies for IBS are available, but rely on patient-physician relationships, and holistic approaches that utilize lifestyle changes, dietary interventions, medication, and behavioral strategies to maximize treatment of IBS (Chey et al., 2015).

Pre-clinical Research

Animal and human studies have shown that cannabinoids play an important role in the regulation of gastric and intestinal secretion. Said cannabinoids reduce production of gastric acid secretion by activating the CB1 receptors. Recent studies have also identified a potential pathophysiologic mechanism for IBS; specifically, deficiencies in the endocannabinoid system (Hill et al., 2017, Brugnatelli et al., 2020). Pre-clinical studies have shown a direct connection

between the endocannabinoid system and regulation of gastrointestinal motility (Storr et al., 2008). In fact, activation of the cannabinoid 1 (CB1) and the cannabinoid 2 (CB2) receptors reduce motility, limit secretion, and decrease hypersensitivity in the gut. Further, in mice models of post-inflammatory IBS, inhibition of transit by endocannabinoid-like compounds has been shown to block CB1 receptor antagonists, therefore modulating gut motility (Hasenoehrl et al., 2016). Additionally, research by Vianna et al., 2012 reported that a deletion of the CB1 receptors in the vagal nerves of mice caused increased gastrointestinal motility. Despite the promising pathophysiologic mechanism, studies examining the impact of an endocannabinoid deficiency on IBS are limited.

Clinical Trials

A clinical trial by Wong et al. in 2011 evaluated the effect of dronabinol on colonic motility and sensation in patients with IBS (Wong et al., 2011). In this study the authors compared IBS patients who received dronabinol (sometimes referred to as marinol), a synthetic tetrahydrocannabinol (THC), to IBS patients who did not receive dronabinol. The authors examine colonic motility (the degree to which the bowel moves waste through it), and colonic compliance (a measure of the pressure needed to reach half the maximum volume of the colon). Notably, the authors found patients who received dronabinol experienced reduced colonic motility and improved colonic compliance compared to a placebo control. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms. These findings presented a promising new treatment for IBS and specifically, IBS-D. In 2012, Wong et al. attempted to recreate the dronabinol effects in IBS-D patients specifically. However, the randomized controlled trial conducted by Wong et al. in 2012 failed to reproduce the findings seen in 2011 (Wong et al. 2012). In addition, a study by Klooker at al., 2011, showed that the cannabinoid receptor agonist delta-9-tetrahydrocannabinols (THC) had no effect on rectal distension or rectal sensitivity in healthy volunteers and IBS patients. Moreover, a placebo-controlled crossover study (a study where patients receive both the treatment and the placebo at different times during a study) reported no significant difference in IBS patient pain scores between CBD and placebo treatments. However, this study was small scale and only recruited women for the study (Anne-Claire B. et al., 2021). Finally, a small clinical trial investigating the impact of cannabidiol therapy on IBS patients found at the group level there was no difference in the pain score of those who received the cannabidiol therapy compared to those who did not receive the cannabidiol therapy (van Orten-Luiten et al., 2021). Overall, while some studies, such as the 2011, Wong et al. have shown the promising potential for dronabinol, several more recent studies have failed to reproduce these findings. Thus, more large-scale clinical trials are needed.

Ongoing Clinical Trials

A search for current ongoing clinical trials was conducted on clinicaltrials.gov. Search terms specific to cannabis and IBS were used to identify clinical trials. Search terms for IBS included Irritable Bowel Syndrome, IBS, IBS-D, IBS-C, and IBS-M. Search terms for Cannabis included cannabis, THC, marijuana, and dronabinol. Currently there are no ongoing clinical trials investigating the potential role of cannabis as a treatment for IBS.

Observational Studies

A retrospective nationwide cohort study of 7,163 patients with IBS sought to examine the potential association between cannabis use and IBS (Choi et al., 2022). The authors examined hospital readmission rates between IBS patients who reported using cannabis and IBS patients who did not use cannabis (Choi et al., 2022). When the authors adjusted for additional variables, they found no significant difference in hospital readmission rates between the IBS cannabis users and the IBS cannabis non-users (Choi et al., 2022). However, Choi et al. did note that IBS patients who used cannabis had lower in-hospital resource utilization during IBS-specific readmission (Choi et al. 2022). Therefore, the authors found that cannabis use had no impact on IBS-specific 30-day hospital readmission rates but did reduce total hospitalization cost and charges.

Adejumo et al. conducted a national survey, using the international classification of disease, 9th edition codes to identify individuals with Cannabis Use Disorder (CUD) and IBS. They found that patients with CUD were significantly more likely to have IBS compared to patients without CUD (Adejumo et al. 2019). These finding suggest that the abnormal use of cannabis may either contribute to the development or exacerbation of IBS and its symptoms. Adding to this, a study of 31,272 patients by Patel et al., 2020, found that patients with CUD had a higher odd for IBS hospitalization compared to patients without Cannabis Use Disorder (Patel et al. 2020). This suggests the use of cannabis among those with CUD may be associated with the development of IBS or exacerbation of IBS symptoms. Therefore, while there is a potential benefit associated with the use of cannabis, the improper use of cannabis poses some risk to the development and aggravation of IBS.

In 2020, a retrospective cohort study of 9,393 IBS patients (246 cannabis users and 9,147 nonusers), reported that cannabis use may decrease inpatient health-care utilization in IBS patients. Specifically, cannabis users were less likely to have upper gastrointestinal endoscopy and lower gastrointestinal endoscopy performed compared to non-cannabis users (Desai et al., 2020). Cannabis users experienced significantly shorter hospital length stays compared to non-cannabis users (Desai et al., 2020, Choi et al., 2022). In contrast, a study by Adeyinka et al., 2019, reported a higher likelihood of hospitalization among people who use cannabis conflicting with prior reports of a shortened stay. This paper also noted that an elevated state of anxiety might countermand the effects of cannabis on the endocannabinoid system (Adeyika et al., 2019). In conclusion, while cannabis as a therapy for IBS shows promise, the data remains inconclusive and more large-scale clinical trial research is needed.

In contrast to IBS, IBD research suggests that the use of small doses of cannabis can help reduce inflammation and reduces the overall IBD symptomology (McCallum et al., 2014, Perisetti et al., 2020). However, consumption of cannabis at high levels can exacerbate IBD symptoms and increase a patient's likelihood to be hospitalized due to severe IBD (UC and CD) (McCallum et al., 2014, Perisetti et al., 2020). Therefore, extreme cause should be taken when using cannabis as a therapy for IBD.

National Medical Organization Recommendations

In 2013, the National Institute of Diabetes and Digestive and Kidney Disease funded a study to examine the relationship between cannabinoids and fasting colonic motility. The study found that cannabinoid agonists reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. However, to date the American College of Gastroenterology and the National Institute of Diabetes and Digestive and Kidney Disease have made no recommendation regarding the use of medical cannabis as a treatment for IBS.

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REVIEW ARTICLE

Medical cannabis for the treatment of chronic pain and other disorders: misconceptions and facts

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KEY WORDS

cannabis, decriminalization, legalization, pain, pharmacotherapy

ABSTRACT

Recently, many countries have enacted new cannabis policies, including decriminalization of cannabis possession as well as legalization of medical and recreational cannabis. In this context, patients and their physicians have had an increasing number of conversations about the risks and benefits of cannabis. While cannabis and cannabinoids continue to be evaluated as pharmacotherapy for medical conditions, the best evidence currently exists for the following medical conditions: chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis. We also reviewed the current state of evidence for cannabis and cannabinoids for several other medical conditions, while addressing the potential acute and chronic effects of cannabis use, which are issues that physicians must consider before making an official recommendation on the use of medical cannabis to a patient. As the number of patient requests for medical cannabis has been increasing, physicians must become knowledgeable on the science of medical cannabis and open to a discussion about why the patient feels that medical cannabis may be helpful.

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Introduction Cannabis is one of the most commonly used substances worldwide. The cannabis plant contains over 400 chemical constituents, more than 100 of which are cannabinoids—chemicals unique to the cannabis plant. In the past 20 years, many countries have enacted new cannabis policies, including decriminalization of cannabis possession as well as legalization of medical and recreational cannabis. In this context of heightened discussion about the risks and benefits of cannabis, various countries have considered cannabis as a possible treatment for several debilitating medical conditions. While this has led to research on the medical indications for cannabis pharmacotherapy, many countries have pushed policy ahead of the science, opting not to wait for the rigorous scientific investigations to provide definitive evidence on the effectiveness of cannabis.

Legal status of medical cannabis in the United States and Poland In the United States, a growing number of states are considering laws legalizing medical cannabis. As of September 2017, 29 states and the District of Columbia have passed medical cannabis laws, and several others will likely vote on this issue in the next 1 or 2 years. Of note, there are 2 cannabinoids, dronabinol and nabilone, that are approved by the United States Food and Drug Administration for nausea and appetite stimulation. Poland has proceeded more cautiously in enacting medical cannabis laws. However, despite the lack of medical cannabis laws, Polish citizens are aware of the intense interest surrounding medical cannabis worldwide, and this has led many of them to ask their physicians about medical cannabis as a treatment for their own medical conditions.

Conditions with moderate- to high-quality evidence **Chronic pain and neuropathic pain** There is a small number of indications for which there is substantial evidence supporting the efficacy of medical cannabis pharmacotherapy (TABLE 1).[1] For example, there have been several studies showing that cannabis can be an effective

TABLE 1 Indications for medical cannabis and the quality of randomized placebo-controlled studies showing its efficacy

Indication	Quality of evidence
Chronic and neuropathic pain	Moderate to high[1-7]
Spasticity associated with multiple sclerosis	Moderate to high[8-22]
Seizure disorders	Moderate to high[23-31]
Gastrointestinal disorders	Moderate[32-39]
HIV and acquired immunodeficiency syndrome	Moderate[40-51]
Glaucoma	Low[52-56]
Posttraumatic stress disorder	Low[57-65]
Parkinson disease	Low[66-72]

pharmacotherapy for both chronic pain and neuropathic pain. The effectiveness of cannabis in treating pain was initially demonstrated in preclinical studies.[2,3] The endocannabinoid system was hypothesized to play an active role in controlling pain, and animal pain models were employed to support this hypothesis.[2] Delta-9-tetrahydrocannabinol (THC) was shown to produce analgesic and antihyperalgesic effects in mice.[4] These analgesic effects have been supported anecdotally in patients with chronic pain, and many clinical studies have aimed to investigate these effects in human models.

Whiting et al[5] conducted a systemic review and meta-analysis of randomized clinical trials of cannabis and cannabinoids. This review analyzed 28 studies assessing chronic pain in a total of 2454 participants. Overall, there was a higher reduction in pain measures with cannabinoids when compared with placebo, but most of these differences were not significant within each study. A recent report released by the National Academy of Science, Engineering, and Medicine in the United States stipulated that there was "conclusive or substantial evidence" that cannabis or cannabinoids are effective treatments for chronic pain.[6] Finally, another review determined that there was "high quality evidence," as demonstrated by multiple positive randomized placebo-controlled trials, to support the administration of cannabis or cannabinoid pharmacotherapy for treating chronic pain and neuropathic pain.[7]

Spasticity associated with multiple sclerosis As of October 2017, there have been at least 14 randomized clinical trials aimed at showing the efficacy of cannabis treatment for spasticity associated with multiple sclerosis. Many of these studies showed that cannabis or cannabinoids were helpful in relieving spasticity.[8-21] The American Academy of Neurology found these results promising, leading to the release of evidence-based guidelines for physicians recommending a cannabis oral extract containing both THC and cannabidiol (CBD) for the treatment of spasticity and pain associated with multiple sclerosis.[22] The symptoms most often found to be alleviated with cannabis were muscle stiffness, spasticity, and sleep disturbances.[11,13,16,18,20]

Seizure disorders Much of the evidence in favor of cannabinoids for epilepsy in children has been based on self-reports and anecdotal evidence.[23] Studies on the perceived efficacy of the use of CBD-enriched cannabis in children with epilepsy have shown a significant reduction of both the frequency and severity of seizures in a variety of seizure disorders.[24,25] In a study of 19 children, aged 2 to 16 years, with diagnoses of Dravet syndrome, Lennox–Gastaut syndrome, and idiopathic epilepsy, complete seizure freedom and an improvement of seizures was reported in 11% and 84% of patients, respectively.[24] In a survey-based study of 117 parents of children with infantile spasms and Lennox–Gastaut syndrome, 14% of patients were completely seizure-free, and 85% of parents reported a reduction in seizure frequency after cannabis pharmacotherapy.[25] Other beneficial effects of CBD in children with epilepsy syndromes include improved sleep, alertness, and mood, as well as an increased appetite.[24-26] In the first reported double-blind placebo-controlled trial of a cannabinoid for Dravet syndrome, CBD significantly reduced the median frequency of convulsive seizures per month and significantly improved the patient's overall condition measured on the Caregiver Global Impression of Change scale, when compared with placebo.[27]

Studies on the effectiveness of cannabinoids in adults with epilepsy have provided mixed results. It was shown that men who used cannabis up to 90 days before hospitalization were at a significantly lower risk for a new seizure than men who did not use cannabis.[28] In another study of adults with epilepsy, most patients associated cannabis use with a reduction in the severity and frequency of seizures.[29] Meanwhile, a recent survey study of patients in a tertiary epilepsy clinic showed that cannabis did not affect the frequency or severity of seizures.[30] While there is much published research regarding the effects of cannabinoid use on seizures in adults, most studies have not been placebo-controlled and have been largely anecdotal, underscoring the need for randomized controlled trials.[31]

There have been only 4 placebo-controlled studies that examined the effectiveness of cannabinoids for epilepsy, but they had small sample sizes and some methodological challenges.[23] While cannabinoids were shown to improve symptoms of epilepsy, the data were insufficient to draw any firm conclusions.

Conditions with low-quality evidence **Gastrointestinal disorders** Cannabinoids affect parts of the intestine through a similar mechanism as certain opioids that are currently used in the treatment of irritable bowel syndrome (IBS). This makes cannabinoids a potentially effective treatment.[32] An endocannabinoid deficiency may be an underlying factor in disorders such as IBS, further suggesting that cannabinoids may provide relief to patients with this condition.[33,34] Cannabinoids appear to target inflammation and diarrhea associated

with IBS. Many patients report that cannabis relieves symptoms of gastrointestinal disorders, such as nausea, spasms, and low appetite.[35]

As with many other indications, there have been very few studies looking at how patients with Crohn disease (CD) respond to cannabis. Most therapies for CD are targeted towards reducing inflammation. However, in some patients, these medications do not eliminate symptoms such as chronic diarrhea, and this is where the use of cannabinoids may provide relief. Research from the last several decades has suggested that cannabis has anti-inflammatory properties.[36,37] CBD is also a promising medication in the treatment of inflammatory bowel diseases; it has been shown to alleviate symptoms and potentially increase the efficacy of other anti-inflammatory drugs that are typically indicated for ulcerative colitis and CD.[38] A small-scale placebo-controlled pilot study showed that cannabis provided significant clinical benefits in patients with CD, such as improved appetite and sleep.[39]

HIV and acquired immunodeficiency syndrome Over the last few decades, several studies have been conducted that examined the use of medical cannabis in patients with HIV or acquired immunodeficiency syndrome. The current use of medical cannabis in this population has been investigated in numerous studies, but the results have been mixed. The rates of cannabis use among HIV-positive patients have been reported to range from 15% to 44%.[40-46] The most common reasons for these patients to use cannabis were to improve appetite, gain weight, and decrease nausea.[41,45] While cannabis use is relatively common in this population, there have been only a handful of clinical trials demonstrating significant effectiveness of medical cannabis in treating HIV-related symptoms. Among these studies, evidence was somewhat strong in favor of medical cannabis for HIV-induced neuropathic pain,[47-49] and of cannabinoid medications, such as dronabinol, for an increased appetite in HIV-positive patients.[50] While there are benefits from using medical cannabis in terms of pain reduction and appetite stimulation, physicians and patients should be aware that some evidence shows that frequent cannabis use may be associated with a decrease in cognitive function in patients with a more advanced stage of HIV.[51]

Glaucoma The use of cannabis to help treat glaucoma has been explored since the early 1970s.[52] Although cannabis seemed promising, mostly due to findings showing that it decreases intraocular pressure in both healthy and glaucomatous eyes, further reviews have shown limited treatment efficacy.[52,53] The American Academy of Ophthalmology does not support the use of cannabis for glaucoma, owing to the limited duration of action of cannabis.[54,55] Furthermore, even though cannabis decreases intraocular pressure temporarily, it also lowers blood pressure. This could lead to a decrease in blood flow to the optic nerve, increasing the risk for loss of vision.[56] Cannabis also has a more serious side effect profile than many current glaucoma treatments; therefore, until more evidence for its efficacy becomes available, most ophthalmologists would recommend that patients continue traditional treatments instead of cannabis for glaucoma.

Posttraumatic stress disorder There is a plausible mechanism to support the possible use of cannabinoids, especially CBD, as pharmacotherapy for posttraumatic stress disorder (PTSD).[57] Many studies have examined the use of medical cannabis in patients with PTSD, but there have been no large-scale randomized controlled trials on the effectiveness of medical cannabis in the treatment of PTSD.[58] Cannabis is commonly used in patients with PTSD, often as a coping mechanism for symptoms such as hyperarousal, intrusive thoughts, and sleep problems.[59-62] However, in a longitudinal cohort of 2276 United States veterans with PTSD, cannabis use was associated with greater severity of PTSD symptoms, violent behavior, and higher rates of alcohol and drug use.[63] By contrast, Greer et al[64] described a 75% reduction in scores on a PTSD symptom scale for individuals who obtained a medical cannabis card to alleviate such symptoms. Individuals with more severe symptoms of PTSD generally reported greater cannabis use problems, cravings, and severity of cannabis withdrawal.[65]

Parkinson disease Anecdotal evidence has led to the study of cannabis and cannabinoids as pharmacotherapy for Parkinson disease. A limited number of studies have been conducted that suggest cannabinoids may improve symptoms associated with Parkinson disease, but most of these studies were observational and did not contain a control group.[66-68] In addition to these observational studies, 4 randomized controlled clinical trials studied the effects of cannabinoids on parkinsonian symptoms, but none of them showed significant improvements in motor symptoms.[69-72]

Risks associated with cannabis use Although physicians may be tempted to recommend cannabis for indications for which there is some evidence of its efficacy, there are many other issues that they must consider before making an official recommendation. Besides the question of whether a physician has the full legal ability to recommend cannabis, there are also possible adverse events associated both with short- and long-term use of cannabis that should be taken into account.[73] Acute cannabis intoxication leads to interference with perceptions of memory and time as well as with motor functions. Cannabis worsens existing anxiety or mood disorders, and, in some instances, it can increase the likelihood that one will develop these disorders.[74-76] Cannabis has also been shown to be strongly associated with the development of psychotic disorders in those with a genetic predisposition to such conditions.[77]

Cannabis use during adolescence can lead to permanent changes in developing brains. Individuals who regularly used cannabis during adolescence had lower gray matter density in both the hippocampus and corpus callosum.[78] Early and regular cannabis use was also associated with up to an 8-point decline in intelligence quotient over time in a large longitudinal study.[79] A preliminary study also showed structural brain changes in the amygdala and nucleus accumbens in occasional cannabis users.[80] Although more research needs to focus on how cannabis affects the developing brain, these preliminary results have deterred many physicians from recommending cannabis to adolescent patients.

How physicians should approach medical cannabis As medical cannabis laws continue to be passed internationally, the number of patient requests for medical cannabis will likely increase. Physicians must take the same steps with these patients as they would with prescribing any other medications to ensure that medical cannabis is recommended appropriately and as safely as possible.

First and foremost, medical cannabis recommendations should be offered to patients who have a condition that is known to be responsive to cannabis, with moderate- to high-quality evidence. Patients who have medical conditions that are known to be exacerbated by cannabis use should not be recommended medical cannabis. Due to the potentially serious adverse effect profile associated with cannabis in comparison with some other treatments, the physician must discuss the risks and benefits of medical cannabis use with the patient.

Physicians should ask their patients why they believe cannabis may be effective in helping their condition. It may be that patients are already using cannabis to help alleviate some symptoms, in which case the physician must ask how it has affected them so far. If the typical first- and second-line treatments for the condition they are attempting to treat have not yet been attempted, physicians should explain that to date these other treatments have more data supporting their efficacy than cannabis. Even if cannabis does not end being used for treatment, engaging in a conversation with patients about their hopes for cannabis treatment increases the likelihood that they will receive treatments, perhaps other than medical cannabis, for their medical conditions that might not have been treated otherwise.

Conclusion As research into cannabis and its efficacy as a medication continues, medical professionals should stay informed on these findings. Cannabis and cannabinoids are promising therapeutics in several areas of medicine. Professionals should rely on facts and research, not public opinion, to inform medical decisions. Cannabis is often used for recreational purposes, but this should not affect how physicians view data collected on its efficacy in treating certain medical conditions.

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REVIEW ARTICLE

The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome

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Abstract *Irritable bowel syndrome (IBS) is a spectrum of disorders characterized by abdominal discomfort and pain, associated with altered bowel habits. Though gut motility, secretion and sensation may be altered in patients with IBS, the pathophysiology of this condition remains to be fully understood. The endocannabinoid system is involved in the regulation of numerous gastrointestinal functions including motility, sensation and secretion under both physiological and pathophysiological conditions. Activation of cannabinoid (CB)$_1$ and CB$_2$ receptors under various circumstances reduces motility, limits secretion and decreases hypersensitivity in the gut. Drugs that alter the levels of endocannabinoids in the gut also reduce motility and attenuate inflammation. In this review, we discuss the role of the endocannabinoid system in gastrointestinal physiology. We go on to consider the involvement of the endocannabinoid system in the context of symptoms associated with IBS and a possible role of this system in the pathophysiology and treatment of IBS.*

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Abbreviations: 2-AG, 2-arachidonyl glycerol; CB$_1$, cannabinoid-1; CB$_2$, cannabinoid-2; ChAT, choline-acetyltransferase; EMT, endocannabinoid membrane transporter; FAAH, fatty acid amide hydrolase; HAPCs, high-amplitude propagated contractions; IBS, irritable bowel syndrome; MAP kinase, mitogen-activated protein kinase; MAGL, monoacylglycerol lipase; SNP, single nucleotide polymorphism; THC, tetrahydrocannabinol; TNBS, trinitrobenzene sulphonic acid; TRPV1, transient receptor potential vanilloid receptor 1.

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder characterized by abdominal discomfort, pain and altered bowel habits.[1,2] The most recent diagnostic criteria, the Rome III criteria, define the syndrome as recurrent abdominal pain or discomfort at least 3 days per month over 3 months, which is associated with two or more of the following characteristics: (i) improvement with defecation, (ii) onset associated with a change in stool frequency and (iii) onset associated with a change in stool form. Symptom patterns can be divided into diarrhoea predominant (D-IBS), constipation predominant (C-IBS) and a mixed pattern (M-IBS).[2] The disorder is incredibly common, with 10–20% of adults throughout the developed world having symptoms consistent

with IBS.[3] Standard clinical investigations such as endoscopy or blood tests generally show no abnormalities, and thus diagnosis is made based on clinical history and patient symptoms.[4]

The pathophysiology of IBS is complex. The current understanding incorporates biological and psychosocial factors as playing a role in the onset and propagation of symptoms, and is known as the biopsychosocial model.[4] Various abnormalities have been found in different groups of IBS patients, including altered gut motility, visceral hypersensitivity, disturbances of brain–gut interactions and central processing of visceral afferent information. In addition, a host of other autonomic, hormonal, psychological, environmental and genetic factors probably contribute to IBS.[4] It is unlikely that a single unifying hypothesis will explain the pathophysiology in all IBS patients; it is thus viewed as an interaction of a variable number of these factors for any given patient.

THE ENDOCANNABINOID SYSTEM IN THE GASTROINTESTINAL TRACT

Cannabinoid receptors

In 1990, the first cannabinoid receptor was cloned by Matsuda *et al.* and named CB_1.[5] Subsequently, a second cannabinoid receptor (CB_2) was identified in 1992, sharing a 48% homology with the CB_1 receptor.[6] The discovery of the endogenous ligands for these receptors provided the basis for the establishment of the 'endocannabinoid system', a term first coined by Di Marzo and Fontana in 1995.[7]

Since then an additional splice variant of the CB_1 receptor (CB_{1A}) has been reported, but its actual function is not yet clear.[8] Furthermore, several other putative CB receptors have been identified, with GPR55 and GPR119 being the most promising CB receptor candidates.[9] The established CB receptors show a distinct distribution in the gastrointestinal tract with CB_1 and recently, CB_2 receptors, being described in the enteric nervous system.[10–12] CB_1 receptors are also localized on epithelial cells[13] and CB_2 receptors are present on immune cells.[6,13] Both receptors are coupled negatively through G_i/G_o-type G proteins to adenylate cyclase and positively to mitogen-activated protein kinase (MAP kinase),[6] but little is known regarding the exact cellular mechanisms involved after their activation in the gastrointestinal tract. Currently, it is not known where the putative novel CB receptors are localized in the gastrointestinal tract.

Immunohistochemistry and functional studies have shown that CB_1 receptors are distributed on intrinsic and extrinsic nerves of the gastrointestinal tract. The intrinsic neurons are located in the myenteric and submucosal plexuses of the enteric nervous system. These plexuses consist of motor neurons, interneurons and primary afferent neurons, and CB_1 receptors appear to be localized on all of these functional classes. Using immunohistochemical staining and co-localization analysis, CB receptors were found on different neuronal subtypes of the enteric nervous system. Double-labelling of CB_1 immunoreactivity with choline-acetyltransferase (ChAT), calretinin and substance P suggests that CB_1 is present on excitatory motor neurons,[10,14] some classes of interneurons and enteric sensory neurons. In addition, the presence of CB_1 receptors on interneurons has been suggested by functional studies.[15] Co-localization with calbindin, an immunohistochemical marker for intrinsic primary afferent neurons, further supports the possibility of CB_1 expression in these enteric sensory neurons.[10] CB_1 receptor is not found on neurons containing nitric oxide synthase.[10,14] CB_2 receptor mRNA was shown in the oesophagus, stomach and ileum of rats and with Western blotting CB_2 receptor protein expression was shown in the rat ileum.[11,12] Recently, using immunohistochemistry, CB_2 receptors were localized on most neurons of the enteric nervous system of the rat ileum,[11] though again it is largely absent from neurons containing nitric oxide synthase.

Endogenous cannabinoid receptor ligands – endocannabinoids

Several endocannabinoids have been reported with affinities to both CB_1 and CB_2 receptors.[6] The first endocannabinoid isolated in the gastrointestinal tract was anandamide, which is not only an endocannabinoid but also an endovanilloid and activates CB_1, CB_2 and TRPV1 (transient receptor potential vanilloid 1) receptors.[6,16,17] The second endocannabinoid isolated from the gut was 2-arachidonyl glycerol (2-AG).[18] Pharmacological studies have demonstrated effects of other putative endocannabinoids on gastrointestinal tissues (for example, noladin ether, *N*-arachidonoyldopamine and virodhamine)[19–21] but evidence that these molecules are present in the gastrointestinal tract is currently lacking.

Endocannabinoid synthesis and degradation

Several components of endocannabinoid metabolism have been characterized. Endocannabinoids like anandamide and 2-AG are synthesized on demand from fatty acid precursors by specific phospholipases

and are then released to the extracellular space.[22–25] The actions of endocannabinoids are terminated intracellularly where enzymatic degradation takes place.[26] Endocannabinoids freely diffuse from the extracellular space through the plasma membrane and additionally an endocannabinoid membrane transporter (EMT) is thought to carry endocannabinoids into the cell for degradation, but it has not yet been cloned and its existence is still controversial.[27] However, drugs that are proposed to be EMT inhibitors have been synthesized.[24] Anandamide breakdown is catalyzed by the enzyme fatty acid amide hydrolase (FAAH), a membrane bound protein,[22,26,28] whereas 2-AG is primarily degraded by the enzyme monoacylglycerol lipase (MAGL). Fatty acid amide hydrolase is present in the gastrointestinal tract, and in mice FAAH mRNA expression is the highest in the duodenum and the distal colon.[29] Monoacylglycerol lipase mRNA and protein was recently shown to be present in the enteric nervous system.[30]

The exact source of endocannabinoids and the specific stimulus for endocannabinoid release in the gut is still unknown. Furthermore, it is unclear whether there is regulation of the expression of endocannabinoid degrading enzymes in the gut, though there are alterations in the levels of endocannabinoids in states of inflammation and in celiac disease.[31,32] Local release of endocannabinoids seems likely and *in vitro* in stimulated cell cultures of dorsal root ganglia anandamide can be released,[33] suggesting that primary afferents can release the molecules. Whether release into the extracellular space involves an active transport mechanism or uncontrolled passive diffusion after their synthesis is unknown. It seems likely that the enteric nervous system is an important source of endocannabinoids, but currently, no information on endocannabinoid release in the gut is available. Macrophages, platelets and epithelia could also be a source of endocannabinoids, especially in states of inflammation.[34,35] Therefore, the peripheral actions of endocannabinoids in the gastrointestinal tract could also be due to a contribution from circulating sources. An overview of the endocannabinoid system is shown in Fig. 1.

IRRITABLE BOWEL SYNDROME, MOTILITY AND ENDOCANNABINOIDS

Studies assessing gut motility in IBS have recently been reviewed.[4,36] Focusing specifically on the colon and rectum, some findings have been shown fairly consistently. Colonic transit[37] and high-amplitude propagated contractions (HAPCs)[38,39] appear to be increased in D-IBS, whereas transit may be slower with less HAPCs in C-IBS.[40,41] Exaggerated phasic colonic contractile responses to a meal have also been shown consistently in IBS patients.[38,39,42] It is unclear, however, whether these findings explain the symptoms, the

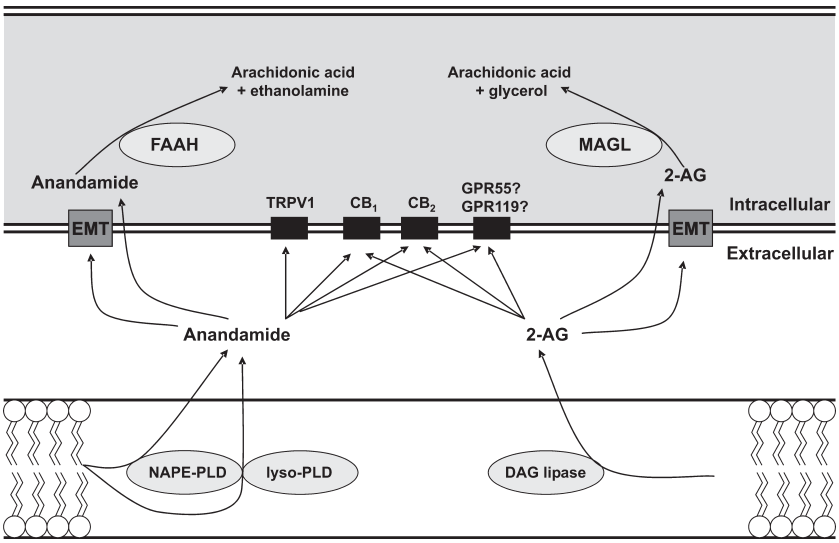

Figure 1 The endocannabinoid system. Biosynthesis of endocannabinoids involves multiple enzymatic steps where endocannabinoids are synthesized from membrane phospholipids. The final step of the biosynthetic pathways involve the enzymes *N*-acyl-phosphatidylethanolamine (NAPE-PLD) and lyso-PLD for anandamide and diacylglycerol-lipase (DAG-lipase) for 2-arachidonylglycerol (2-AG). After diffusion to the extracellular space the endocannabinoids act on cannabinoid (CB_1), CB_2, transient receptor potential vanilloid 1 (TRPV1) and possibly on G-protein-coupled receptors (GPR) 55 and 119. Their action is terminated by uptake in the intracellular space by passive diffusion or a specific endocannabinoid membrane transporter (EMT) and enzymatic degradation by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol-lipase (MAGL).

patients with IBS experience. Considering that shifts in bowel habit are a feature of IBS, even between the extremes of stool consistency (for example, from constipation-predominance to diarrhoea–predominance),[43] it remains questionable whether transit and HAPC frequency alone account for these symptoms.[44]

A substantial amount of evidence shows that stimulation of CB_1 receptors slows motility throughout the gut, including the colon.[45–47] This is in contrast to CB_2 receptors, which do not appear to have a significant effect on gut motility under physiological circumstances, but potentially regulate motility in pathophysiological states.[11,18] CB_1 receptors are located prejunctionally on cholinergic nerves and inhibit acetylcholine release when activated. These findings have been reviewed in detail elsewhere.[45–47] *In vitro* studies in multiple species have shown that CB_1 receptor agonists inhibit contraction of muscle throughout the gastrointestinal tract. These effects are largely reversed by CB_1 receptor selective antagonists demonstrating the involvement of CB_1 receptors.[12,48–50] Similar findings were reported in human colonic tissue *in vitro*, suggesting that the endocannabinoid mechanisms in control of motility, which have been characterized in laboratory animals are similar in humans.[51–54]

The physiological involvement of the endocannabinoid system in the regulation of gastrointestinal motility was demonstrated *in vitro* and *in vivo*. Treatment of animals with CB_1 receptor antagonists resulted in increased motility, suggesting that gastrointestinal motility is under a tonic suppression by the endocannabinoid system.[15,55,56] In addition, studies using FAAH blockers or EMT inhibitors *in vivo* demonstrate a slowing of gastrointestinal motility.[29] These results further support the concept that the endocannabinoid system is tonically active under physiological conditions, once again stressing the important role of the endocannabinoid system in the regulation of motility.[29]

In vivo studies in rodents have shown inhibition of intestinal and colonic transit by CB_1 receptor agonists[57] and increased transit with the CB_1 receptor antagonist rimonabant.[58] In humans, the CB_1/CB_2 receptor agonist dronabinol [synthetic Δ^9-tetrahydrocannabinol (THC)] taken orally decreased postprandial colonic tone and increased compliance[59] but did not affect colonic transit.[60] Clinical trials with selective CB receptor agonists and/or antagonists are required to translate present knowledge from laboratory animals to humans.

The only large clinical trials with CB_1 receptor antagonists were performed in patients with metabolic disorders and obesity.[61,62] From these trials, it seems very likely that gastrointestinal motility in humans is under control of the endogenous cannabinoid system. The clinical trials using the CB_1 antagonists rimonabant and taranabant showed that diarrhoea and other gastrointestinal motor side effects like nausea and vomiting being frequently observed, though often transient.[61–63]

It thus appears that the effects of the cannabinoid system on motility in humans are similar to those in rodents. Cannabinoid agents (agonists or antagonists) have not been studied clinically in IBS patients, but this may be worthwhile. From a motility standpoint, cannabinoid agonists might be helpful in conditions associated with diarrhoea and cannabinoid antagonists might be helpful in conditions associated with constipation. However, it has to be taken into account that the use of CB_1 receptor agonists is limited by the central psychotropic side effects. It is also important to point out that CB_1 receptor antagonists such as rimonabant and taranabant, are also accompanied by central side effects, since in clinical trials with rimonabant and taranabant, anxiety and a risk of depressive symptoms were noted.[62,63] CB_2 receptor-mediated effects on motility are less well characterized but there is strong evidence that these drugs alter motility in pathophysiological conditions and should therefore be considered in IBS. It remains speculative whether peripherally restricted compounds like Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone are devoid of the central side effects and would therefore be suitable for use in humans.[64] Another option is drugs targeting endocannabinoid degradation like FAAH blockers and EMT inhibitors, which increase endogenous cannabinoid levels and seem to be largely free of central side effects. Drugs targeting endocannabinoid degradation are presently developed by different companies (see below). Furthermore, drugs targeting endocannabinoid generation could be useful but no such drugs have yet been described.

THE ENDOCANNABINOID SYSTEM IN VISCERAL HYPERSENSITIVITY AND PAIN

Abdominal pain is a common symptom of gastrointestinal diseases and is influenced by both peripheral and central mechanisms of pain perception and transmission. In functional gastrointestinal disorders, like IBS, there is strong evidence for peripheral and central neural structures being involved in mechanisms resulting in visceral hypersensitivity.[65–67] Acute or chronic inflammation has been suggested as a possible trigger for the development of IBS.[66,68,69] Cannabinoids have well-described analgesic effects in various animal models of acute and chronic pain.[70] The finding that components of the endocannabinoid system are involved in pain transmission and modulation makes the endocannabi-

noid system a promising target for therapies in disorders where visceral pain is prominent.[71]

Animal models of visceral pain recently provided evidence that the endocannabinoid system is involved in visceral sensation.[72,73] Both CB_1 and CB_2 receptor agonists reduce the visceromotor responses in rodents to graded colorectal distention.[73] Two publications independently showed that after inducing hyperalgaesia by rectal instillation of trinitrobenzene sulphonic acid (TNBS), lower doses of CB receptor agonists were needed to reduce sensitivity to colorectal distention.[72,73] This clearly indicates that during hyperalgesic states the endocannabinoid system is more sensitive, and suggests that in these states, like IBS, patients might be more sensitive to cannabinoid treatment.

Whether the endocannabinoid system is involved in the pathophysiology of IBS is unknown, but as the CB_1 receptor antagonist rimonabant increases hypersensitivity in rectal distention models, a role of the CB_1 receptor in the physiological regulation of visceral sensitivity is conceivable.[73] In contrast, the CB_2 receptor antagonist SR 144528 did not alter thresholds to colorectal distention in these models making a physiological involvement of the CB_2 receptor in the regulation of visceral hypersensitivity unlikely.[72,73]

The location of the CB receptors involved in the regulation of visceral hypersensitivity remains unclear, but for the CB_2 receptor a peripheral site seems likely, as CB_2 receptor activation reduces mesenteric afferent activity in response to bradykinin in mice *in vivo*, whereas such influences of CB_1 receptors on mesenteric afferent neuronal activity was not shown.[74]

Whether these findings can be translated into human disease remains to be shown. In healthy volunteers, dronabinol slightly increased sensory ratings for pain during phasic colonic distention, whereas thresholds for gas sensation were unchanged.[59] Interestingly, this occurred despite an increase in colonic compliance and decreased postprandial colonic tone. Further research is needed to clarify whether the endocannabinoid system is involved in the origination, perpetuation, or resolution of painful symptoms in patients with IBS and whether drugs acting at CB receptors or other elements of the endocannabinoid system reduce visceral hypersensitivity in patients with IBS.

It is important to keep in mind that endocannabinoids, like anandamide, also act as agonists at other receptors, including the TRPV1 receptor and other members of the TRP family of receptors. It is worth mentioning that involvement of the TRPV1 receptors in visceral hypersensitivity was reported using animal models of colorectal distension.[75] TRPV1 immunoreactivity was reported in dorsal root ganglia and in the gastrointestinal tract,[76] which is consistent with them having a role in gastrointestinal pain transmission. A recent publication identified that cannabinoids exert analgesic effects in postinflammatory pain models by activation of Transient Receptor Potential A1 receptors, once again highlighting the overlap of the endocannabinoid system and the endovanilloid system.[77]

Evidence also exists for a role of TRPV1 in visceral hypersensitivity in humans. Immunohistochemical studies in patients with rectal hypersensitivity showed increased TRPV1 staining suggesting an activated endovanilloid system[78] and a recent study confirmed the increase of TRPV1 positive nerve fibres in colonic biopsies of patients with IBS and abdominal pain.[79]

It is presently unknown whether raising endocannabinoid levels with FAAH blockers or combination treatment with agonists at CB_1, CB_2 and TRPV1 receptors show additive or synergistic effects on rectal pain sensation. This needs to be addressed in future animal models, since if so, combination therapy could help to limit central side effects. Additionally, it has not been investigated whether compounds like anandamide which acts on both CB_1 and TRPV1 receptors as an agonist, results in analgesic or algesic effects, as these effects would be elicited upon activation of either the CB_1 or the TRPV1 receptor and the level of expression of these receptors under pathophysiological conditions may influence the overall dominant response.

ENDOCANNABINOIDS AND THE ENDOCANNABINOID SYSTEM IN SECRETION

Fluid secretion into the intestinal lumen contributes to digestive processes and the passage of gut contents. A role of intestinal secretion in the pathophysiology of IBS is still controversial.[80] In the distal ileum and colon, excess fluid is absorbed limiting water loss in the stool and contributing to normal bowel movements. Any failure to absorb water or excessive secretion leads to diarrhoea. The control of secretion and absorption is tightly regulated by neural, humoral and paracrine factors. Under physiological conditions cannabinoids inhibit intestinal secretion *in vitro* when administered exogenously.[81] It has been shown that CB_1 receptors are present in the submucosal plexus where they act to limit cholinergic nerve-mediated secretion. Interestingly, in the guinea pig it was reported that CB_1 receptors, present on capsaicin-sensitive extrinsic primary afferents, mediated the inhibitory actions of exogenous agonists on secretion assessed in isolated ileal preparations.[82] Rats given rimonabant had higher fecal water content than

animals treated with vehicle.[58] Similarly, they also had higher levels of fluid accumulation in the small intestine. Under pathophysiological conditions, rimonanbant enhanced cholera toxin-induced fluid accumulation, whereas the CB_2 receptor antagonist SR144528 had no effect.[83] Conversely, the EMT inhibitor VDM11 reduced cholera toxin-induced fluid secretion, suggesting the endocannabinoids released in the wall of the gut normally limit the degree of secretion through activation of CB_1 receptors. In both these studies, the authors provided evidence that these actions were mediated peripherally, presumably at the level of the enteric nervous system.

The role of endocannabinoids in IBS-related secretory abnormalities or in the control of secretion in animal models of IBS has not been evaluated. Given the potential role of the cannabinoid system, notably CB_1 receptors, in regulating epithelial function in the gut,[84] these studies are warranted.

ENDOCANNABINOIDS AND THE ENDOCANNABINOID SYSTEM IN INFLAMMATION

Postinfectious IBS is one accepted subgroup in IBS accounting for between 4% and 30% of IBS patients.[69,85,86] A recent meta-analysis revealed that the odds of developing IBS are increased sixfold after acute gastrointestinal infection[85] but some recent studies suggest lower odds ratios.[87,88] In addition, morphological studies indicate that inflammatory cell infiltration of the intestinal wall can be observed in many patients with IBS.[89,90] In this context, the potential role of the endocannabinoid system in the pathophysiology of intestinal inflammation is of interest, with the perspective that targeting the endocannabinoid system might protect against intestinal inflammation. Most of the information discussed here comes from animal models mimicking features of inflammatory bowel disease (IBD) thus the results must be interpreted cautiously with respect to IBS.

Gastrointestinal anti-inflammatory mechanisms of cannabinoids are presently characterized only in animal models. Activation of the endocannabinoid system has been described in a model of acute inflammation. The administration of croton oil in mice, increased the expression of CB_1 receptors and the CB_1/CB_2 receptor agonist WIN 55,212-2 was more effective in slowing motility in inflamed animals compared to control.[91] This strongly suggests a physiological protective role of the endocannabinoid system in inflammation-associated motility alterations, but there is little information on the involvement of possible downstream mechanisms.[55,91] Treatment with exogenous cannabinoids attenuates inflammation in experimental models of colitis and treatment with selective agonists in receptor deficient mice ($CB_1^{-/-}$ and $CB_2^{-/-}$), show that both CB_1 and CB_2 receptors are involved in the protective mechanisms against colitis that are activated by exogenous cannabinoids,[31,92–94] a finding that is further supported by CB_1 receptor upregulation and increased levels of anandamide during colitis.[31,93] Anandamide is an endovanilloid and, consistent with this, the TRPV1 receptor is also involved in protective mechanisms.[95–97] The involvement of not only CB_1 but also CB_2 receptors in protective mechanisms against TNBS colitis highlights the importance of the entire endocannabinoid system in colitis. Interestingly, the protective actions of CB_2 receptor agonists were also observed in the oil of mustard model of colitis, which has a substantial neurogenic component,[92] suggesting the involvement of neuronal mechanisms in the protective actions. This highlights the potential for cannabinoids to act on various elements in the gut wall to regulate inflammatory processes.[92,98–101]

Aside from direct receptor activation, there is evidence that manipulation of endocannabinoid degradation elicits beneficial effects. Attenuation of endocannabinoid degradation can be accomplished by blocking endocannabinoid membrane transport and/or by inhibiting FAAH (genetically); both potentially lead to elevated levels of endocannabinoids and have beneficial actions in colitis.[31,94]

The mechanisms of cannabinoid-mediated protection in colitis are less well described, and presently increased epithelial wound healing has been suggested,[13] but increased epithelial wound healing does not explain all the actions of cannabinoids. In other models of inflammation, cannabinoids have been shown to reduce inflammation by reducing chemotaxis of activated T cells, attenuating proinflammatory cytokine production and by shifting the balance of T-cell activation from Th1 to Th2 type responses,[102–104] but such mechanisms have not been shown for the gastrointestinal tract or patients with IBS. Many of these findings are attributed to CB_2 receptor activation, and the role of CB_1 receptors has either not been shown or not been investigated.

In summary, the endocannabinoid system is physiologically involved in mechanisms of protection against intestinal inflammation and several studies suggest activation of the endocannabinoid system during inflammation. Agents affecting the cannabinoid system have not yet been studied for their anti-inflammatory properties in humans due to the incomplete characterization of the anti-inflammatory

mechanisms and side effects of CB receptor agonists. However, manipulation of this system with pharmacological approaches offers the potential to reduce inflammation without utilizing CB receptor agonists. The potential role of the endocannabinoid system in the pathophysiology of postinflammatory IBS has yet to be determined as well as the possible treatment of these states with cannabinoids.

THE ENDOCANNABINOID SYSTEM AND GUT MICROBIOTA

The gut microflora is comprised numerous bacterial species that reside in the lumen along the length of the gut. Certain probiotics have been reported to alter abdominal symptoms associated with IBS in humans[105] and reduce visceral hypersensitivity in rats and mice.[106,107] In a recent study, a link has been made between gut microflora and the expression of CB_2 receptors.[108] In cell culture experiments, *Lactobacillus acidophilus* increased CB_2 mRNA expression in epithelial cells compared to untreated cells or cells treated with other bacteria. Enhanced CB_2 (and mu opioid) receptor expression was upregulated after chronic treatment (15 days) with *Lactobacillus acidophilus in vivo*. Interestingly, the CB_2 receptor antagonist AM630 reduced the *Lactobacillus acidophilus*-induced reduction in rectal sensitivity, suggesting that contact of *Lactobacillus acidophilus* with epithelial cells is able to induce CB_2 expression and contribute to the restoration of the normal perception of visceral sensation. It is presently unknown whether the normal gut microbiota alters CB_2 expression and thus visceral sensitivity and whether acute or chronic alterations of the gut microbiota, as they occur in patients with postinfectious IBS results in ongoing changes of CB_2 expression and are involved in the pathophysiology of IBS. There is presently no information available whether bacteria cause alterations of CB_1, FAAH or MAGL expression and whether such alterations are involved in the regulation of visceral sensitivity.

Though CB receptor activation is known to be involved in numerous immune mechanisms, no further information is available whether the endocannabinoid system is involved in regulation of gut microbiota or to the extent gut microbiota alters the activity of the endocannabinoid system. The above mentioned study reveals such interactions and concomitant functional alterations, but further studies are needed to establish the potential pathophysiological role of the endocannabinoid system in patients with postinfectious IBS or functional alterations associated with small intestinal bacterial overgrowth.

CANNABINOID DRUG DEVELOPMENT

Dronabinol (Marinol®; Solvay Pharmaceuticals, Bruxelles, Belgium), an agonist of both CB_1 and CB_2 receptors, is marketed as an appetite stimulant and anti-emetic in many countries. The CB_1 receptor antagonist Rimonanbant (Acomplia®; Sanofi-Aventis, Paris, France) is available to treat obese patients in some countries, notably in Europe. In Canada, the oromucosal spray containing THC and cannabidiol is marketed under the brand name Sativex® (GW Pharmaceuticals, Salisbury, UK) for the alleviation of pain and spasticity in multiple sclerosis patients and is expected to be approved in other countries soon.

Cannabinoid research is a hot topic not only amongst academic institutions but also in industry, including global pharmaceutical companies such as AstraZeneca, Bayer AG, Bristol-Myers Squibb, Eli Lilly, Indevus Pharmaceuticals, Merck & Co, Novartis, Pharmos, Pfizer, Sanofi-Aventis, Schering, SmithKline Beecham, GW Pharmaceuticals and Solvay Pharmaceuticals. A patent search (Google patent search) shows that numerous pharmacological inventions in this field were filed in recent years with gastrointestinal indications forming part of nearly all of them. Some of the inventions are focused on gastrointestinal uses, with agents affecting gastrointestinal motility, gastrointestinal pain and gastrointestinal inflammation indicating the high impact industry attributes to targeting the endocannabinoid system in functional gastrointestinal disorders. These pharmacological inventions include novel receptor-selective agonists and antagonists with higher selectivity and higher potency and also drugs such as neutral antagonists (devoid of inverse agonist properties), agonists specific for peripheral receptors or agonists with limited blood–brain barrier penetration. Other interesting compounds include drugs with CB_2 agonistic/CB_1 antagonistic properties, novel non-psychotropic cannabinoids and cannabinoids with alterations in absorption characteristics and improved tissue penetration. In addition, patents have been filed for drugs acting on endocannabinoid degradation such as novel FAAH inhibitors and EMT blockers. Presently, no information is available whether these drugs are already tested in Phase 1 or Phase 2 clinical trials.

THE ENDOCANNABINOID SYSTEM IN THE GENETICS OF IBS

Though the pathophysiology of IBS remains uncertain, hereditary factors are likely to have a role.[109] Studying single nucleotide polymorphism (SNP) phenotype associations is one way to study hereditary factors.

Recently, an SNP in the FAAH gene (C385A), which was shown to result in enhanced sensitivity to proteolytic degradation of FAAH,[110] was shown to be associated with changes in colonic transit time and with distinct phenotypes of IBS.[111] Though unproven, it may be hypothesized that in subjects homozygous for the FAAH SNP, endocannabinoid metabolism is impaired and degradation of endocannabinoids is reduced, which might result in increased local endocannabinoid levels and subsequently altered gastrointestinal function. In this study, the FAAH SNP was significantly associated with accelerated colonic transit in patients with D-IBS. However, in other patient groups (C-IBS; M-IBS, functional dyspepsia) no associations with colonic transit, gastric emptying or rectal sensation thresholds in rectal barostat investigations were found. Interestingly, further associations of the FAAH SNP were found for D-IBS and M-IBS phenotype, but not with C-IBS or functional dyspepsia phenotype. The functional alterations caused by the FAAH SNP remain to be fully characterized, limiting further mechanistic interpretation of these data; however, this novel observation opens the door for more detailed studies in the future.

Though these findings support the general hypothesis that the endocannabinoid system may be relevant in the pathophysiology of IBS, some caution is warranted. Given the small number of individuals homozygous for this SNP, the small numbers of patients included in this genetic association study, and the fact that significance testing is performed against the mixed heterozygous/homozygous group and not against homozygotes only, these observations have to be regarded as preliminary. It is worth mentioning that these genetic findings are unique to IBS; in patients with IBD no such genetic associations were identified.[94] Whether reported SNPs in the CB_1 or CB_2 receptor genes are also associated with changes in gastrointestinal function is presently unknown.

OUTLOOK

It is too early to speculate whether or not the endocannabinoid system is involved in the pathophysiology of IBS. However, there are many potential components in this system and whether through endocannabinoid deficiency,[112] specific CB receptor defects, enzyme defects affecting endocannabinoid synthesis or breakdown, the endocannabinoid system could contribute to the symptoms of IBS. For certain factors implicated in the pathophysiology of IBS, such as altered motility, for example, involvement of the endocannabinoid system appears plausible and pharmacological targeting of the endocannabinoid system may be beneficial. On the other hand, the role of the endocannabinoid system in other circuits potentially involved in the pathophysiology of IBS is not well understood. For example, it is unknown whether the endocannabinoid system plays a role in the psychosocial dimensions of IBS. Furthermore, although the endocannabinoid system is involved in stress responses in laboratory animals, it is not known whether it is involved in emotional stress, a well-known exacerbating factor in the symptom severity of many IBS patients. Recent evidence supporting an important role for the endocannabinoid system in the pathophysiology of at least one form of IBS warrants further investigation.[107] A summary of the potential role of the endocannabinoid system in IBS is shown in Fig. 2.

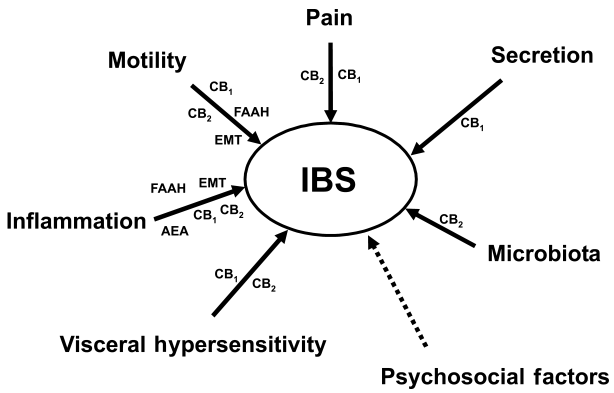

Figure 2 Possible roles of the endocannabinoid system in irritable bowel syndrome (IBS). The endocannabinoid system is involved in the regulation of many of the factors that have been implicated in the pathophysiology of IBS. The arrows indicate each of these factors and the components of the endocannabinoid system supported by current evidence that influence the respective function, and thus might be targeted to treat IBS. Anandamide (AEA), endocannabinoid membrane transporter (EMT), fatty acid amide hydrolase (FAAH). The dashed arrow indicates no current information.

Besides exploring the role of the endocannabinoid system in the pathophysiology IBS, cannabinoid agents might be treatment options for IBS patients by targeting the underlying alterations in motility, inflammation, pain and sensation. Clinical trials would be helpful in elucidating the potential benefit of cannabinoid drugs in IBS.

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The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease

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Background and Purpose

In ancient medicine, extracts of the marijuana plant *Cannabis sativa* were used against diseases of the gastrointestinal (GI) tract. Today, our knowledge of the ingredients of the *Cannabis* plant has remarkably advanced enabling us to use a variety of herbal and synthetic cannabinoid compounds to study the endocannabinoid system (ECS), a physiologic entity that controls tissue homeostasis with the help of endogenously produced cannabinoids and their receptors. After many anecdotal reports suggested beneficial effects of *Cannabis* in GI disorders, it was not surprising to discover that the GI tract accommodates and expresses all the components of the ECS. Cannabinoid receptors and their endogenous ligands, the endocannabinoids, participate in the regulation of GI motility, secretion, and the maintenance of the epithelial barrier integrity. In addition, other receptors, such as the transient receptor potential cation channel subfamily V member 1 (TRPV1), the peroxisome proliferator-activated receptor alpha (PPARα) and the G-protein coupled receptor 55 (GPR55), are important participants in the actions of cannabinoids in the gut and critically determine the course of bowel inflammation and colon cancer. The following review summarizes important and recent findings on the role of cannabinoid receptors and their ligands in the GI tract with emphasis on GI disorders, such as irritable bowel syndrome, inflammatory bowel disease and colon cancer.

Keywords

Cannabis; cannabinoid receptors; colon cancer; GPR55; IBD; IBS

The endocannabinoid system in the GI tract

Cannabis has a long history as a traditional therapeutic agent for the treatment of abdominal pain and gut dysfunction. This beneficial effect is based on the fact that the gastrointestinal (GI) tract is endowed with cannabinoid (CB) receptors and their endogenous ligands. Together they make up the endocannabinoid system (ECS), a physiologic entity that controls

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homeostasis in the gut. There is also a wide range of cannabinoid compounds of exogenous origin. Next to herbal cannabinoids, such as Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol, tetrahydrocannabivarin, cannabichromene, cannabigerol and others, there is a large array of synthetic cannabinoids. In general, cannabinoid compounds can be divided into five distinct classes, i.e. classical cannabinoids (e.g., Δ^9-THC); non-classical cannabinoids (e.g., CP-55,940); indoles (e.g., WIN55,212), eicosanoids, and antagonist/inverse agonists (e.g., rimonabant) (1). For a detailed description of the ECS in the gut, the reader is referred to more comprehensive reviews (2,3).

In short, the ECS consists of the CB receptors 1 and 2 (CB_1, CB_2), their endogenous ligands ("endocannabinoids") as well as their degrading and synthesizing enzymes. CB_1 receptors can be found throughout the GI tract. There, they are predominantly located in the enteric nervous system (ENS) (4) and the epithelial lining (5). Additionally, CB_1 is found in extrinsic fibers of the ENS, plasma cells, and in smooth muscle cells of blood vessels within the colonic wall (6,7). Within the ENS, the CB_1 receptor is expressed prejunctionally in cholinergic, but not nitrergic neurons, explaining why CB_1 activation can depress excitatory transmitter release (8). CB_2 receptors are mainly present in immunocytes, myenteric plexus neurons, and in epithelial cells during ulcerative colitis (7,9). In addition to CB receptors, the orphan G-protein coupled receptor 55 (GPR55) and the transient receptor potential cation channel subfamily V member 1 (TRPV1) are endocannabinoid-responsive receptors and may be responsible for non-CB_1/CB_2 receptor effects of cannabinoids in the GI tract and are therefore regarded as part of an expanded ECS (10,11). PPAR receptors, in particular PPARα and PPARγ, are also responsive to herbal, synthetic and endogenous cannabinoids and may mediate many of the analgesic and anti-inflammatory effects observed in cannabinoid treatment [rev. in (12)]. The abovementioned receptors are present in the GI tract, e. g. on nerve terminals of extrinsic primary afferents (TRPV1) (2), and the ENS and enterocytes (PPARα, GPR55) (2,13).

Endocannabinoids are short-lived bioactive lipids and produced "on demand". Arachidonoyl ethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) are among the best characterized endocannabinoids and are synthesized by N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipases (DAGL), respectively. They are degraded by specific enzymes: anandamide primarily by fatty acid amide hydrolase (FAAH) and 2-AG by monoglyceride lipase (MGL; or monoacylglycerol lipase, MAGL) (rev. in (3)). In the GI tract, FAAH and MGL were shown to be expressed in epithelial cells, the ENS, and in immune cells during ulcerative colitis (6,7,14). Endocannabinoids may be also degraded by cyclooxygenase-2 (COX-2) and lipoxygenase to give rise to prostaglandin ethanolamides, glyceryl prostaglandins, hydroxyeicosatetraenoic acid and hydroperoxyeicosatetraenoic acid derivatives (15,16). In contrast to the degrading enzymes, the synthesizing enzyme of anandamide, NAPE-PLD, and of 2-AG, DAGL α and β, have been observed in epithelial, myenteric plexus and lamina propria cells, and also in the smooth muscle layer (7).

Acylethanolamides other than anandamide, like palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), can be classified as endocannabinoid-like compounds. They do not directly activate CB receptors but they can activate GPR55 (predominantly PEA) and

GPR119 (only OEA) and are able to influence the signaling of anandamide via an entourage effect (17). PEA and OEA also activate PPARα and are present in high levels within the gut. Both of them are degraded by FAAH, however, PEA is preferentially degraded by another amidase, N-acylethanolamine-hydrolyzing acid amidase (NAAA), which is strongly expressed in immune cells and active particularly in the intestine, suggesting a potentially pathophysiological role in the GI tract (rev. in (17)). In summary, the GI tract is able to locally produce its own endocannabinoid ligands according to its physiological needs and may rapidly react to disturbances in the gut to maintain homeostasis.

Cannabinoids in GI motility and secretion

Cannabinoids affect gut motility mainly by activating CB_1 receptors present on enteric neurons (18). Activation of CB_1 receptors results in the inhibition of acetylcholine release which consequently causes a decrease of intestinal smooth muscle contractility and peristalsis (19). Early studies demonstrated that the plant-derived CB receptor agonist Δ^9-THC, the main component of *Cannabis*, decreases intestinal transit and inhibits electrically evoked contractions in guinea pig explants (20,21). Synthetic CB receptor agonists likewise reduce gastric emptying, upper GI transit, and colonic propulsion (reviewed in (2)). In contrast, rimonabant (SR141716), an inverse agonist of CB_1 receptors, increased electrically-evoked contractions and peristalsis in isolated intestinal segments (22,23), as well as intestinal motility *in vivo* (24). Although CB_2 receptors are expressed in the ENS, they are suggested to play a minor role in the regulation of gut motility under basal conditions but might become important under pathophysiological settings (9). Indeed, JWH-133, a CB_2 receptor agonist, but not arachidonyl-2'-chloroethylamide (ACEA), a CB_1 receptor agonist, attenuated gut transit dose-dependently in the inflamed gut of rats, an effect that was prevented by a CB_2 receptor antagonist (25). There is also increasing evidence that GPR55 is involved in the regulation of gut motility since its agonist O-1602 was able to slow down whole gut transit in mice (13). Both PEA and OEA inhibit intestinal transit in mice but the mode of action is unclear because neither CB receptors nor PPARα seem to be involved in that process (26,27); however, in a mouse model of postinflammatory IBS (mustard oil-induced), inhibition of transit by PEA could be blocked with a CB_1 receptor antagonist, but was not significantly modified with a PPARα antagonist (28).

Acute inhibition of endocannabinoid-synthesizing or - degrading enzymes also modulates intestinal motility. Thus, inhibition of DAGLα was able to normalize gut motility in a mouse model of genetically-induced constipation (29). Pharmacological inhibition of FAAH or MGL led to a decrease in gut motility through mechanisms that involved a rise in anandamide or 2-AG levels, respectively, and the activation of CB_1 receptors (14,30,31). Interestingly, FAAH-deficient mice did not show alterations in basal gut motility; however, pharmacological inhibition or genetic deletion of FAAH normalized endotoxin-induced hypermotility (31). Taschler et al. demonstrated that MGL-deficient mice did not show alterations in basal gut motility but that they were insensitive to CB receptor agonist treatment due to desensitization of intestinal CB_1 receptors (30).

It has to be noted that also the gut brain-axis may account for the regulation of gut motility by cannabinoids. For instance, intracerebroventricular injection of the CB receptor agonist

WIN55,212-2 attenuated whole gut transit in mice (32). Additional evidence that gut motility might be regulated by central CB receptors was provided by Vianna *et al.* who showed that deletion of CB_1 receptors specifically in the vagal nerves of mice caused an increase in GI motility (33). Similar to rodents, CB_1 receptors are functionally present in the human small and large intestines (34–36). Thus, WIN55,212-2 and ACEA inhibited electrically-evoked contractions in a healthy human colon and this effect was completely blocked by rimonabant (37). Also 2-AG and anandamide were shown to inhibit acetylcholine-induced contractions in explants of human colonic longitudinal and circular muscle, however, this effect could not be blocked with CB_1 or CB_2 antagonists (38). The authors suggested a non-cannabinoid or alternative cannabinoid pathway mediating this effect (38). It is possible that the non-CB effects by anandamide may have been brought about by GPR55 which causes relaxation in the murine colon (13).

There is evidence that cannabinoids play an important role in the regulation of gastric and intestinal secretion in rodents and humans. Studies revealed that cannabinoids reduce the production of gastric acid secretion by activating CB_1 receptors (19). In mice, intestinal hypersecretion induced by cholera toxin was reduced by CB_1 receptor activation (39). In another study, pharmacological inhibition or genetic deletion of FAAH provided beneficial effects against diclofenac-induced gastric irritation (40). In contrast, enhanced secretion was observed in humans treated with the CB_1 antagonist rimonabant (41). In summary, a large body of evidence demonstrates that (endo-) cannabinoids affect physiologic functions of the gut, a property that could be therapeutically exploited. Activation of CB_1 receptors by increased levels of endocannabinoids and, as a consequence, a slowed gut motility might have beneficial effects for patients with symptoms of hypermotility. On the other hand, inhibition of endocannabinoid synthesis or blockade of CB_1 receptors might enhance gut motility in GI disorders associated with constipation. If central side effects of cannabinoids could be overcome, modulation of cannabinoid levels would certainly represent a valuable pharmacological approach for the treatment of GI disorders. Another possibility could be the use of non-psychotropic cannabinoids like cannabidiol, which has been described as a ligand of many receptors including GPR55, TRPV2, PPARγ and 5-HT1A but not of CB receptors (but might modulate their actions) (42). Cannabidiol has shown relaxant effects on croton oil- and sepsis-induced hypermotility in mice (43,44).

Cannabinoids in emesis and nausea

The dorsal vagal complex (DVC) in the brainstem is the site responsible for the vomiting reflex while the neural circuitry responsible for nausea is less known. CB receptors and particularly FAAH and MGL are present in the DVC and area postrema suggesting an important role of endocannabinoids in the control of emesis (45–47). Cannabis has been traditionally used as an antiemetic agent, and exogenous cannabinoids are presently prescribed for people with chemotherapy-induced nausea and vomiting (48). However, due to central side effects, cannabinoids are not used as first line drugs.

The endocannabinoids anandamide and 2-AG have been shown to reduce emesis in experimental models (46). Drugs that can raise endocannabinoid levels without causing the typical cannabinoid agonist-induced central side effects are therefore potential options to

treat emesis. The FAAH inhibitor URB597 reduced LiCl-induced emesis via CB_1 and CB_2 receptors (46). Reduction of emesis by the MGL inhibitor JZL184 was shown to be sensitive to CB_1 antagonism (49). Also cannabidiol showed anti-emetic and anti-nausea effects in animal models, the effects were brought about by indirect agonism of $5\text{-}HT_{1A}$ somatodendritic autoreceptors in the dorsal raphe nucleus (50).

The role of endocannabinoids has been investigated more recently in detail in the conditioned gaping model in rats and results indicate that 2-AG and the visceral insular cortex (VIC) could play an important role in nausea (51). Exogenous 2-AG, but not exogenous anandamide, applied by bilateral intra VIC infusion, dose-dependently suppressed conditioned gaping (51). The effect could not be blocked with the CB_1 antagonist AM251, but instead with the COX inhibitor indomethacin (51). Interestingly, bilateral VIC infusion with the MGL inhibitor MJN110 also suppressed conditioned gaping but here, the effect could be blocked with AM251 (52).

Endocannabinoids have been clearly established as important messengers in the neuronal network that controls vomiting and nausea. Interference with endocannabinoid degradation may represent a valuable therapeutic approach not only against emesis but also against anticipatory nausea in chemotherapy patients.

Cannabinoids and functional bowel disorders

Irritable bowel syndrome (IBS) and functional dyspepsia are the most frequent functional bowel disorders encountered globally. The previous view that functional GI disorders lack histopathological and biochemical alterations has been challenged by studies demonstrating low grade inflammation, increased presence of immune and mast cell, changes in the epithelial barrier, and bacterial overgrowth in IBS patients. These alterations together with a derangement of the gut-brain axis may be involved in the development of visceral hyperalgesia and motility disturbances. The predominant presence of CB_1 receptors along the gut-brain axis may allow cannabinoids to positively influence derangements along this axis (3,53). The role of the ECS in IBS has been already described in a previous review by Storr&Sharkey (53). Here, more recent results will be summarized and discussed.

IBS: visceral hypersensitivity and the ECS

Symptoms of IBS, such as abdominal pain, discomfort, and altered bowel habits, have been previously linked with visceral hypersensitivity and aberrant 5-hydroxytryptamine (5-HT) signaling (53). Feng et al. explored the link between 5-HT and the ECS and observed increased levels of 5-HT, but a decrease in anandamide, in the duodenal mucosa of patients with postinfectious IBS (PI-IBS) (54). Using a rat model, they showed that acute luminal administration of 5-HT into the duodenum induced anandamide release via vagal $5\text{-}HT_3$ receptors, whereas chronic 5-HT treatment decreased anandamide levels via $5\text{-}HT_3$, indicating that 5-HT may be involved in the regulation of intestinal anandamide content. In addition, luminally-applied CB_1 receptor agonists attenuated 5-HT-induced hyperalgesia (54). In IBS-D (diarrhea-predominant) patients, no changes in anandamide levels but a decrease in PEA was observed in comparison to healthy subjects. The decrease was associated with abdominal pain (55). The IBS-D patients also had an increase in 2-AG while

IBS-C patients had higher levels of OEA (55). It is interesting that levels of PEA were also found decreased in a mouse model of inflammation-induced hypermotility (croton oil-induced) (56). The decrease was reduced by a non-psychoactive *Cannabis* extract, cannabichromene, in a CB receptor-independent manner (56). In contrast, in a mouse model of postinflammatory IBS (mustard oil-induced), PEA slowed gut transit, an effect that was dependent on CB_1 receptors (28). By use of a trinitrobenzenesulfonic acid (TNBS)-induced model of visceral hypersensitivity, Iwata et al. showed that a CB_2 receptor agonist was effective in improving pain thresholds in a dose-dependent manner without signs of central CB_1 receptor activation (40,57). Considering these data it is possible that low levels of endocannabinoids in IBS patients may contribute to hyperalgesia and abdominal pain and cause perturbations in the bowel motility which could be improved by endo- or exocannabinoids via CB- and possibly non-CB receptor pathways. This leads to the idea that FAAH inhibitors could be valuable therapeutics against PI-IBS and possibly other forms of IBS. In accordance with this concept, several studies reported that pharmacological inhibition of FAAH and also MGL significantly reduced visceral nociception in rodent models of colorectal distension and acetic acid-induced abdominal stretching (40,58,59). In this context it is worth to mention the role of mast cells in IBS. Activated mast cells have been shown to correlate with abdominal pain in IBS (60). Since mast cells express CB receptors and are also targets of PEA (61), which is thought to modulate mast cells activation, endocannabinoids may regulate activity of mast cells and hence interfere with IBS symptoms like abdominal pain; however, this remains to be shown.

IBS: stress, pain and the ECS

Chronic stress can induce visceral hyperalgesia via the hypothalamic–pituitary–adrenal axis and probably adds to the pain that IBS patients perceive. Recent work in rat models has shown that chronic stress causes reciprocal changes in 2-AG and COX-2/FAAH levels in L6–S2, but not L4–L5 dorsal root ganglia (DRGs) (62). Moreover, CB_1 receptors were downregulated while TRPV1 receptors were upregulated in L6–S2 but not in L4–L5 DRGs, indicating region-specific changes in primary sensory fibers innervating the distal colon (62). A report suggests that epigenetic regulation in the DRG neurons could be responsible for these changes: while chronic stress was associated with methylation in the promoter region of the Cnr1 gene (encodes the CB_1 receptor), histone acetylation at the Trpv1 promoter and expression of the TRPV1 receptor were increased (63). These findings point out that reciprocal changes in the endovanilloid and endocannabinoid system occur in visceral sensory fibers and that these changes could contribute to hyperalgesia and abdominal pain.

Stress and visceral pain may be also regulated by the ECS within the CNS. It is known that chronic stress reduces levels of anandamide (but increases 2-AG) in the brain and downregulates CB_1 receptors, and that these changes may contribute to the stress response (64). In line with this, both the FAAH inhibitor PF 3845 and the dual FAAH/MAGL inhibitor JZL 195 were effective in inflammatory and mechanically evoked visceral pain models suggesting that an increase in endocannabinoid levels alleviates visceral pain (59). A more thorough description of this topic is given in (65).

IBS: genetic variations and the ECS

Genetic variations of ECS components (CB receptors, synthesizing/degrading enzymes) may be associated with the pathogenesis of functional bowel disorders. Polymorphism in the *FAAH* gene (C385A) leads to a mutant FAAH enzyme and reduces breakdown of anandamide (66). A study in patients with constipation predominant (C-) IBS, D- and M- (mixed) IBS, with chronic abdominal pain and functional dyspepsia, showed a clear association of the non-wild type *FAAH* genotype with functional bowel disease phenotypes and with accelerated colonic transit in IBS-D patients (67). However, no statistically significant association between the *FAAH* genotype and sensation measurements was observed (67). A polymorphism in the *CNR1* gene, rs806378, was found to be significantly associated with IBS symptom phenotype, colonic transit in IBS-D, and sensation rating of gas, but not with pain (68). In line with a possible role of *CNR1* variants in the development of IBS symptoms, allele frequencies of AAT triplet repeats in *CNR1* were observed to be associated with IBS in a study of a Korean population (69). Similar results, namely the detection of eight *CNR1* alleles with AAT triplet repeats, were reported in a Chinese IBS cohort, whereas no association could be detected between C385A *FAAH* polymorphism and IBS pathogenesis (70). Interestingly, FAAH activity was recently determined in whole colon samples from patients who underwent colectomy for slow transit constipation (71).The results revealed a strong decrease in activity in these patients as compared to individuals free of transit dysfunction (71). The FAAH enzyme, therefore, seems to be a key molecule for the regulation of endocannabinoid levels and colon motility, but not for GI pain sensation.

Effect of CB receptor agonists in IBS patients

From animal studies it was rightfully concluded that cannabinoid agonists could improve visceral pain thresholds in humans. In a previous study performed in healthy volunteers to investigate the effect of dronabinol (Δ^9-THC) on colonic motility and sensation, 7.5 mg dronabinol induced relaxation of colon motility and tone postprandially (72). The effect of dronabinol on visceral perception to rectal distension was then tested in IBS patients (positively diagnosed by Rome II criteria) and healthy subjects in a small trial, but no differences in sensory thresholds and discomfort were observed between the cohorts (73). A different study revealed inhibitory effects of dronabinol on fasting colonic motility and an increase in colonic compliance, particularly in patients with diarrhea predominant forms of IBS, but failed to demonstrate effects on sensation and tone (74). The report also suggested that *FAAH* and *CNR1* variants could have had an impact on the effects of dronabinol (74). In a subsequent trial performed in IBS-D patients, no significant effect of dronabinol on colonic transit was observed; however, in a subset of patients with the *CNR1* polymorphism rs806378, dronabinol moderately delayed colonic motility (75).

Thus, it seems that CB receptor activation in IBS has potential therapeutic value, but probably only in IBS-D patients with genetic variations of ECS components.

Functional dyspepsia

There is good indication that the ECS may be involved in functional dyspepsia. Tack et al. have previously shown that early satiety and symptoms of functional dyspepsia are caused by a disturbed gastric accommodation (76). In addition, hypersensitivity to gastric balloon

distension was observed to be present in a subset of patients with functional dyspepsia (77). A cross-over, randomized, controlled clinical trial in healthy individuals now demonstrated that CB_1 receptor antagonist rimonabant was able to inhibit meal-induced gastric accommodation, but did not affect fasting gastric compliance or sensitivity to gastric balloon distension, indicating that gastric accommodation is controlled by endocannabinoids (78). However, it was not clear from the study whether the ECS controls accommodation via centrally-mediated pathways or via the ENS. A new study has recently addressed the question as to whether CB_1 receptors in the brain are involved in functional dyspepsia and could demonstrate that increased availability to a CB_1 receptor radioligand was predominantly found in brain regions involved in the regulation of visceral pain and satiety (79).These findings would argue for a role of central CB receptors in the regulation of gastric accommodation in humans. It is, therefore, possible that both, central and peripheral CB receptors are involved in the development of functional GI disorders, and that pharmacological manipulation of exclusively peripheral CB receptors may not provide full benefit for patients with these disorders.

Microbiota and the ECS

A change in the microbiotic population of the gut may alter the permeability and lead to metabolic endotoxemia and hence to metabolic disorders associated with obesity. Endocannabinoids are involved in the regulation of energy metabolism and food intake and communicate in this respect with the microorganisms of the gut (80). The epithelial lining expresses CB receptors and they are most likely involved in these mechanisms. 2-AG and PEA cause an increase in epithelial barrier function (“gate keeper”) while anandamide is thought to be a “gate opener” (81). Thus, the intestinal ECS may have an important role in the control of microbial products entering the bloodstream and in the development of metabolic diseases. A detailed review on this topic is given in (81).

Dysbiosis (alteration in the composition of gut microbiota) has been also suggested as one of the potential causes of IBS, especially in the case of PI-IBS (82). It is known that antibiotic therapy provides certain benefits for IBS patients (83), however, it is not quite clear how eradication of bacteria could contribute to symptom relief. In this context it is interesting that *Lactobacillus acidophilus* NCFM could induce CB_2 receptor expression in the rodent gut mucosa (84). When applying NCFM in a model of chronic colonic hypersensitivity, it caused analgesia which was abrogated by i.p. blockade with AM630, suggesting that CB_2 receptors may provide a link between gut microbiota and visceral hypersensitivity (84). However, in a human trial, CB_2 receptors were not found to be upregulated in colonic mucosal biopsies from persons that were given *Lactobacillus acidophilus* NCFM over a period of 21 days (85). On the other hand, treatment of mice with antibiotics reduced pain-related responses to i.p. application of acetic acid or intracolonic capsaicin (86). The effect was accompanied by a small rise in CB_2 receptor transcripts in colon tissue, as well as a decrease of CB_1 and mu-opioid receptors. Additionally, total luminal bacterial counts correlated with CB receptor expression (86) suggesting a possible interaction between microbial products and CB receptors.

Cannabinoids and intestinal inflammation

Chronic inflammatory conditions of the GI tract are known as inflammatory bowel disease (IBD) and occur in two major forms, ulcerative colitis (UC) and Crohn's disease (CD). IBD is thought to originate from a complex interaction of the gut microbiota (or their products) with the epithelial barrier, based on the genetic background and the immune system of the host (87). To investigate the role of cannabinoids in IBD, mostly animal models that rely on chemically-induced mucosal inflammation have been used.

The endocannabinoid system as a therapeutic target in IBD

Evidence gathered from several studies in rodents points to a therapeutic relevance of the ECS in IBD. As reviewed by Izzo & Sharkey (2) and Alhouayek & Muccioli (88), endocannabinoid signaling is largely enhanced in the inflamed intestine. Expression of CB_1 (89) and CB_2 receptors (90), and of anandamide (91) were increased, whereas FAAH levels were reduced in the initial phase of colitis (92). Pharmacological strategies to enhance endocannabinoid levels, either by inhibition of endocannabinoid degradation (92–94) or of the transport across the plasma membrane (91,92) ameliorated inflammation. In particular, inhibition of FAAH by PF-3845 (94) and FAAH/COX blockade by ARN2508 (95) dramatically reduced damage in experimental colitis models. In the latter study, raised levels of anandamide, PEA and OEA were measured that most likely contributed to the beneficial effect (95). A recent work by Alhouayek *et al* showed that inhibition of NAAA, which preferentially degrades PEA, caused significant improvement of experimental colitis suggesting that PEA is an important acylethanolamide in the regulation of intestinal inflammation (96). In accordance, oral administration of PEA (which is interestingly sold as an over-the-counter drug and advertised to mitigate symptoms of GI disorders) exerted anti-inflammatory effects in the gut (97). Experiments on cultured human colonic biopsies derived from UC patients showed that PEA caused a decrease in expression and release of inflammatory mediators which was dependent on PPARα (98).

Activation of the CB_1 (89) or CB_2 receptor (90,99) with specific agonists also protected from colitis. Accordingly, genetic ablation or pharmacological antagonism of CB_1 (89,100) or CB_2 receptors (90,100) left mice more susceptible to intestinal inflammation. Moreover, treatment with Δ^9-THC was reported to reduce colitis in rats (101). The limitations of using *Cannabis* for treatment of gut inflammation, however, are the psychoactive effects that arise from activation of CB_1 receptors in the brain. Investigation of pharmacologically active cannabinoids with low or no affinity for CB_1 receptors and of atypical cannabinoids would be therefore of high interest. Indeed, it has been shown that cannabidiol and cannabigerol, two non-psychotropic ingredients of *Cannabis*, have proven beneficial in various models of intestinal inflammation (101–105). Also, the atypical cannabinoid O-1602 was reported to reduce disease severity in a CB_1-/ CB_2 receptor-independent way by inhibiting neutrophil recruitment (106). Recently, GPR55, which is part of the "expanded" ECS, has been investigated in experimental colitis. A pro-inflammatory role of GPR55 could be established because genetic deletion of GPR55 and treatment with the GPR55 antagonists CID16020046 or ML-191 alleviated intestinal inflammation (97,106,107). In this context, cannabidiol, which is known to act as a GPR55 antagonist (108), showed inhibition of GI inflammation

in an LPS-induced model by targeting enteric reactive gliosis (103). Interestingly, only parts of the beneficial effects of cannabidiol in this model were mediated by PPARγ (103) raising the possibility that GPR55 could have been involved in this effect. Cannabidiol may also exert a protective effect on the intestinal barrier. In a Caco-2 cell monolayer stimulated by EDTA, cannabidiol concentration-dependently caused rapid recovery of the barrier and this effect was inhibited by a CB_1 antagonist (109). Since cannabidiol has no affinity to CB_1 receptors, the authors argued that cannabidiol could have antagonized CB_1-mediated increases in permeability mediated by locally produced endocannabinoids (109). Activation of CB_2 receptors also attenuated cytokine-evoked mucosal damage in human colonic explants (110).

Cannabis for the treatment of IBD?

Questionnaires among IBD patients revealed that *Cannabis* is commonly used as a self-medication to relieve IBD-related symptoms like abdominal pain, diarrhea, and loss of appetite (111,112). A retrospective study reported significant improvements in 21 out of 30 CD patients after *Cannabis* use (113). In a small prospective placebo-controlled study of CD patients, a beneficial clinical response was achieved in 10 out of 11 subjects in the treatment group (114). A more recent questionnaire confirmed that the use of *Cannabis* subjectively improved pain and other symptoms in IBD patients, but also pointed out that *Cannabis* use for more than six months was a strong predictor in CD patients for requiring surgery (115).

Despite these interesting findings, the exact mechanisms how the ECS operates in IBD have not yet been unraveled but evidence gathered so far points to an overall protective role (Fig. 1). The up-regulation of ECS components possibly constitutes an attempt to restore homeostatic balance (3). Cannabinoids have been shown to influence the recruitment of immune cells to the site of intestinal inflammation (93,106,107) and to reduce the release of pro-inflammatory cytokines, i.e. TNF-α, IFN-γ, IL-1β and IL-6 (93,102,103,105). Activation of the CB_1 receptor might also lead to enhanced wound closure during colitis (5). Of particular interest are recent findings that gut microorganisms may influence the expression of intestinal ECS components (81). 2-AG and PEA were mostly associated with beneficial effects on the gut-barrier function (81). The crosstalk between gut microbiota and the ECS is therefore worthy to be further examined in future studies.

Collectively, cannabinoids show great potential in the treatment of IBD and further research is warranted to gain a better insight into the mechanistic actions of (endo-) cannabinoids.

Cannabinoids and colon cancer

Differential expression of components of the ECS in colorectal cancer (CRC) was first reported by Ligresti et al. (116). In this study, anandamide and 2-AG contents were found to be higher (3-fold and 2-fold, respectively) in CRC lesions as compared to normal colonic mucosa and, interestingly, their levels were higher in adenomatous polyps than in carcinomas (116). Increased endocannabinoid synthesis in CRC was also reported in a more recent study (117). Here, anandamide, as well as its synthesizing enzyme NAPE-PLD, were up-regulated approximately 2-fold in cancer tissues. Intriguingly, mRNA expression and activity levels of FAAH were also increased. Most likely, as a consequence of increased

FAAH activity, elevated levels of arachidonic acid, the main product of anandamide and 2-AG degradation, were also detected (117). In another study, the main degrading enzyme of 2-AG, MGL, was also found increased in CRC specimens (118).

Examination of CB_1 expression revealed a down-regulation of mRNA levels in 18 out of 19 colon cancer samples as compared to adjacent non-neoplastic colon mucosa (119). The reason for this silencing was found to be DNA hypermethylation at CpG islands around the transcription start site of *CNR1.* In parallel to the epigenetic regulation, also protein levels of CB_1 receptors were reduced in colon cancer specimens as shown by Western blotting (119). These findings were corroborated by Cianchi et al. who reported CB_1 receptor expression to be higher in normal colonic epithelium than in colonic tumor tissue (120). However, a comprehensive study describing the correlation between CB_1 receptor immunoreactivity and patient outcome conducted in 534 Korean patients found no differences in overall survival between patients with carcinomas of either high or low CB_1 receptor immunoreactivity (121). Distant metastasis was found to be lower in patients with high CB_1 receptor expression, but there were no differences in lymph node metastasis, tumor invasion, or tumor size. Surprisingly, in stage IV patients, high CB_1 immunoreactivity even correlated with a poorer survival rate (121). Similar observations were made in a cohort of 487 Swedish patients (122). There, high CB_1 expression was reported to correlate with poorer disease-specific survival in stage II microsatellite stable CRC patients (122). Reduced overall survival has also been reported for patients who were either homo- or heterozygous for the 1359 G/A single nucleotide exchange in the *CNR1* gene although it is not yet known how this polymorphism affects cannabinoid signaling (123). CB_2 receptor mRNA expression was found in 28.6% of CRC samples and significantly correlated with lymph node involvement (124), however, no consistent data on protein expression were available. So far, the human studies indicate increased endocannabinoid activity in colon cancer while the role of CB receptors remains less clear.

Cannabinoids reduce carcinogenesis in animal models of colon cancer

In mice, colon cancer can be induced either chemically or, for instance, by germline mutation of the adenomatous polyposis coli (*Apc*) gene. $Apc^{Min/+}$ mice spontaneously develop multiple polyps in the intestine. Additional knock out of *Cnr1* or inhibition of the CB_1 receptor with AM251 in these mice caused a strong increase in intestinal polyp burden, whereas activation of CB_1 receptors with methanandamide significantly reduced the number of polyps (119). Genetic deletion of *Cnr2* (the gene encoding CB_2 receptor), had no effect on polyp growth in this model (119). Chemically, colon cancer develops after multiple intraperitoneal injections of the carcinogen azoxymethane (AOM). In this model, anandamide and 2-AG were found increased in the colon of AOM-treated mice (125). In addition, inhibition of FAAH with *N*-arachidonoyl-serotonin (AA-5-HT) reduced the development of precancerous lesions, and furthermore, the non-selective, synthetic CB_1/CB_2 receptor agonist, HU210, was able to mimic this effect (125).

Antitumorigenic effects in the AOM model were also observed with non-psychotropic cannabinoids. For instance, cannabidiol was shown to reduce the formation of aberrant crypt foci (ACF), polyps, and tumors in the colon and the AOM-induced up-regulation of p-Akt

(126). It also counteracted caspase-3 inactivation. In colorectal carcinoma cell lines, it protected DNA from oxidative damage and it reduced cell proliferation in a CB_1-, TRPV1- and PPARγ-antagonists sensitive manner (126). A “cannabidiol botanical drug substance” (a *Cannabis sativa* extract with high content of cannabidiol) had similar effects in the same model, reducing ACF, polyp and tumor formation via CB_1 and CB_2 receptor activation (127), whereas treatment with cannabigerol reduced the number of ACFs only (128). In yet another murine model, in which colitis-associated colon cancer was induced through the application of AOM and dextran sulfate sodium (DSS), the atypical cannabinoid O-1602 showed antitumorigenic properties (129). The drug reduced the number and area of tumors by 30% and 50%, respectively. In addition, activation of the oncogenic transcription factor STAT3 was decreased while pro-apoptotic factors p53 and Bax were increased in O-1602 treated mice (129). Perhaps surprisingly, one study showed that antagonism of CB_1 receptors with rimonabant reduced the formation of ACFs with 4 or more crypts in mice with AOM-induced colon cancer (130).

Potential applications of cannabinoids and related substances have also been studied in xenograft models. The semi-synthetic cannabinoid quinone HU-331 (131) and the hexahydrocannabinol analogue LYR-8 (132) reduced tumor growth of xenografts derived from HT-29 cells. Likewise, the CB_2 receptor agonist CB13 inhibited the growth of DLD-1 derived tumors (120). A “cannabidiol botanical drug substance” (127) and cannabigerol (128) decelerated or even halted the growth of HCT116 xenografts, respectively.

Anticarcinogenic mechanisms of cannabinoids: reduction of cancer cell proliferation and inhibition of angiogenesis and metastasis

Cannabinoids have been shown to exert anti-proliferative effects on colon cancer cells through apoptosis via activation of CB_1/CB_2 receptors, or through receptor-independent mechanisms (rev. in (133)). The molecular mechanisms underlying the induction of apoptosis upon CB_1/CB_2 receptor activation have been discussed in detail by Velasco et al. (134). Briefly, *de novo* synthesis of the pro-apoptotic sphingolipid ceramide (120), down-regulation of the protein survivin (inhibitor of apoptosis) (119), inhibition of PI3K/Akt signaling (135,136), and induction of endoplasmic reticulum stress that leads to autophagy-mediated cell death (136), have all been reported. Notably, cannabinoids with low or no affinity for CB receptors (like cannabidiol and O-1602) are also known to exert anti-proliferative effects, although the underlying mechanisms have not yet been fully clarified (126,127,129). A cannabinoid-like compound LYR-8, for instance, was demonstrated to decrease angiogenesis in a xenograft model using chick chorioallantoic membranes (132). Concomitantly, the expression of factors that modulate the tumor microenvironment, like vascular endothelial growth factor, COX-2, and hypoxia-inducible factor 1α was reduced in this model (132). Inhibition of MGL, either pharmacologically or through silencing with siRNA, attenuated the invasion of colon cancer cells (118), suggesting a role of endocannabinoid degrading enzymes in CRC progression. Importantly, adhesion and migration of highly metastatic colon cancer cells was shown to be diminished after treatment with cannabidiol or a GPR55 inhibitor (108).

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In conclusion, data obtained so far point to a deregulation of the ECS in colon cancer that could be interpreted as an attempt to restore the original healthy state. Despite controversial data on the role of the ECS in human colon cancer, promising preclinical data on the reduction in tumor growth by typical and atypical cannabinoid compounds warrant further exploration on the cause of ECS deregulation in colon carcinogenesis. It should be of prime interest to investigate known and hitherto unknown components of the ECS to better understand the complexity of CB receptor signaling by endocannabinoids and the regulation of their synthesizing and degrading enzymes.

Concluding remarks

Cannabinoids have a long history of being used to treat diseases or to alleviate symptoms. In modern medicine, this is not fully translated, and cannabinoids or cannabinoid-derived drugs are rarely used mainly due to the lack of clinical trials supporting such use. Over the last decades, cannabinoid research was driven by basic scientists who characterized pharmacological actions of cannabinoids, who discovered the ECS with all its constituents, and who taught us how activation or blockade at different sites may be helpful for the treatment of GI diseases. The GI tract is one of the regions where cannabinoid signaling is involved in many physiological and pathophysiological regulatory mechanisms, this is now clearly understood. The last decade has added more translational studies, and we have learned where cannabinoids are involved in pathophysiological states and human disease and where and how cannabinoids alter physiological or pathophysiological conditions. Through a recent meta-analysis we are also better informed on side effects associated with cannabinoid treatment. The analysis revealed that there was an increased risk of short-term adverse events with cannabinoids, mostly dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, drowsiness, but also cardiac (1.42; 0.58-3.48; odds ratio; 95% CI) and hepatobiliary (3.07; 0.12-76.29; odds ratio; 95% CI) disorders were among them (137). Nevertheless, the opportunities are multifold with targeting the numerous involved receptors with agonists and antagonists, and with targeting synthesizing and degrading mechanisms. To harvest the potential therapeutic effects is now challenging, but based on the broad cannabinoid platform built by basic researchers, clinical trials are urgently wanted. From a scientist’s perspective and all the caveats in mind, it seems to be a matter of time when cannabinoid compounds will be used in the treatment of GI disease

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Abbreviations

ACEA	arachidonyl-2'-chloroethylamide
ACF	aberrant crypt foci
2-AG	2-arachidonoylglycerol

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AOM	azoxymethane
AA-5-HAT	*N*-arachidonoyl-serotonin
CB	cannabinoid
CI	confidence interval
CRC	colorectal cancer
CD	Crohn's disease
COX-2	cyclooxygenase-2
DAGL	diacylglycerol lipase
DRG	dorsal root ganglion
DVC	dosal vagal complex
ECS	endocannabinoid system
ENS	enteric nervous system
FAAH	fatty acid amide hydrolase
GI	gastrointestinal
GPR55	G-protein coupled receptor 55
GPR119	G-protein coupled receptor 119
5-HT	5-hydroxytryptamine
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
MGL	monoglyceride lipase
NAPE-PLD	N-acyl phosphatidylethanolamine phospholipase D
NAAA	N-acylethanolamine-hydrolyzing acid amidase
OEA	oleoylethanolamide
PEA	palmitoylethanolamide
PPARα	peroxisome proliferator-activated receptor alpha
PPARγ	peroxisome proliferator-activated receptor gamma
Δ^9-THC	Δ^9-tetrahydrocannabinol
TNBS	trinitrobenzenesulfonic acid
TRPV1	transient receptor potential cation channel subfamily V member 1

UC ulcerative colitis

VIC visceral insular cortex.

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Key points

- The endocannabinoid system (ECS) represents an important homeostatic entity of the gut that consists of cannabinoid receptors, their endogenous ligands (the “endocannabinoids”), and their synthesizing/degrading enzymes.
- A large number of studies have confirmed that the ECS is crucially involved in the control of motility, secretion and mucosal integrity of the gut and may even determine the course of intestinal inflammation and cancer. The ECS provides many drug targets for human gastrointestinal disorders, such as irritable bowel syndrome, inflammatory bowel disease and colon cancer.
- Conduction of clinical trials and translation into clinical application of cannabinoids are important future goals in this field.

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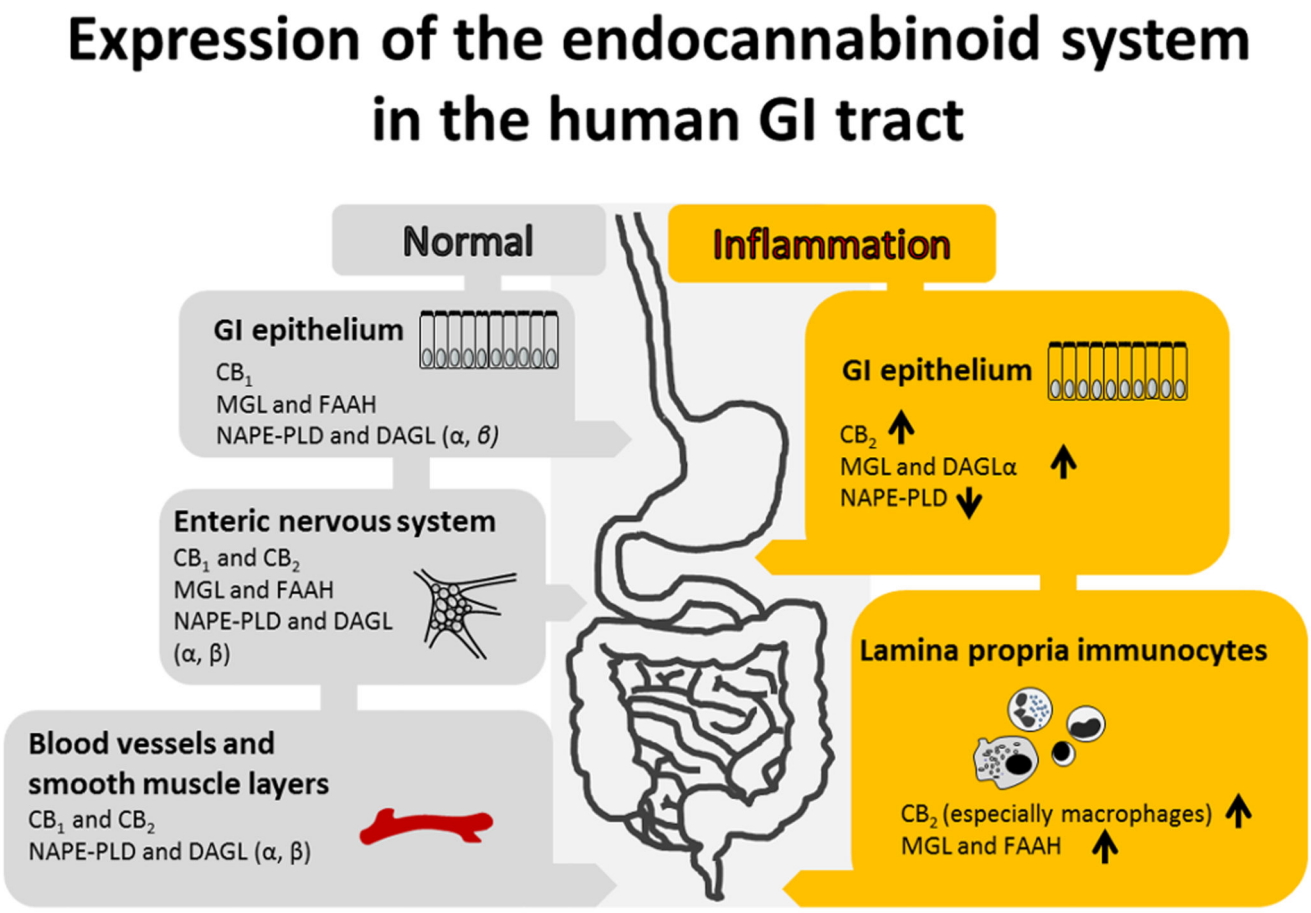

Fig. 1.

Expression of receptors and synthesizing/degrading enzymes of the endocannabinoid system (ECS) in the normal and acutely inflamed human gastrointestinal (GI) tract. Data were taken from Wright et al. (5) and Marquéz et al. (7). CB_1, CB_2, cannabinoid receptors 1 and 2; FAAH, fatty acid amide hydrolase; MGL, monoacylglycerol lipase; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase D; DAGL, diacylglycerol lipase.

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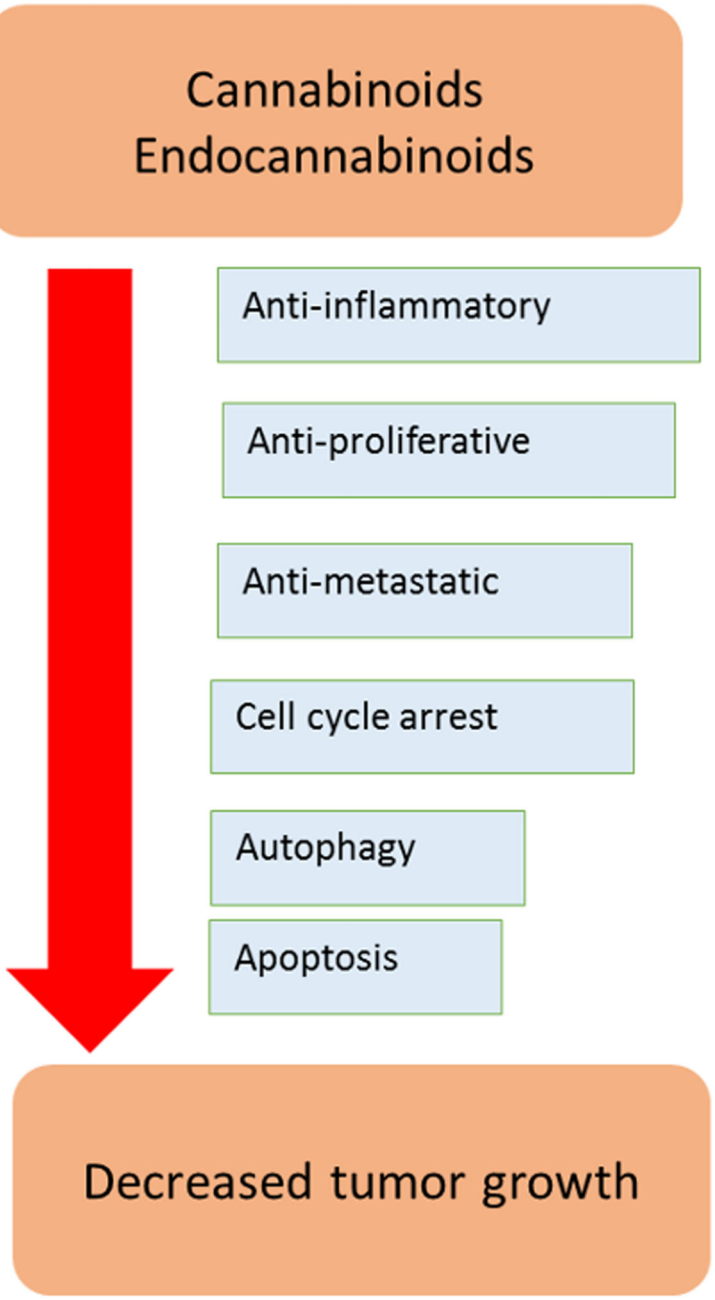

Fig. 2.

(Endo-) cannabinoids exert various anti-tumorigenic effects in colon cancer. For a more detailed description of molecular mechanisms in which cannabinoids and endocannabinoids could play a role, the reader is referred to Velasco et al. (134).

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OPINION
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Irritable Bowel Syndrome: Manipulating the Endocannabinoid System as First-Line Treatment

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INTRODUCTION

Irritable Bowel Syndrome (IBS) is a functional disorder characterized by abdominal pain, spasms, and altered bowel movements, either predominantly diarrhea (IBS-D), or predominantly constipation (IBS-C), or alternating between those states (Saha, 2014). In the Western world it affects the 10–15% of the population (Canavan et al., 2014). IBS represents a visceral hypersensitivity, with features of gastrointestinal (GI) allodynia and hyperalgesia. Considered a life-long condition, it is clear that significant gastrointestinal insults, such as food poisoning or antibiotic administration, may generate attacks that persist, often indefinitely. Attacks are associated with anxiety and depression, but controversy carries on to which incites the other (Saha, 2014). It is possible that some patients may develop a vicious cycle of worsening physical and psychological symptoms (Jones et al., 2013, 2017).

Currently, IBS sufferers are prescribed opioids, anticholinergics, and antidepressants, however with quite suboptimal results. Other compounds have been formulated to interact with serotoninergic circuitry, nevertheless these have been withdrawn from certain markets due to association with ischemic colitis (alosetron, cilansetron) and cardiovascular events (tegaserod), leaving, *de facto*, an urgent clinical need (Ford et al., 2014; Lexicomp Online, 2017).

The Endocannabinoid System (ECS) is known to modulate several functions, including mood, anxiety, and memory retrieval of traumatic events and it directly coordinates GI propulsion, secretion, inflammation, and nociception, providing a rationale for agents capable of interacting with the ECS as treatment candidates for IBS (Russo, 2016).

IRRITABLE BOWEL SYNDROME AND THE ENDOCANNABINOID SYSTEM

Endocannabinoid System in the Bowel

The ECS is ubiquitously expressed in the human body and it actively controls gut homeostasis. The best characterized ECS receptors are the cannabinoid receptors 1 (CB1) and 2 (CB2) (Mackie, 2005).

CB1 has been found in intestinal epithelial and in the enteric nervous system (ENS) (Coutts and Izzo, 2004).

Physiologically, the activation of presynaptic CB1 attenuates large and small bowel muscle tone and inhibits GI motility, mainly by reducing the release of acetylcholine from enteric nerves and also by inhibiting all the components of the peristaltic reflex (Wright et al., 2005). Moreover, CB1 activation, via the purinergic system, inhibits spontaneous ileal contractions and modulate the activity of vagal neurotransmission, reducing intestinal peristalsis (DiPatrizio, 2016).

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CB2 has been found on enteric neurons but it is predominantly expressed by intestinal immune cells (Izzo, 2007). Targeting intestinal CB2 decreases inflammation through the reduction of cytokine and chemokine production from activated immune cells (Wright et al., 2008). In pathophysiological conditions, CB2 controls intestinal motility (Wright et al., 2008) and its activation slows down gut transit (Mathison et al., 2004).

Bot1 and CB2 have been identified in the intestinal neuronal circuitry of the transmission of visceral pain and their activation reduce visceral sensation and nociception (Hohmann and Suplita, 2006).

N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG) are the best characterized endocannabinoids; they are synthesized from membrane phospholipids on demand: AEA is synthesized by N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD); and 2-AG by diacylglycerol lipase (DAGL), then they are released and induce a local response by activating CB1 and/or CB2 receptors (the latter being involved mainly in pathophysiological conditions) (Izzo and Camilleri, 2008). These compounds are involved in the control of food intake and hunger (DiPatrizio, 2016; Lee et al., 2016). Specifically, AEA seems to regulate appetite and energy balance, while 2-AG may serve as a general hunger signal (Di Marzo and Matias, 2005; DiPatrizio, 2016). AEA, via CB2, plays also a pivotal role in maintaining immunological health in the gut (Acharya et al., 2017).

Subsequent to their activation, endocannabinoids are inactivated by reuptake from the degradative enzymes fatty acid amide hydrolase (FAAH), located in cells of the myenteric plexus and monoacylglycerol lipase (MAGL), present in the nerve cells and fibers throughout the muscle mucosal layers of the intestine (Di Marzo, 2006).

Inhibition of MAGL and FAAH in the gut significantly reduces experimental colitis in mice, through mechanisms that involve a rise in 2-AG or AEA levels, respectively, and the stimulation of both CB1 CB2 signaling (Massa et al., 2004; Sałaga et al., 2014; Vera and Fichna, 2017).

N-palmitoylethanolamine (PEA) and other N-acylethanolamides (NAEs) are also expressed in the gut (Izzo and Sharkey, 2010). NAEs are atypical endocannabionoids: their structures resemble the classical endocannabinoids and they are preferentially metabolized by FAAH, but they do not bind CB receptors (Izzo and Sharkey, 2010; Ahn et al., 2014). NAEs, especially PEA, are involved in the control of various functions, including food intake, neuroprotection, nociception, and inflammation (Suardíaz et al., 2007; Ahn et al., 2014; Lowin et al., 2015).

Other components of the ECS are the transient receptor potential (TRP) channels, such as TRPV1, TRM8, and others (Storozhuk and Zholos, 2018). These receptors, widely expressed throughout the digestive tract, are involved in numerous processes: taste, chemo- and mechanosensation, thermoregulation, pain and hyperalgesia, mucosal function, gut homeostasis, and control of motility, amongst others (Kaneko and Szallasi, 2014).

GPR55, another potential cannabinoid receptor, seems to be also implicated in gut motility. Its inhibition reduce motility in mice and this effect was reversed by cannabidiol (CBD), but not by CB1 or CB2 receptor antagonists (Li et al., 2013).

The ECS is also an important modulator of the gut-brain axis. In the gut, receptors of the ECS (especially TRPs) are involved in sensory transduction of a large number of external and noxious stimuli (Holzer, 2011). In the brain, the ECS controls nausea and vomiting, especially through CB1 receptors in the dorsal vagal complex of the brainstem, and stress-induced alterations of the ECS have been linked to altered visceral sensations (Sharkey and Wiley, 2016).

The main role of ECS in the GI tract is controlling intestinal hyper-contractility. Moreover, it modulates visceral sensations, intestinal inflammation and gut–brain communications, all functions that appear to be dysregulated in IBS.

IBS and Endocannabinoid Deficiency

Clinical Endocannabinoid Deficiency (CED) has been confirmed as a plausible feature in a series of difficult-to-characterize psychosomatic pathologies, which display hyperalgesia, anxiety, and depression (Russo, 2004, 2016); Migraine, fibromyalgia and IBS fall in this category, often showing comorbidity in the three diagnosis (Nicolodi and Sicuteri, 1996; Sperber et al., 1999; Peres et al., 2001). CED occurs either as a congenital disorder, or as a result of epigenetic changes.

IBS subtypes exhibit distinct variations of the ECS tone. IBS-D patients show genetic alterations affecting endocannabinoid metabolism, variants of the CNR1 and FAAH genes, and lower levels of Oleoylethanolamine (OEA) and PEA compared to healthy subjects (Fichna et al., 2013). Specifically, the CNRI rs806378 CT/TT genotype shows a significant association with colonic transit in IBS-D (Camilleri et al., 2013). Conversely, IBS-C patients show levels of OEA higher than healthy volunteers, and reduced levels of FAAH mRNA in intestinal tissues (Fichna et al., 2013).

Some of these changes may occur as the result of chronic stress, which profoundly impacts the ECS: it silences the Cnr1 gene promoter via an increased methylation by DNA (cytosine-5)-methyltransferase 1, but it also activates the Trpv1 promoter via acetylation (Hong et al., 2015). This results in reduced levels of CB1 and increased levels of TRPV1 in the sensory neurons localized in the pelvic organs, including the colon, which is a feature of visceral pain, as later discussed (Fichna et al., 2013).

Stress in the early-life stage is also an important contributor to IBS development and it is associated with epigenetic changes that lead to visceral hypersensitivity (Moloney et al., 2015). Maternal deprivation increases the expression of the endocannabinoid genes Cnr1, Cnr2a, Cnr2b, and GPR55 in the frontal cortex of male rats, whereas in female rats, increased expression was reported only in the hippocampus, a difference that may underline the prevalence of IBS in the female population (Marco et al., 2014). The relevance of pediatric stress in IBS is supported by the fact that infantile colitis, characterized by visceral sensitivity and dysphoria and resistant to most pharmacotherapies, seem to be offset by the endocannabinoids present in maternal milk, reason for it is hypothesized that this condition may also be a CED (Russo, 2004). Taken these data together, genetic polymorphisms and alterations in gene

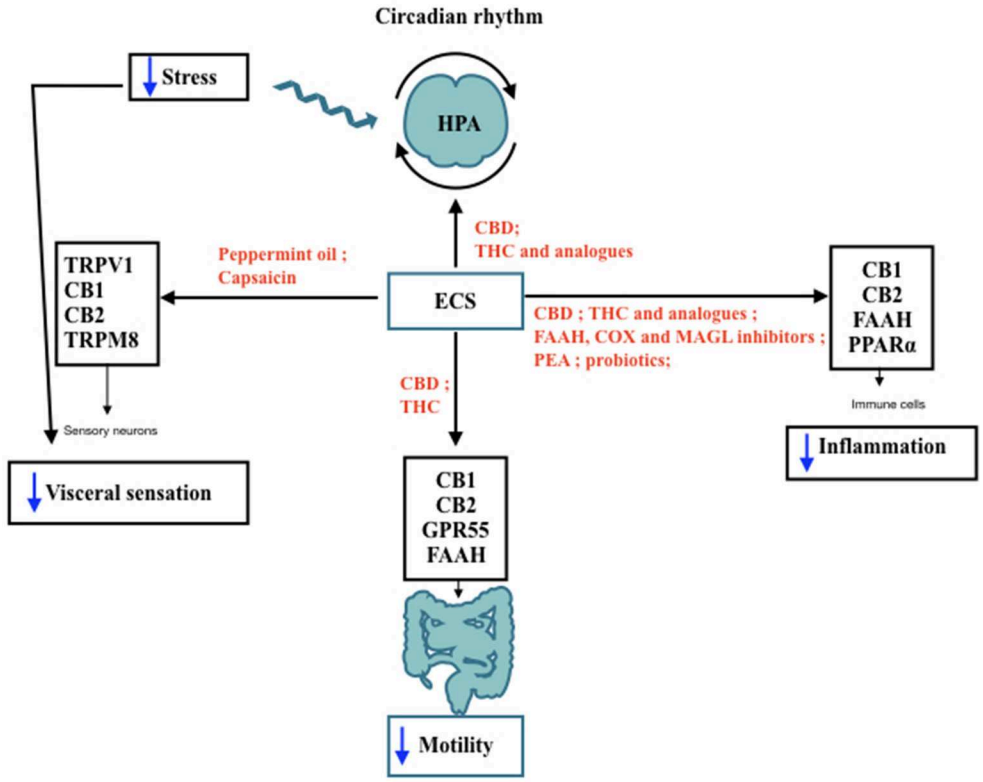

FIGURE 1 | IBS features modulated by ECS. Schematic representation of the Endocannabinoid System (ECS) involvement in IBS features and its interaction with hypothalamic-pituitary-adrenal (HPA) axis throughout day/night. The black arrows indicate the receptors and the target sites controlled by ECS components. In red are shown the agents capable of modulating ECS activities that may be useful to improve IBS symptoms, such as motility, visceral pain, and low-grade inflammation. Blue arrows indicate a decrease in the functions targeted by ECS stimulation. TRPV I, Transient receptor potential vanilloid I; CB I, Cannabinoid Receptor I; CB2: Cannabinoid Receptor 2; TRPM8, Transient receptor potential melastatin 8; CBD, cannabidiol; THC, tetrahydrocannabinol; FAAH, fatty acid amide hydrolase; COX, cyclooxigenase; MAGL, monoacyl glycerol lipase; PEA, palmitoylethanolamide; PPARa: Peroxisome proliferator-activated receptor a.

expression are associated with disturbances in GI motility and sensation, supporting the pathophysiologic significance of alterations in the ECS in the gut (Moloney et al., 2015).

UTILIZING ECS-MODULATING AGENTS FOR IBS

ECS-Modulating Agents

Gut health devoid of pain and maintenance of balanced body weight seems to require a complex interplay between diet, enteric flora, and endocannabinoid balance (Clarke et al., 2012; Russo, 2016). Oral administration of *Lactobacillus acidophilus NCFM* induce a direct increase of the cannabinoid receptors CNR2 mRNA (Rousseaux et al., 2007). This result corresponded with an enhancement of morphine analgesic effect in rats, which was inhibited by administration of the CB2 antagonist, AM-630 (Rousseaux et al., 2007). Cannabinoids may also directly alter the microfloral balance, as underscored by the finding that THC affected the F*irmicutes:Bacteroidetes* ratio in obese mice, preventing their weight gain despite a high-fat diet (Cluny et al., 2015).

The interaction of the microbiome–gut–brain axis is highly dependent on hypothalamic–pituitary–adrenal (HPA) stress modulation, which is dysregulated in IBS patients (Chang et al., 2009). The ECS regulates basal and circadian HPA axis activation (Patel et al., 2004; Liedhegner et al., 2014), and these changes relate to the differences in visceral sensation that feature in IBS (Gschossmann et al., 2001). Linkage of the cannabinoid–vanilloid pathway to the HPA axis has been demonstrated by experiments monitoring rats inoculated with corticosterone, mimicking chronic stress, which developed visceral hyperalgesia (Hong et al., 2011); moreover, as also shown by another stressed rat model (Hong et al., 2009), the levels of AEA and the expression and phosphorylation of TRPV1 increased in the animals, whilst CB1 expression decreased in lumbosacral primary afferent neurons localized in the colon, but not in those innervating the lower extremities (Hong et al., 2009, 2011). AEA is an endogenous agonist at both CB1 and TRPV1 (McPartland et al., 2007), receptors that co-localize in nociceptive primary sensory neurons (Ahluwalia et al., 2000). Activation of CB1 inhibits nociception, whereas agonism at TRPV1 increases pain perception (Malik et al., 2015). Treatment of stressed rats with the CB1 agonist WIN 55,212-2 or the TRPV1 antagonist capsazepine

prevented visceral hyperalgesia (Hong et al., 2009). Similar data have been observed in biopsies from IBS sufferers, which show a 3.5-fold elevation in TRPV1-immunoreactive nerve fibers (Akbar et al., 2008).

Considering this evidences, it has been posited that chronic stress causes down-regulation or loss of CB1, activation of the HPA stress response, anxiety, and induces visceral hyperalgesia that involve region-specific changes in endovanilloid and endocannabinoid pathways in sensory neurons innervating the pelvic viscera (Morena et al., 2016). Thus, a rationale exists for the use of compounds that boost AEA and PEA levels and desensitize TRPV1, to treat hypersensitivity and pain in IBS. While some authors have encouraged the use of the phytocannabinoid cannabidiol (CBD), no clinical trials have tested this hypothesis (Russo, 2004; Pandey et al., 2020). CBD may be an useful therapeutic intervention as it desensitizes TRPV1 and inhibits PEA and AEA hydrolysis and uptake (Bisogno et al., 2001).

Targeting endocannabinoid-degrading enzymes to increase AEA may be an interesting model (Sakin et al., 2015), given their role in the tonic disinhibition of periaqueductal gray region of the brainstem to promote analgesia and chronic stress-induced anxiety (Lau et al., 2014; Sakin et al., 2015). A dual FAAH and COX inhibitor has been shown to increase AEA and PEA levels, reducing features of colitis in mice (Sasso et al., 2015).

Clinical Trials With ECS-Acting Agents

Despite the numerous lines of evidence showing the involvement of ECS in the regulation of IBS features and the promising data from pre-clinical studies, few clinical trials tested the effect of ECS-modulating agents in IBS.

On the other hand, ECS alteration in IBS patients has been clearly documented.

As ECS is known to decrease motility, effects of dronabinol, a non-selective agonist of the cannabinoid receptors, have been tested on IBS patients (Wong et al., 2011). In a 2011 clinical trial, dronabinol reduced fasting colonic motility in all IBS-D patients, particularly those carrying the CB1 receptor polymorphism rs806378 (Wong et al., 2011). Another clinical study carried out a few years later, failed to replicate these results, obtaining only modest delay in motility, maybe for differences in methods (manometry vs. radioscintigraphy) and the lower number of patients enrolled (Wong et al., 2012). Dronabinol can also improve visceral sensitivity and colonic relaxation, as showed in a double-blind, placebo-controlled trial (Esfandyari et al., 2007).

As mentioned before, Fichna et al. showed that lower PEA levels are associated with cramping abdominal pain (Fichna et al., 2013). A randomized placebo-controlled multicenter study assessing the efficacy of PEA in IBS, revealed that PEA may be an useful tool for pain management in this condition (Barbara et al., 2014).

Since visceral hypersensitivity is linked to an increase in Ts regard, a 2011 pilot study found that ingesting capsaicin-containing enteric-coated pills desensitized TRPV1 and decreased the intensity of abdominal pain and bloating in IBS patients vs. placebo (Bortolotti and Porta, 2011). Another study confirmed that TRPV1 desensitization reduced visceral hypersensitivity, symptoms, and abdominal pain (Wouters et al., 2016).

Menthol-induced analgesia and pain relief is mediated mainly by TRPM8 (Liu et al., 2013). This is the rationale for various trials that analyzed the efficacy of peppermint oil (containing menthol) in IBS. Even with some limitations mainly due to the delivery system of peppermint oil in the digestive tract, it turned out an effective treatment capable of improving IBS symptoms, especially abdominal pain, even in children suffering IBS (Kline et al., 2001; Cappello et al., 2007; Merat et al., 2010; Cash et al., 2016).

CONCLUSIONS

Although the pathophysiology of IBS remains unclear, targeting the ECS may represent a promising strategy to modulate gut motility, visceral hyperalgesia, low-grade intestinal inflammation, and gut–brain axis alteration, all features that may improve IBS symptoms onset. It is also evident that both an IBS-diet (Wouters et al., 2016) and a stress-relief practice are required to boost the beneficial effects of any of the agents suggested.

In light of this, agents capable of modulating the ECS may provide a strategy worth attempting even first line treatment for IBS patients (**Figure 1**). This is due to the fact that compounds such as PEA, CBD and peppermint oil display a very large safety profile and have been proving beneficial to improve IBS symptoms (Halford et al., 2018); PEA, peppermint oil, THC and its synthetic analogs may be recommended in IBS patients to improve abdominal spasms, cramps and visceral pain. THC and CBD may alter ECS-driven response to the pathology. However, there is still a wide gap in the current understanding of IBS mechanism and in the use of cannabis containing both CBD and THC as potential therapy, which can only be bridged by randomized clinical trials.

AUTHOR CONTRIBUTIONS

VB and FT contributed to conception and design of the study and wrote sections of the manuscript. VB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Behavioral/Systems/Cognitive

Cannabinoid Receptor 1 in the Vagus Nerve Is Dispensable for Body Weight Homeostasis But Required for Normal Gastrointestinal Motility

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The cannabinoid receptor 1 (CB_1R) is required for body weight homeostasis and normal gastrointestinal motility. However, the specific cell types expressing CB_1R that regulate these physiological functions are unknown. CB_1R is widely expressed, including in neurons of the parasympathetic branches of the autonomic nervous system. The vagus nerve has been implicated in the regulation of several aspects of metabolism and energy balance (e.g., food intake and glucose balance), and gastrointestinal functions including motility. To directly test the relevance of CB_1R in neurons of the vagus nerve on metabolic homeostasis and gastrointestinal motility, we generated and characterized mice lacking CB_1R in afferent and efferent branches of the vagus nerve (*Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice). On a chow or on a high-fat diet, *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice have similar body weight, food intake, energy expenditure, and glycemia compared with *Cnr1*$^{flox/flox}$ control mice. Also, fasting-induced hyperphagia and after acute or chronic pharmacological treatment with SR141716 [*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole carboxamide] (CB_1R inverse agonist) paradigms, mutants display normal body weight and food intake. Interestingly, *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice have increased gastrointestinal motility compared with controls. These results unveil CB_1R in the vagus nerve as a key component underlying normal gastrointestinal motility.

Introduction

The cannabinoid receptor 1 (CB_1R) belongs to the endocannabinoid system (Matsuda et al., 1990; Piomelli, 2003) and is widely expressed in the mammalian body. In central and peripheral neurons, CB_1R modulates neurotransmitter release (Marsicano and Lutz, 1999; Piomelli, 2003). Pharmacological blockade of CB_1R reduces food intake and exerts anti-obesity effects in mice and humans and also improves lipid and glucose profiles of overweight and diabetic subjects (Ravinet Trillou et al., 2003; Després et al., 2005, 2006; Van Gaal et al., 2005; Addy et al., 2008). Deletion of CB_1R in mice leads to reduced food intake, body adiposity, and increased insulin sensitivity (Cota et al., 2003; Ravinet Trillou et al., 2004). Interestingly, CB_1R null mice are hypophagic after fasting and are insensitive to the anorectic actions of SR141716 [*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole carboxamide] (CB_1R inverse agonist), suggesting that CB_1R mediates the inhibitory effect of this drug on food intake (Di Marzo et al., 2001). In summary, CB_1R exerts important functions on the control of body energy, glucose, and lipid balance.

The use of cell-specific CB_1R genetic manipulation has indicated some of the critical sites in which CB_1R regulates metabolic homeostasis. For example, CB_1R in glutamatergic neurons has been reported to be required for the orexigenic effect of cannabinoids (Bellocchio et al., 2010). Also, CB_1R in forebrain and sympathetic neurons has been shown to be required for normal energy expenditure (Quarta et al., 2010). Nevertheless, the role of CB_1R in other neuronal sites, for example, the parasympathetic branch of the autonomic nervous system, is yet to be known.

The CB_1R also regulates gastrointestinal functions, for instance, motility. Of note, diarrhea is a frequent untoward side effect observed in patients treated with CB_1R inverse agonist (Despres et al., 2005; Addy et al., 2008), and hypermotility of food through the intestines may reduce absorption of water and nutrients by the intestine and be an underlying cause of diarrhea. In rodents, inhibition of CB_1R increases gastrointestinal motility, whereas activation of CB_1R inhibits it (Colombo et al., 1998; Izzo et al., 1999; Landi et al., 2002; Pinto et al., 2002; Capasso et al., 2005). Also, CB_1R null mice have increased gastrointestinal motility (Yuece et al., 2007). Moreover, it has been suggested that CB_1R modulates acetylcholine release from myenteric neurons (Coutts and Pertwee, 1997; Coutts and Izzo, 2004).

Neurons of the vagus nerve have been shown to control body energy/glucose metabolism (Williams et al., 2000; Rossi et al.,

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2011) and upper gastrointestinal functions. CB_1R is abundantly expressed in both vagal afferent and efferent neurons (Burdyga et al., 2004). Capsaicin deafferentation ablates the orexigenic effect of CB_1R agonist (Gómez et al., 2002), and vagotomy impairs CB_1R regulation of gastrointestinal motility (Krowicki et al., 1999). Thus, it has been suggested that CB_1R in these neurons regulates feeding/body energy balance and gastrointestinal motility. To directly test these hypotheses, we generated and characterized mice lacking CB_1R in vagal afferent and efferent neurons located in the nodose ganglia and dorsal motor nucleus of the vagus (DMV).

Materials and Methods

Animal care. Care of animals and all procedures were approved by University of Texas Southwestern Medical Center Institutional Animal Care and Use Committee. Mice were housed in groups of four to five mice on a 12 h dark/light cycle with *ad libitum* access to water and food, unless otherwise specified. Mice were fed on a standard chow diet or, if mentioned, on a high-fat diet (TD88137; Harlan Teklad). All studies were performed using male mice.

Generation of Cnr1$^{flox/flox}$; Phox2b–Cre *mice.* Mice containing a Cre-conditional *Cnr1* null allele (*Cnr1*$^{flox/wt}$) were generated in the laboratory of Pierre Chambon for Sanofi-Aventis and then imported by University of Texas Southwestern Medical Center. The targeting plasmid was constructed using genomic DNA of mouse strain 129/Sv. The single encoding exon of *Cnr1* was flanked by loxP sites. The first loxP site was cloned upstream of *Cnr1* start codon, and the loxP–FRT–Neomycin–FRT cassette was cloned downstream of *Cnr1* stop codon. The targeting vector contained 2.1 kb of genomic DNA between loxP sites and 3.8 and 3 kb of genomic DNA as 5′ and 3′ homologous arms, respectively. The targeting plasmid was electroporated into 129 embryonic stem (ES) cells, and Neomycin-resistant clones were screened for homologous recombination as described below. Screening of 3′ end homologous recombination was performed by PCR using ES cell genomic DNA as template and the following primers: Neomycin forward (Neo F), AGGGGCTCGCGCCAGCCGAAGTGTT; and 3′ end reverse (3′ end R), ACAGCAGTCTCAATGATGCTACCAG. If ES cells contain a targeted allele, the expected PCR amplicon is ~4 kb. Screening of 5′ end homologous recombination was performed by Southern blot using NheI as restriction enzyme and a probe between the 5′ end NheI site and the 5′ end edge of the construct. Expected bands are 12 kb (*Cnr1* targeted) and 10 kb (*Cnr1*^{wt}). Targeting was further confirmed by Southern blot in ES cell genomic DNA digested with restriction enzymes NheI or HindIII and a probe against the Neomycin cassette. Expected bands are 12 kb (NheI DNA fragment) and 7.2 kb (HindIII DNA fragment). Chimeric mice (F0) were bred to wild-type mice to generate mice bearing the targeted *Cnr1* allele (F1). These F1 mutants were bred to a ubiquitously expressing FLPe recombinase (Flp) transgenic line. Successful removal of the flippase recognition target (FRT)-flanked phosphoglycerate kinase (PGK)–Neomycin cassette was confirmed by PCR in *Cnr1*$^{flox/wt}$ mice bearing a ubiquitously expressing Flp transgene (F2). These F2 mice were bred to wild-type mice, and offspring mice containing the FLP-recombined FRT-flanked PGK–Neomycin (F3) were selected by PCR genotyping. These F3 mutant mice were used to establish the Cre-conditional *Cnr1* null line. *Cnr1*$^{flox/flox}$ mice were mated to *Phox2b–Cre* transgenic mice (line 1; Scott et al., 2011) to obtain the study groups that were in a mixed C57BL/6 and 129 genetic background. Mice were genotyped by PCR using primers CB_1R forward (ACCACCTTCCTCATGTTAACCT) and CB_1R reverse (GACCAGAGACAGCTCCAGA) for amplification of the *Cnr1*^{wt} (197 bp) or *Cnr1*^{flox} allele (247 bp) and CB_1R forward and CB_1R-D (GGGTAGTTAGGCTTCAGATTTGGA) for amplification of the Cre-recombined *Cnr1* null allele (*Cnr1*$^{\Delta}$) (419 bp). Mice that underwent the "delta event," which has been described previously (Balthasar et al., 2004), were excluded from the studies. To genotype for *Phox2b–Cre* allele, a PCR reaction was performed, as described previously (Scott et al., 2011), using the following primers: Phox2b forward, CCGTCT

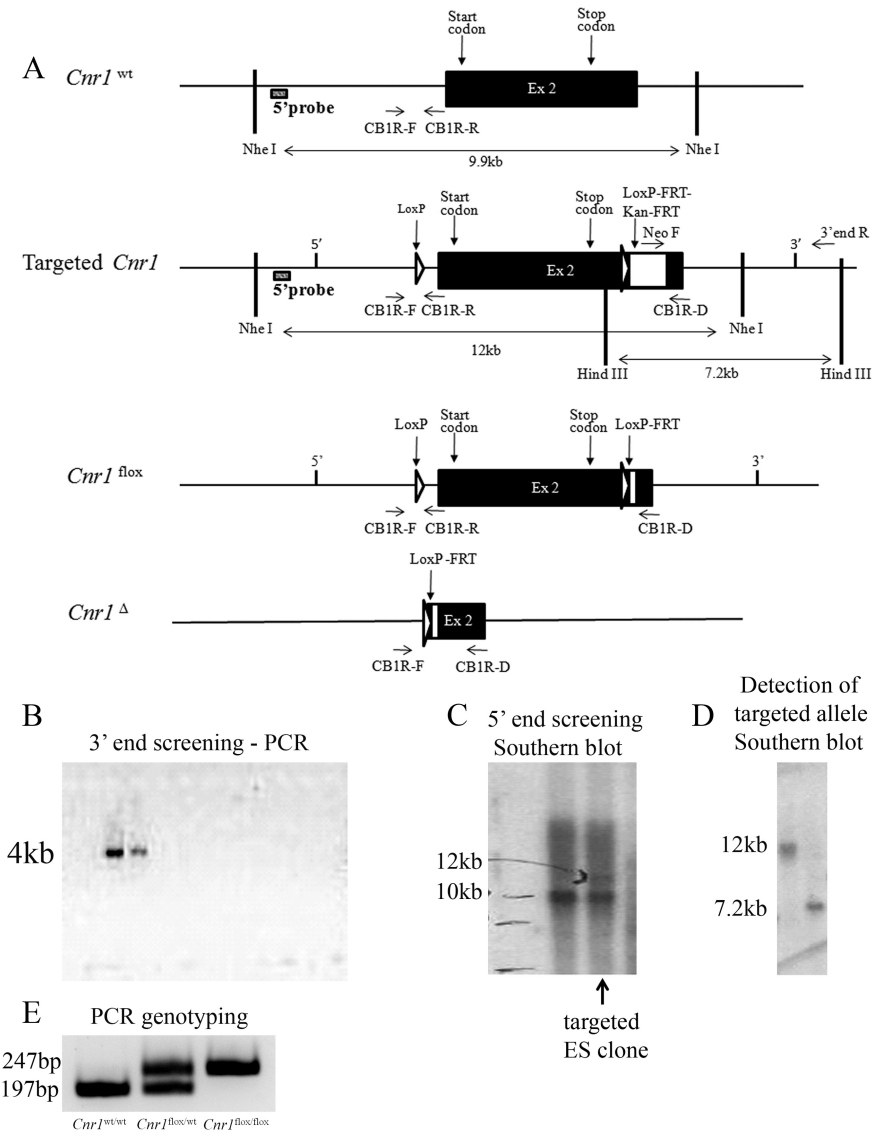

Figure 1. Generation of mice bearing a Cre-conditional *Cnr1* null allele (*Cnr1*$^{flox/wt}$). Schematic representation of the targeting strategy. Represented are *Cnr1*^{wt}, targeted *Cnr1*, *Cnr1*^{flox}, and *Cnr1*$^{\Delta}$ alleles (***A***). Screening of 3′ end homologous recombination by PCR. A 4 kb PCR amplicon expected in ES cells bearing *Cnr1* targeted allele (***B***). Screening of 5′ end homologous recombination by Southern blot using NheI as the restriction enzyme and a probe upstream of 5′ edge of the construct. Expected 12 kb (*Cnr1* targeted) and 10 kb (*Cnr1* wt) bands are indicated (***C***). Detection of the *Cnr1* targeted sequences in the single clone deemed targeted according to ***B*** and ***C*** (***D***). NheI and HindIII were the restriction enzymes used on left and right lanes, respectively, and the probe was against the Neomycin cassette (***D***). Expected PCR amplicons from tail genomic DNA of *Cnr1*$^{w/w}$, *Cnr1*$^{flox/wt}$, and *Cnr1*$^{flox/flox}$ mice (***E***).

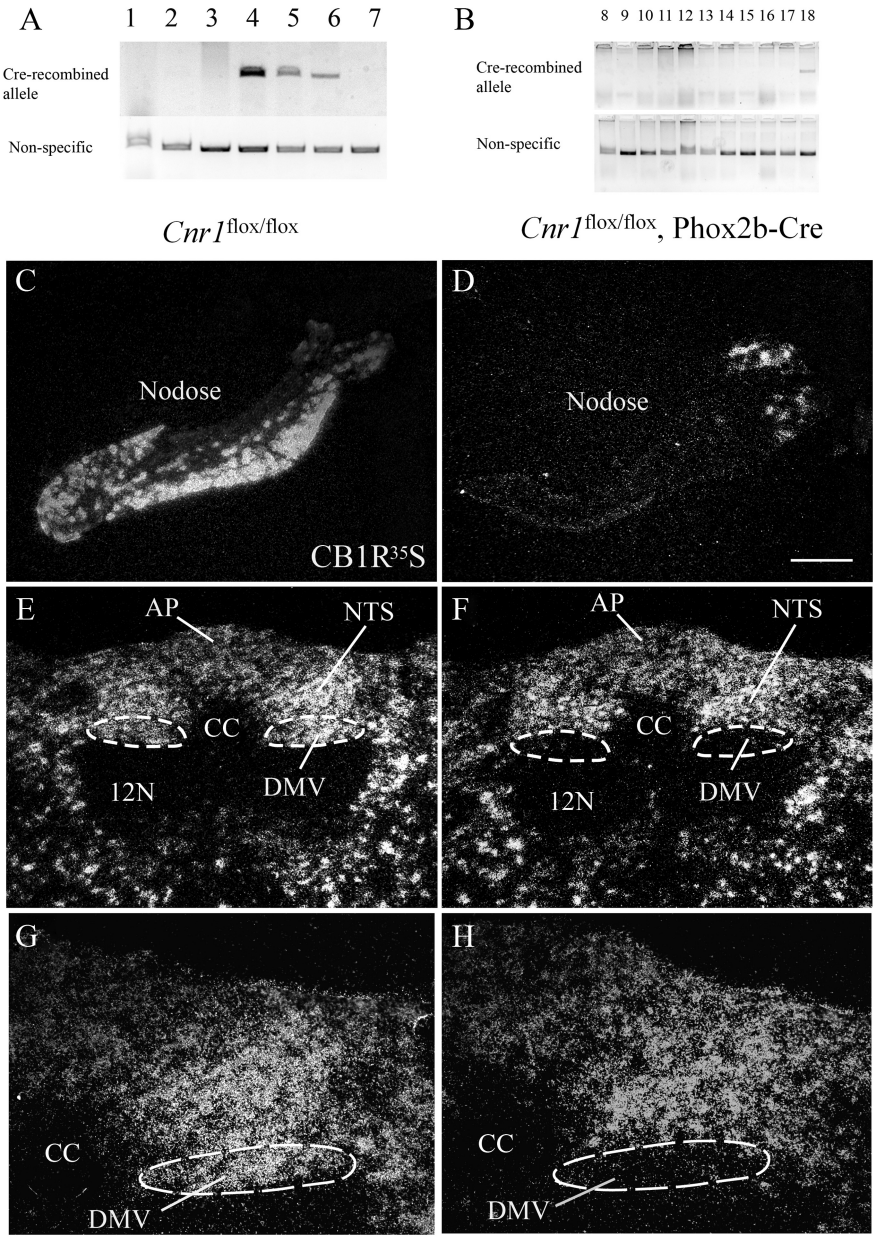

Figure 2. Deletion of CB_1R in nodose and DMV neurons. Detection of Cre-recombined *Cnr1* null allele by PCR using genomic DNA of a $Cnr1^{flox/flox}$; *Phox2b–Cre* mouse [***A***: ***1***, forebrain; ***2***, hypothalamus; ***3***, pituitary; ***4***, midbrain; ***5***, hindbrain; ***6***, nodose; ***7***, tail as negative control; ***B***: ***8***, heart; ***9***, kidney; ***10***, stomach; ***11***, duodenum; ***12***, jejunum; ***13***, ileum; ***14***, colon; ***15***, pancreas; ***16***, liver; ***17***, perigonadal white adipose tissue; ***18***, positive control, hindbrain]. *In situ* hybridization histochemistry for *Cnr1* mRNA (*in situ* probe complementary to *Cnr1* exon 2) in nodose and hindbrain sections of $Cnr1^{flox/flox}$ (***C***, ***E***, ***G***) and $Cnr1^{flox/flox}$; *Phox2b–Cre* (***D***, ***F***, ***H***) male mouse. Scale bar: ***C–F***, 200 μm; ***G***, ***H***, 100 μm. AP, Area postrema; 12N, 12 nerve; CC, central canal; NTS, nucleus of the solitary tract.

CCACATCCATCTTT; Phox2b reverse, GTACGGACTGCTCTGGTGGT; and Cre reverse, ATTCTCCCACCGTCACTACG. Male mice littermates were used for all the experiments performed.

In situ *hybridization histochemistry.* Mice were anesthetized with chloral hydrate (500 mg/kg, i.p.) and perfused transcardially with diethylpyrocarbonate (DEPC)-treated water 0.9% PBS, followed by 10% neutral buffered Formalin. Brains and nodose ganglion were dissected and placed in the same fixative for 4–6 h at 4°C, immersed in 20% sucrose in DEPC-treated PBS, pH 7.0, at 4°C for 24 h. Tissue was sliced into 25 μm sections on a freezing microtome. Sections from brain and nodose ganglion were mounted onto SuperFrost plus slides (Thermo Fisher Scientific) and stored at −20°C. Before hybridization, sections were fixed in 4% formaldehyde for 20 min, dehydrated in ascending concentrations of ethanol, cleared in xylene for 15 min, rehydrated in descending concentrations of ethanol, and placed in prewarmed 0.01 M sodium citrate buffer, pH 6.0. Sections were pretreated for 10 min in a microwave, dehydrated in ethanol, and air dried. The CB_1R riboprobe was generated by *in vitro* transcription with [^{35}S]UTP. The ^{35}S-labeled probe was diluted (10^6 dpm/ml) in hybridization solution containing 50% formamide, 10% dextran sulfate, and 1× Denhardt's solution (Sigma). The hybridization solution (120 μl) was applied to each slide, and they were incubated overnight at 57°C. Sections were then treated with 0.002% RNAase A solution and submitted to stringency washes in decreasing concentrations of sodium chloride/SSC. Sections were dehydrated and enclosed in x-ray film cassettes with BMR-2 film (Eastman Kodak) for 48 h. Slides were dipped in NTB2 autoradiographic emulsion (Eastman Kodak), dried, and stored at 4°C for 14 d. Slides were developed with a D-19 developer (Eastman Kodak).

The CB_1R probe (antisense) was transcribed from PCR fragments amplified using the following primers: forward, CTG CAA GAA GCT GCA ATC TG; and reverse, TGG CGA TCT TAA CAG TGC TC. This sequence is complementary to part of exon 2, which is the single encoding exon in *Cnr1*. Hybridization with the sense probe was performed as negative control.

Gastrointestinal motility. Gastrointestinal motility was measured using the charcoal method as described previously (Rossi et al., 2003). Male mice at 10–12 weeks of age were fasted overnight with water *ad libitum* and received a single injection of vehicle or SR141716 (10 mg/kg, i.p.) at time 0. At 30 min, mice received 100 μl of a solution of 10% charcoal–5% Arabic gum in saline (Sigma-Aldrich) by oral gavage, and, at 50 min, mice were killed by cervical dislocation and the intestine were quickly dissected. Immediately after dissection, the intestine was placed in cold 10% Formalin solution until the tissue was straightened, and the distance traveled by the solution was measured.

mRNA content. Four-hour-fasted mice were killed, and stomach and small intestine were quickly dissected, snap frozen in liquid nitrogen, and stored at −80°C until additional processing. Total RNA was isolated using Trizol (Invitrogen) following the protocol of the manufacturer. RNA samples were treated with DNase I (Roche Applied Science) and retro-transcribed using SuperScript III First-Strand Synthesis System (Invitrogen). qPCR analysis was performed using TaqMan assays (Applied Biosystems).

Stool analysis. Mice were individually housed, and stool samples were collected from the cages. Calorimetric and fat content analysis was performed by Central Analytical Lab, University of Arkansas Poultry Science, using ANSI/ASTM D2015-77 and AOAC 920.39C methods, respectively.

Body weight, metabolic rate, and food intake. Body weight measurement was performed weekly starting at 5 weeks of age. Metabolic rate parameters (oxygen consumption, carbon dioxide production, and respiratory exchange ratio) and food intake were measured by indirect calorimetry using the TSE labmaster system (TSE Systems). Approximately 8-week-old mice were transferred to the TSE labmaster system and allowed to acclimatize for 4 d, and data were collected for the following 3–4 d.

Pharmacological SR141716 treatment. Single-housed 7- to 8-week-old mice were fasted for 24 h, and, right before the dark cycle, mice received a single intraperitoneal injection of vehicle or SR141716 (3 mg/kg). Food intake was measured for the following 2 h.

For chronic treatment with SR141716, mice were fed on high-fat diet for ~8 weeks. Mice were single housed, and blood glucose, serum metabolites, and body composition were assessed before and after the pharmacological treatment. Blood glucose was measured using a standard glucometer (One Touch Ultra; Lifescan). Blood was centrifuged to collect serum for analysis of insulin (Crystal Chem), fatty acids (Wako Diagnostics), and triglycerides levels (Wako Diagnostics). Body composition was analyzed using the Echo MRI-100 system (Echo Medical Systems).

Data analyses. All values are reported as mean ± SEM. Analyses of the data were performed using GraphPad Prism software (GraphPad Software). Statistical significance was determined by two-tailed unpaired Student's *t* test or two-way ANOVA, followed by Bonferroni's *post hoc* test (** $p < 0.05$ and *** $p < 0.01$).

Results

Generation and validation of *Phox2b–Cre; Cnr1$^{flox/flox}$* mice

A Cre-conditional *Cnr1* null allele (*Cnr1^{flox}*) was generated by flanking exon 2 of *Cnr1* allele with loxP sites (Fig. 1*A*). A 4 kb PCR amplicon was observed in two ES clones screened for homologous recombination at the 3′ end (Fig. 1*B*). In one of these clones, the two expected bands at 12 and 10 kb, from *Cnr1* targeted and *Cnr1*^{wt} allele, were detected by Southern blot (Fig. 1*C*). Additional analysis of this single clone by Southern blot allowed the detection of a 12 and 7.2 kb band in the DNA digested with the restriction enzymes NheI and HindIII, respectively (Fig. 1*D*). *Cnr1$^{flox/wt}$* mice were mated, and *Cnr1$^{w/w}$*, *Cnr1$^{flox/wt}$*, and *Cnr1$^{flox/flox}$* offspring were obtained at the expected ratio according to the Mendelian distribution of alleles (Fig. 1*E*). *Cnr1$^{flox/wt}$* mice were crossed to *Phox2b–Cre* transgenic mice (Scott et al., 2011) to generate the study groups.

To determine whether *Cnr1$^{flox/flox}$; Phox2b–Cre* mice have Cre-recombined *Cnr1* allele in Phox2b neurons, we first performed PCR assays using genomic DNA from different brain areas and different organs/tissues. The Cre-recombined *Cnr1* allele is present in midbrain, hindbrain, and nodose ganglia (Fig. 2*A*), all sites in which Phox2b neurons are located. Cre-recombined *Cnr1* allele was not detected in all other tissues tested, including the stomach, different parts of the small intestine, and colon (Fig. 2*B*). Second, we performed *in situ* hybridization histochemistry to detect *Cnr1* mRNA in brain tissue. In *Cnr1$^{flox/flox}$; Phox2b–Cre* mice, distribution of *Cnr1* mRNA was similar to the pattern observed in *Cnr1$^{flox/flox}$* mice, including parabrachial nucleus (data not shown) and nucleus of the solitary tract (Fig. 2*E–H*). However, *Cnr1* mRNA was not detected in great part of nodose ganglia and DMV (Fig. 2*C–H*). Thus, these results show that *Cnr1$^{flox/flox}$; Phox2b–Cre* mice lack CB_1R in nodose ganglia and DMV neurons.

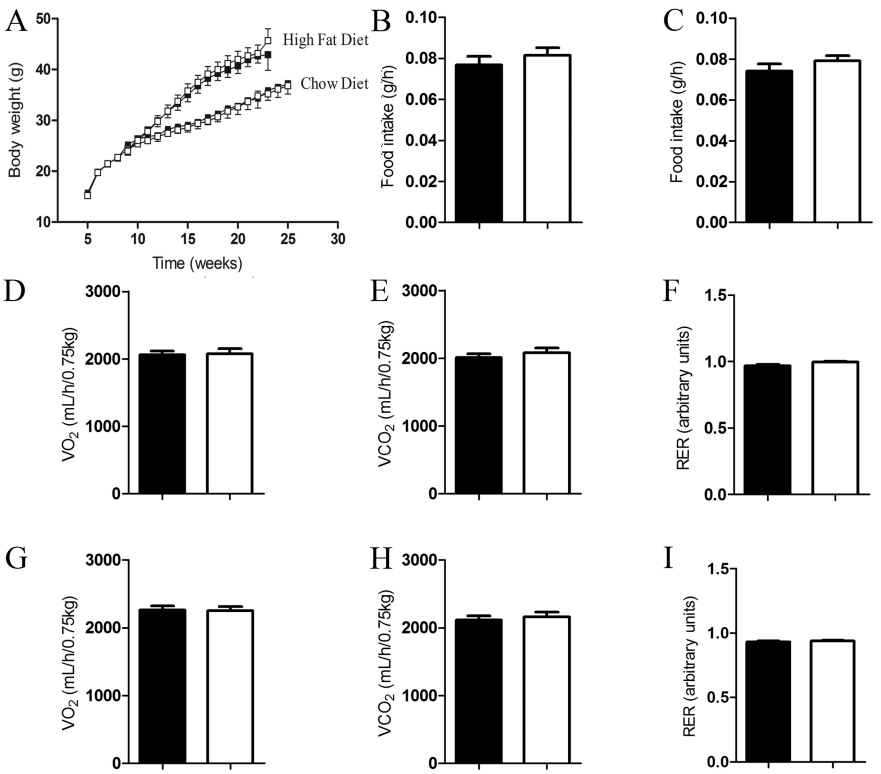

Figure 3. CB_1R in nodose and DVM neurons does not regulate body energy balance. Body weight curve of standard chow or high-fat fed mice (***A***) (chow diet: *Cnr1$^{flox/flox}$*, $n = 7$ and *Cnr1$^{flox/flox}$; Phox2b–Cre*, $n = 7$; high-fat diet: *Cnr1$^{flox/flox}$*, $n = 13$ and *Cnr1$^{flox/flox}$; Phox2b–Cre*, $n = 16$). Food intake of mice fed on standard chow (***B***) or high-fat diet (***C***). Oxygen consumption, carbon dioxide production, and respiratory exchange ratio of mice fed on chow (***D–F***) or high-fat diet (***G–I***) (chow diet: *Cnr1$^{flox/flox}$*, $n = 13$ and *Cnr1$^{flox/flox}$; Phox2b–Cre*, $n = 13$; high-fat diet: *Cnr1$^{flox/flox}$*, $n = 12$ and *Cnr1$^{flox/flox}$; Phox2b–Cre*, $n = 12$). Filled black symbols/bars and open symbols/bars represent *Cnr1$^{flox/flox}$* and *Cnr1$^{flox/flox}$; Phox2b–Cre* mice, respectively. Results are expressed as means ± SEM. Statistical analyses were performed using two-tailed unpaired Student's *t* test.

Body weight homeostasis in *Phox2b–Cre; Cnr1$^{flox/flox}$* mice

CB_1R controls food intake, energy expenditure, and thus body weight homeostasis (Cota, 2007; Quarta et al., 2010). To test whether CB_1R in the nodose/DMV is required for body weight homeostasis, we measured body weight, food intake, and energy expenditure in mice lacking CB_1R in the nodose/DMV neurons. On chow or high-fat diet feeding regimens, *Cnr1$^{flox/flox}$; Phox2b–Cre* mice have similar body weight compared with *Cnr1$^{flox/flox}$* controls (Fig. 3*A*). Food intake, oxygen consumption, carbon dioxide production, and respiratory exchange ratio were also similar between *Cnr1$^{flox/flox}$; Phox2b–Cre* and *Cnr1$^{flox/flox}$* mice (Fig. 3*B–I*).

CB_1R also regulates fasting-induced hyperphagia and mediates the anorexigenic effect of SR141716 (Di Marzo et al., 2001). Thus, we tested whether CB_1R in the nodose/DMV neurons is required for normal fasting-induced hyperphagia. Food intake after 24 h fasting was also similar between *Cnr1$^{flox/flox}$* and *Cnr1$^{flox/flox}$; Phox2b–Cre* mice (Fig. 4*A*). SR141716-treated *Cnr1$^{flox/flox}$* mice significantly reduce food intake compared with vehicle-treated *Cnr1$^{flox/flox}$* mice, similar to previously reported results (Fig. 4*A*) (Di Marzo et al., 2001). The anorexigenic effect of SR141716 in *Cnr1$^{flox/flox}$; Phox2b–Cre* mice was similar to the effect observed in *Cnr1$^{flox/flox}$* mice (Fig. 4*A*). Interestingly, SR141716-treated *Cnr1$^{flox/flox}$; Phox2b–Cre* mice tended to have longer meals and reduced rate of food intake compared with *Cnr1$^{flox/flox}$* mice, but the differences between the groups were not statistically significant (data not shown). In the chronic SR141716 treatment study, *Cnr1$^{flox/flox}$* mice treated with

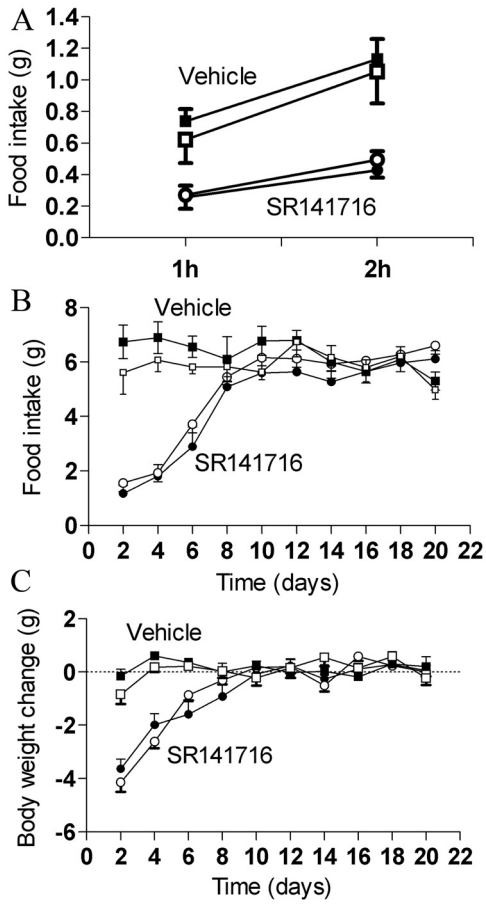

Figure 4. CB_1R in nodose and DVM neurons is not required for the anorexigenic effect and anti-obesity effect of SR141716. Fasting-induced hyperphagia (***A***) of mice fed on chow diet. Food intake (***B***) and body weight (***C***) curves of mice fed on high-fat diet and treated with 10 mg/kg SR141716 or vehicle (vehicle treated: *Cnr1*$^{flox/flox}$, $n = 6$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 7$; SR141716 treated: *Cnr1*$^{flox/flox}$, $n = 8$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 10$). Mice received daily intraperitoneal injections right before the beginning of dark cycle. Symbols represent *Cnr1*$^{flox/flox}$ (filled) and *Cnr1*$^{flox/flox}$*; Phox2b–Cre* (open). Results are expressed as means ± SEM.

SR141716 had reduced food intake during approximately the first week compared with vehicle-treated *Cnr1*$^{flox/flox}$ mice (Fig. 4*B*). The anorexigenic effect of SR141716 was transient as reported previously (Ravinet Trillou et al., 2003; Cota et al., 2009). Also, body weight reduction was observed in SR141716-treated compared with vehicle-treated *Cnr1*$^{flox/flox}$ mice (Fig. 4*C*). In *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice, the anorexigenic and body weight reducing effects of SR141716 were similar to those observed in *Cnr1*$^{flox/flox}$ mice (Fig. 4*B*,*C*). Fed and fasted blood glucose, fatty acids, and triglycerides were similar between *Cnr1*$^{flox/flox}$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice either before treatment or after treatment (data not shown). As for body composition analysis, fat mass was reduced in SR141716-treated compared with vehicle-treated *Cnr1*$^{flox/flox}$ mice, but similar fat mass was observed in *Cnr1*$^{flox/flox}$*; Phox2b–Cre* compared with *Cnr1*$^{flox/flox}$ mice, either before or after treatment (data not shown). Altogether, these results suggest that CB_1R in the nodose/DMV neurons is not required to control body weight, food intake, energy expenditure, blood glucose, fatty acids, triglycerides, and fat mass and to mediate the effects of SR141716 on these parameters.

Gastrointestinal motility in *Phox2b–Cre; Cnr1*$^{flox/flox}$ mice

Pharmacological administration of CB_1R antagonist (SR141716) or genetic deletion of CB_1R in mice increases gastrointestinal motility (Coutts and Izzo, 2004; Yuece et al., 2007). *In vitro* data suggest that CB_1R in cholinergic fibers of the parasympathetic branch neurons mediate this effect (Coutts and Pertwee, 1997; Coutts and Izzo, 2004). However, the CB_1R-expressing sites that mediate this effect are unknown. Here we tested whether CB_1R in nodose/DMV neurons is required to regulate gastrointestinal motility. On chow diet, *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice had increased gastrointestinal motility compared with *Cnr1*$^{flox/flox}$ mice (Fig. 5*A*). Also, SR141716-treated mice had increased gastrointestinal motility compared with vehicle-treated mice (Fig. 5*A*). These results suggest that CB_1R in nodose/DMV neurons is required for normal gastrointestinal motility in chow diet feeding conditions.

High-fat diet increases gastrointestinal motility (Izzo et al., 2009). Thus, we investigated the relevance of CB_1R in nodose/DMV neurons on regulation of gastrointestinal motility in the context of high-fat diet. On high-fat diet, *Cnr1*$^{flox/flox}$*; Phox2b–Cre* mice had increased gastrointestinal motility compared with *Cnr1*$^{flox/flox}$ mice (Fig. 5*B*), but this parameter was not affected by SR141716 treatment in both genotypes (Fig. 5*B*). These results suggest that CB_1R in nodose/DMV neurons is required for normal gastrointestinal motility also in the high-fat diet feeding condition.

To exclude the possibility that the increase in gastrointestinal motility observed in *Cnr1*$^{flox/flox}$*; Phox2b–Cre* was a result of the transgene per se, we performed experiments using *Cnr1*$^{w/w}$*; Phox2b–Cre* and *Cnr1*$^{w/w}$ mice fed on chow diet. We observed similar gastrointestinal motility in both groups (data not shown), indicating that the increase in gastrointestinal motility in *Cnr1*$^{flox/flox}$*; Phox2b–Cre* results from deletion of CB_1R in Phox2b neurons and not by an effect attributable to the *Phox2b–Cre* transgene itself.

CB_1R is expressed in several neurons of the small intestine, and the majority of those are cholinergic (Coutts et al., 2002).

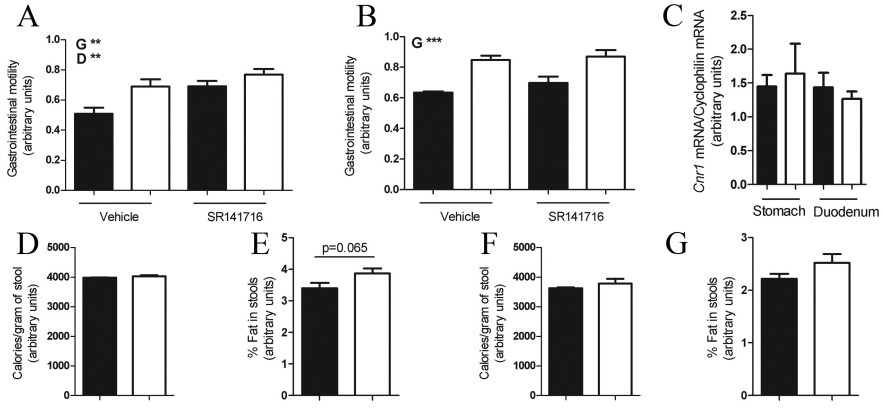

Figure 5. CB_1R in nodose and DMV neurons is required for gastrointestinal motility. Gastrointestinal motility in vehicle- or SR141716-treated mice fed on standard chow (***A***) (vehicle treated: *Cnr1*$^{flox/flox}$, $n = 10$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 10$; SR141716 treated: *Cnr1*$^{flox/flox}$, $n = 9$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 9$) or high fat (***B***) (vehicle treated: *Cnr1*$^{flox/flox}$, $n = 6$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 6$; SR141716 treated: *Cnr1*$^{flox/flox}$, $n = 7$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 7$). qPCR analysis of stomach and duodenum total mRNA (*Cnr1*$^{flox/flox}$, $n = 5$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 5$) (***C***). Calorimetric analyses or percentage of fat content of stools of mice fed on standard chow (***D***, ***E***) or high fat (***F***, ***G***) (*Cnr1*$^{flox/flox}$, $n = 6$ and *Cnr1*$^{flox/flox}$*; Phox2b–Cre*, $n = 6$). Bars represent *Cnr1*$^{flox/flox}$ (filled) and *Cnr1*$^{flox/flox}$*; Phox2b–Cre* (open). Results are expressed as means ± SEM. Statistical analyses were performed using two-way ANOVA (***A***, ***B***) or Student's *t* test (***C–G***). For ***A***, genotype (G), $F_{(1,31)} = 8.6$, $p < 0.05$; drug (D), $F_{(1,31)} = 8.9$, $p < 0.05$; and interaction, $F_{(1,31)} = 1.3$, $p = 0.25$. For ***B***, genotype (G), $F_{(1,17)} = 23.3$, $p < 0.05$; drug, $F_{(1,17)} = 1.16$, $p = 0.29$; and interaction, $F_{(1,17)} = 0.3$, $p = 0.61$.

To investigate whether the phenotype on gastrointestinal motility could be a result of reduced *Cnr1* mRNA expression in the stomach or small intestine, we measured *Cnr1* mRNA levels in those tissues. In either the stomach or duodenum, similar levels of *Cnr1* mRNA was detected in samples from $Cnr1^{flox/flox}$ and $Cnr1^{flox/flox}$*; Phox2b–Cre* mice (Fig. 5*C*). Thus, these results indicate that the phenotype on gastrointestinal motility is not the result of reduced *Cnr1* mRNA expression in the stomach or small intestine.

To further investigate whether increased gastrointestinal motility would result in reduced absorption of nutrients, we performed calorimetric and fat content analysis in the stools. Similar calories per gram or fat content was observed in stools of $Cnr1^{flox/flox}$ and $Cnr1^{flox/flox}$*; Phox2b–Cre* mice fed on chow diet (Fig. 5*D*,*E*). Of note, fat content tended to be higher in stools of $Cnr1^{flox/flox}$*; Phox2b–Cre* mice, but differences were not statistically significant. Also, similar calories per gram or fat content was observed in $Cnr1^{flox/flox}$ and $Cnr1^{flox/flox}$*; Phox2b–Cre* mice fed on a high-fat diet (Fig. 5*F*,*G*). Therefore, these data suggest that increased gastrointestinal motility does not lead to reduced absorption of nutrients, a result that is in agreement with the unchanged energy balance of $Cnr1^{flox/flox}$*; Phox2b–Cre* mice.

Discussion

CB_1R is widely expressed and regulates several physiological processes. Genetic deletion studies have demonstrated that CB_1R regulates body weight and gastrointestinal motility; nevertheless, the sites mediating these actions remain to be identified. Several results show that the vagus nerve controls aspects of energy metabolism, including food intake and blood glucose homeostasis (Williams et al., 2000; Fan et al., 2004; Rossi et al., 2011). Moreover, CB_1R in the vagus nerve has been suggested as an important molecule underlying normal feeding and consequentially body weight homeostasis. By using the Cre/loxP system, we generated mice lacking CB_1R in afferent (sensory) and efferent (motor) vagal neurons. Notably, deletion of CB_1R expression in vagal neurons did not significantly alter energy balance regulation or glucose homeostasis. In contrast, we found that CB_1R expressed by Phox2b neurons is required for the regulation by CB_1R of gastrointestinal motility.

SR141716 was considered a promising pharmacological drug for the treatment of obesity and diabetes. However, because of its psychotropic effect (increased depression), the process of additional development of this drug was halted (Di Marzo, 2008). However, the concurrent effects of CB_1R inverse agonist on mood and body weight may be separated if the CB_1R sites governing mood and body weight were to be identified. Thus, it is of interest to identify the sites expressing CB_1R that regulate energy balance in an attempt to dissociate the beneficial effects of SR141716 on body weight reduction from its psychiatric side effect. Notably, if CB_1R expressed by the nodose/DMV neurons is relevant for control of body energy metabolism, it would represent a possible target for brain-impermeable CB_1R inverse agonist anti-obesity drugs. However, our data support the view that CB_1R in those neurons are not required for regulation of body energy balance, and, as such, these sites should be ruled out as potential targets for development of anti-obesity CB_1R inverse agonist drugs.

Diarrhea is a frequent side effect reported by patients treated with SR141716 (Van Gaal et al., 2005; Addy et al., 2008). Indeed, this is a common side effect of anti-obesity drugs (Cahoon, 2010), and increase in gastrointestinal motility is one underlying cause of diarrhea. Importantly, despite the discomfort that it may generate, alteration in gastrointestinal motility is often observed in gastrointestinal diseases, such as irritable bowel syndrome (prevalence of 9–23% worldwide according to the International Foundation for Functional Gastrointestinal Disorders) and may lead to severe consequences, such as inflammation of the gastrointestinal tract. Several studies indicate that CB_1R controls gastrointestinal motility; nevertheless, the neurons that express CB_1R that mediate it are unclear. It has been suggested that CB_1R acts to control acetylcholine release from neurons of the myenteric neurons (Coutts and Pertwee, 1997). CB_1R colocalizes with several cholinergic neurons of the enteric nervous system (Coutts et al., 2002), but we do not observe deletion of *Cnr1* mRNA in the duodenum and stomach of $Cnr1^{flox/flox}$*; Phox2b–Cre* mice. Indeed, it has been reported previously that the *Phox2b–Cre* transgenic line used in this study does not express the transgene in the enteric nervous system (Ferreira-Gomes et al., 2011). The transgenic *Phox2b–Cre* mouse line used in this study has been reported to express Cre in a few other sites in addition to the nodose/DMV (Rossi et al., 2011), but we do not believe that these sites contribute to the phenotype observed because they have not been suggested previously to regulate gastrointestinal motility. Our results suggest that CB_1R in the nodose/DMV is required for control of gastrointestinal motility.

Anandamide levels increase during fasting in small intestine, and it has been suggested that it is a metabolic cue signaling through the vagal circuitry to stimulate feeding (Gómez et al., 2002). Conversely, given the fact that during fasting there is no major need of motility to have the food traveling through the digestive tract, it is plausible that anandamide may serve as a cue to suppress gastrointestinal motility.

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Cannabis Use is Associated With Reduced 30-Day All-cause Readmission Among Hospitalized Patients With Irritable Bowel Syndrome

A Nationwide Analysis

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Background: Cannabinoid receptors are potential therapeutic targets in a variety of gastrointestinal tract disorders. The authors hypothesize that the use of cannabis use is associated with better control of symptoms associated with irritable bowel syndrome (IBS). This study aimed to examine the utilization of inpatient services by patients with IBS who did and did not report the use of cannabis.

Methods: This is a retrospective cohort study that utilized the 2016 Nationwide Readmissions Database. Inclusion criteria included a principal diagnosis of IBS. The primary outcome was 30-day hospital readmission rates for IBS-specific causes. Secondary outcomes included the 30-day hospital readmission rates for all causes, resource utilization, and the 5 most common principal diagnoses and independent risk factors associated with readmission.

Results: Of the 7163 patients with IBS identified in the National Readmission Database, 357 reported the use of cannabis. The 30-day IBS-specific readmission rates were 1.5% in patients who reported cannabis use and 1.1% in those who did not report cannabis use ($P=0.53$). Among the cannabis users, none of the variables evaluated served as a significant predictor of IBS-specific readmission; median income was a predictor for readmission among those who did not report cannabis use (odds ratio, 2.77; 95% confidence interval, 1.15-6.67; $P=0.02$). The 30-day readmission rates for all causes were 8.1% and 12.7% for patients who did and did not report cannabis use, respectively. After adjusting for confounders, the odds of 30-day readmission for all causes were lower among patients who reported cannabis use compared with those who did not (adjusted odds ratio, 0.53; 95% confidence interval, 0.28-0.99; $P=0.04$). The 5 most frequent diagnoses at readmission among patients who did not report cannabis use were enterocolitis because of *Clostridioides difficile*, IBS without diarrhea, sepsis, noninfective gastroenteritis and colitis, and acute kidney failure. By contrast, the 5 most frequent readmission diagnoses for cannabis users were cyclical vomiting, IBS with diarrhea, endometriosis, right upper quadrant abdominal pain, and nausea with vomiting. A discharge disposition of "against medical advice" was identified as an independent risk factor for 30-day hospital readmission for all causes among patients who reported cannabis use. By contrast, higher comorbidity scores and discharges with home health care were independent predictors of 30-day hospital readmission for all causes among patients who did not report cannabis use. Private insurance was an independent factor associated with lower rates of readmission for all causes among those who did not report cannabis use.

Conclusion: Our review of the National Readmission Database revealed no statistically significant differences in 30-day readmission rates for IBS-specific causes when comparing patients who reported cannabis use with those who did not. However, the authors found that cannabis use was associated with reduced 30-day hospital readmission rates for all causes.

Key Words: cannabis, cannabinoids, irritable bowel syndrome, readmission, resource utilization

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Irritable bowel syndrome (IBS) is one of the most common diagnoses that result in referrals to gastroenterologists.[1] IBS is a functional disorder that can involve alternating diarrhea and constipation and that is often associated with painful abdominal distention and spasms.[2] Acute exacerbations of IBS symptoms can be triggered by numerous factors including infection, diet, or emotional stress.[2] IBS has a significant negative impact on patients' quality of life and is associated with substantial utilization of both traditional and alternative health care resources[3] because of its fluctuating and relapsing nature. The effectiveness of cannabis when used to treat gastrointestinal (GI) disorders may be because of its actions at mitigating pain through interactions with cannabinoid receptors found throughout the enteric nervous system together with its anti-inflammatory and immunomodulatory effects.[1,4] Approximately 30% to 40% of patients with IBS report heightened sensitivity to colonic or rectal distention because of visceral and somatic hypersensitivity.[3,5–7] A study by Esfandyari et al[8] documented that administration of the nonselective cannabinoid agonist, cannabinol, relaxed colonic tone and reduced postprandial colonic motility in a group of healthy patients. However, recent clinical trials by Wong et al and Klooker et al reported that the administration of cannabinoid receptor agonists had no significant effects on colonic motility or sensation.[1,9–11]

Although cannabis may be useful for the management of IBS given its analgesic, anti-inflammatory, immunomodulatory,

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and prokinetic properties, few, if any, high-quality studies have been performed that explore these possibilities. We hypothesize that if cannabis use is associated with better control of IBS symptoms, its use should also be associated with more effective utilization of health care resources. As such, the current study aims to evaluate the utilization of inpatient services by patients with IBS who did and who did not report cannabis use.

METHODS

Data Source and Patient Selection

This is a retrospective cohort study that utilized data from the 2016 National Readmission Database (NRD). The NRD is one of the largest all-payer readmission databases currently available in the US The NRD is made publicly available by the Agency for Healthcare Research as a part of the Healthcare Cost and Utilization Project.[12,13] Each hospital discharge is weighted to make the NRD more representative of the nation as a whole (weight = total number of discharges from all acute care hospitals in the United States divided by the number of discharges included in NRD). The NRD contains both patient- and hospital-level information. Up to 15 procedures and 35 discharge diagnoses are collected for each patient using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM).[14] The NRD has been found to provide reliable estimates of the burden of GI diseases in the United States.[14,15]

Study Population

The study group included patients aged 18 years or older with a principal diagnosis of IBS based on the following ICD-10-CM codes: K58, K58.0, K58.1, K58.2, K58.8, and K58.9. Because the NRD captures admissions in a single calendar year (ie, January 1 to December 31) with no links to admissions during a previous or following year, index hospitalization discharges during December were excluded from our analysis. Each patient included in the NRD is assigned a unique database identification number.[12,13] This number was used to identify all hospital admissions within a given state for each patient during the calendar year 2016. As this was a retrospective study performed with previously de-identified data, no institutional review board approval was deemed necessary. The study design is demonstrated in Figure 1.

Study Outcomes

The primary outcome evaluated in this study was the rate of hospital readmissions for IBS-specific causes. A readmission was defined as any hospital admission for any principal diagnosis other than the trauma that occurred within 30 days of discharge after the index admission. If a patient experienced multiple readmissions within 30 days of discharge after the index admission, then only the date of the first readmission was included in our analysis.[12] Patients who died in the hospital during the index admission were excluded from the denominator.

Secondary outcomes evaluated in this study included (a) 30-day hospital readmissions for all causes; (b) the 5 most common principal diagnoses associated with readmissions among patients with IBS; (c) resource use associated with IBS-specific and all-cause readmissions, including the length of stay (LOS), total charges, and total cost of hospitalization; and (d) independent risk factors associated with IBS-specific and all-cause readmissions.

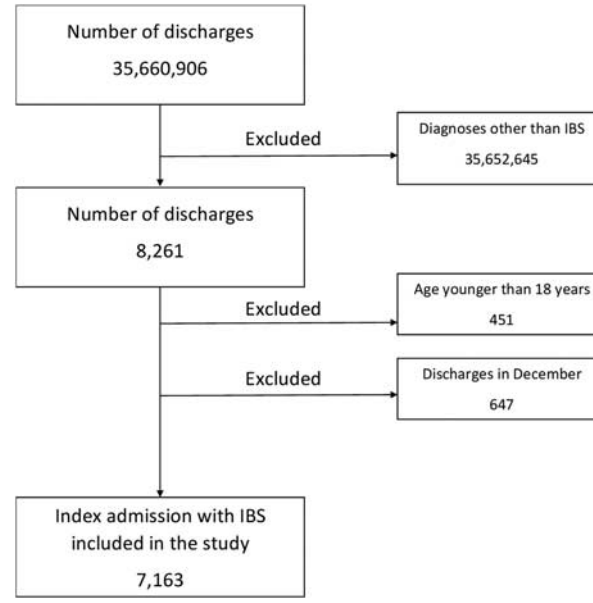

FIGURE 1. Study design. IBS indicates irritable bowel syndrome.

Definition of Variables

We extracted data from the NRD that identified each patient's age (in years), sex, median household income (in US dollars) for patient's zip code (1) US$1 to US$42,999; (2) US$43,000 to US$53,999; (3) US$54,000–US$70,999; or (4) ≥ US$71,000. We also identified primary expected payer (Medicare, Medicaid, private insurance, or uninsured), hospital status (teaching or nonteaching), hospital size based on the number of beds (small, medium, or large), and postdischarge disposition (ie, transfer to short-term facility, other transfer, home health care, or leaving the hospital against medical advice).[12,16] Overall comorbidity burden was calculated utilizing the Deyo modification of the Charlson Comorbidity Index.[17]

The 5 most common reasons for readmission were determined by tallying the principal diagnoses recorded for each patient at readmission. Variables including LOS and total hospitalization charges are directly coded in the NRD. Total hospital charges represent the amount billed by each hospital for the entire, but do not reflect the actual cost of care. The Healthcare Cost and Utilization Project provides information on hospital-specific cost-to-charge ratios based on all-payer inpatient costs. This cost information is obtained from the hospital accounting reports collected by the Centers for Medicare and Medicaid Services.[14,18] Using this information, total hospitalization costs were calculated by multiplying total hospital charges by the corresponding cost-to-charge ratio.[18]

Statistical Analyses

All data analyses were conducted using STATA, version 14.0 (StataCorp, College Station, TX). NRD is based on a complex sampling design that included stratification, clustering, and weighting. Weighting of patient-level observations was implemented to obtain estimates for the entire population of hospitalized patients with IBS in the US Proportions were compared using the Fisher exact test and continuous variables were compared using the Student *t* test. Univariate linear (continuous outcomes) or logistic (dichotomous outcomes) regression analysis was used to calculate unadjusted odds ratios (ORs) for the

TABLE 1. Patient Demographics and Hospital Characteristics Among Patients With IBS, by History of Cannabis Use

IBS (N = 7163)	Noncannabis Users (N = 6798), %	Cannabis Users (N = 357), %	*P*
Patient age, mean (95% CI)	53.3 (52.6-54.1)	36.7 (34.5-38.9)	< 0.01
Sex			< 0.01
Female	81.0	62.3	
Male	19.0	37.7	
IBS subtype			
Diarrhea predominant	49.9	42.1	0.08
Constipation predominant	3.2	0.6	0.05
Mixed	0.9	0.8	0.24
Insurance			
Medicare	43.7	12.6	< 0.01
Medicaid	18.8	49.1	< 0.01
Private	33.3	29.7	0.35
Self-pay	4.2	8.6	< 0.01
Household median income			
Lowest quartile	28.9	33.8	0.27
Second quartile	26.8	24.8	0.57
Third quartile	25.4	23.1	0.55
Highest quartile	18.8	18.4	0.85
Hospital teaching status			
Metropolitan, nonteaching	27.8	22.0	0.09
Metropolitan, teaching	65.2	74.7	0.02
Nonmetropolitan	7.0	4.3	0.16
Bed size			
Small	16.4	13.2	0.32
Medium	29.	26.3	0.48
Large	54.6	60.6	0.16
Charlson Comorbidity Index			
0	48.2	65.7	< 0.01
1	26.1	26.6	0.89
2	12.9	4.5	< 0.01
3	12.8	3.3	< 0.01
Disposition			
Routine	86.7	93.0	< 0.01
Transfer to short-term hospital	0.3	0.9	0.15
Other transfers*	4.7	0.4	< 0.01
Home health care	7.2	2.5	< 0.01
Against medical advice	1.1	3.3	< 0.01

*Other transfers include the following facilities: physical rehabilitation, skilled nursing facility, and intermediate care.

CI indicates confidence interval; IBS, irritable bowel syndrome.

primary and secondary outcomes. Multivariate regression analysis was performed to adjust the results for potential confounders. The final multivariate logistic regression model was built by including those factors associated with the outcome in univariate analysis with $P < 0.20$. All statistical analyses were 2-tailed, with $P < 0.05$ considered as statistically significant.

RESULTS

Baseline Demographics

The study included 7163 patients diagnosed with IBS. Of this group, 357 of the patients with IBS reported cannabis use. Table 1 summarizes the patient characteristics. Patients who used cannabis were younger (mean age, 36.7 vs. 53.3 y, $P < 0.01$), less likely to be female individuals (62.3% vs. 81.0%, $P < 0.01$), less likely to be insured by Medicare (12.6% vs. 43.7%, $P < 0.01$), and more likely to be insured by Medicaid (49.1% vs. 18.8%, $P < 0.01$) than those patients who did not report cannabis use. Patients who used cannabis were diagnosed with fewer comorbidities (proportion of patients with Charlson score ≤ 1 was 92.3% vs. 74.3%, $P < 0.01$). These patients were also more likely to be discharged to home (93.0% vs. 86.7%) or to leave the hospital against medical advice (3.2% vs. 1.1%) and were less likely to be transferred to rehabilitation, skilled nursing, or intermediate care facilities (0.4% vs. 4.7%) or to home health care (2.5% vs. 7.2%) than were patients who did not report cannabis use ($P < 0.01$). Income distribution was similar in these 2 groups, as was the proportion of patients treated at teaching, metropolitan, or large hospitals. Approximately 50% of patient cases had ICD-10-CM codes that specified an IBS subtype, predominantly IBS-associated diarrhea in both cannabis users and nonusers (42.1% vs. 49.9%, $P = 0.08$).

30-day IBS-specific and All-cause Readmission Rates

Thirty-day IBS-specific hospital readmission rates were 1.5% among patients who reported cannabis use and 1.1% for those who did not use cannabis ($P = 0.53$). After adjusting for confounders, the adjusted odds ratios (aORs) associated with 30-day IBS-specific readmission were similar between the 2 groups [aOR, 0.99; 95% confidence interval (CI), 0.28-3.46; $P = 0.99$]. The 30-day hospital readmission rate for all causes was 8.1% among patients with IBS who used cannabis and 12.7% for those who did not report cannabis use. After adjusting for confounders, the OR associated with 30-day readmission for all causes was lower among patients who used cannabis compared with those who did not (aOR, 0.53; 95% confidence interval, 0.28-0.99; $P = 0.04$). Among patients who used cannabis, the 5 most common principal diagnoses on readmission were cyclical vomiting, IBS with diarrhea, endometriosis, right upper quadrant abdominal pain, and nausea with vomiting. By contrast, readmission diagnoses for patients who did not use cannabis were enterocolitis due *Clostridioides difficile*, IBS without diarrhea, sepsis, noninfective gastroenteritis and colitis, and acute kidney failure (Table 2).

Utilization of Healthcare Resources During the Index Admission

The mean LOS for the index admission was shorter for patients who reported the use of cannabis compared with those who did not [adjusted mean difference −0.44 (−0.84 to −0.03) d; $P = 0.04$]. Similar findings were obtained for total hospitalization charges. Specifically, total hospitalization

TABLE 2. Most Common Reasons for 30-day Readmission in Patients With IBS With and Without Cannabis Use

IBS Without Cannabis	IBS With Cannabis
Enterocolitis because of *Clostridioides difficile* 5.6%	Cyclical vomiting 16.2%
IBS without diarrhea 3.8%	IBS with diarrhea 10.6%
Sepsis 3.0%	Endometriosis 7.4%
Noninfective gastroenteritis and colitis 3.0%	Right upper quadrant abdominal pain 7.4%
Acute kidney failure 2.8%	Nausea with vomiting 6.3%

IBS indicates irritable bowel syndrome.

charges were lower for patients who reported cannabis use [US$25,446 (US$22,561-US$28,331)] compared with those who did not [US$29,210 (US$27,696-US$30,724)] with an adjusted mean difference of −US$3473 (−US$6773 to −US $174; $P = 0.04$). However, differences in total hospitalization costs were not statistically significant at US$6266 (US $5704-US$6874) for those using cannabis and US$7040 (US $6781-US$7299) for those who did not; the adjusted mean difference was −US$583 (−US$1298 to US$133; $P = 0.11$).

Utilization of Healthcare Resources Associated With Readmission

Patients who reported the use of cannabis had a mean LOS, total hospitalization costs, and total hospitalization charges for IBS-specific readmissions of 4.1 (2.8-5.5) days, US $4981 (US$3015-US$6945), and US$17,153 (US$12,133-US $22,174), respectively. For those who did not use cannabis, these values were 4.3 (3.38-5.25) days, US$10,176 (US$8970-US $11,382), and US$31,732$ (US$24,382-US$39,082), respectively. After adjusting for confounders, the 2 groups had similar adjusted mean LOS [mean adjusted difference, −0.1 (−2.3 to +2.2) d; $P = 0.99$]. However, cannabis use was associated with lower total hospitalization costs [mean adjusted difference, −$5468 (−US$10,890 to −US$47); $P = 0.04$] and total hospitalization charges [mean adjusted difference −US$32,026 (−US $61,333 to −$2720); $P = 0.03$], respectively.

When evaluating 30-day hospital readmission for all causes, patients who used cannabis had a mean LOS, total hospitalization costs, and total hospitalization charges of 5.5 (2.0-9.0) days, US$10,914 (US$4690-US$17,138), and US$37,469 (US $19,510-US$55,429), respectively. For those who did not use cannabis, these values were 5.1 (4.6-5.6) days, US$10,176 (US $8970-US$11,382), and US$44,302 (US$38,758-US$49,846), respectively. After adjusting for confounders, the mean LOS, total hospitalization costs, and total hospitalization charges were similar when comparing the 2 patient groups, with mean adjusted differences of 0.77 (−2.6 to 4.2) days ($P = 0.66$), US$1246 (−$5117 to +US$7608; $P = 0.70$), and −US$5365 (−US$25,828 to +US$15,097; $P = 0.61$), respectively.

Independent Predictors of 30-day IBS-specific and All-cause Readmission

Specific variables were screened and to identify independent predictors of readmission, including (1) patient-based variables: age, estimated median income based on residential zip code, type of medical insurance, and Charlson comorbidity score, (2) hospital-based variables: number of beds, teaching status, and urban location, and (3) LOS and postdischarge disposition. The median income in the zip code where the patient resided was identified as the sole predictor of 30-day IBS-specific readmission for patients who did not use cannabis (OR, 2.77; 95% CI, 1.15-6.67; $P = 0.02$). Among patients who used cannabis, none of the variables evaluated were identified as predictors of 30-day IBS-specific readmission. Independent predictors of 30-day hospital readmission for all causes among patients who did not use cannabis included higher Charlson scores (aOR, 1.13; 95% CI, 1.05-1.21; $P < 0.01$) and discharge with home health care (aOR, 1.91; 95% CI, 1.34-2.72). For patients in the group who did not report cannabis use, having private insurance rather than Medicare (aOR, 0.55; 95% CI, 0.40-0.76; $P < 0.01$) was negatively associated with 30-day all-cause hospital readmission. By contrast, a departure from the hospital against medical advice was the only independent predictor of 30-day readmission for patients reporting cannabis use (OR, 25.2; 95% CI, 5.03-126.5; $P < 0.01$) (Table 3). The details regarding both univariate and multivariate logistic regression analyses for 30-day hospital readmission rates for IBS and all causes are included in Tables 3 and 4, respectively.

DISCUSSION

This is the first large, national-level study that addresses the impact of cannabis use on hospital readmission among patients with IBS. Our findings revealed that cannabis use had no impact on IBS-specific 30-day hospital readmission rates, but was associated with lower rates of hospital readmission for all causes. Cannabis use was also associated with lower in-hospital resource utilization during IBS-specific readmissions, as determined by lower mean total hospitalization costs and total hospitalization charges. In-hospital resource utilization was similar for both patient groups during readmissions for all causes. No single factor among those evaluated was found to predict IBS-specific readmission among those who reported cannabis use; the only factor that was identified as an independent predictor of 30-day readmission for all causes was leaving the hospital against medical advice. Among patients with IBS who did not report cannabis use, the third quartile group of median incomes as estimated by residential zip code was a factor that predicted IBS-specific readmission. By contrast, higher Charlson score and discharge with home health care were independent predictors of hospital readmissions for all causes. Interestingly, private insurance was negatively associated with hospital readmissions for all causes when compared with results from patients insured by Medicare.

Marijuana is the generic term used to describe preparations derived from the herbaceous plant, *Cannabis sativa*, and is a mixture of > 60 chemicals.[19,20] Marijuana has both medical and psychoactive uses and has been used to treat GI disorders and symptoms including nausea, vomiting, anorexia, and abdominal pain.[21] The main cannabinoid receptors, cannabinoid receptor 1 (CB1) and 2 (CB2), have been identified throughout the GI tract. These receptors may serve to mediate the effects of marijuana on the regulation of food intake and GI motility, visceral sensation, and intestinal inflammation.[22,23] Although there is no direct evidence linking these mechanisms to the impact of cannabis on symptoms of IBS, indirect evidence has been provided from studies of patients with inflammatory bowel disease (IBD). Among these findings, increased expression of CB2 was observed specifically in the intestinal epithelium of patients diagnosed with IBD, suggesting a regulatory role for this receptor.[24] Likewise, activation of CB2 in experimental models of IBD resulted in decreased proliferation and apoptosis of T cells.[24–27] These findings relate to the concept of clinical endocannabinoid deficiency that has been introduced as an explanation of both GI and non-GI conditions, including migraine, fibromyalgia, IBS, and other neurophysiological conditions.[2,28] Russo[28,29] suggested that an endocannabinoid deficiency could be at the root of a number of diverse conditions and that these disorders might respond to an approach that includes endocannabinoid supplementation. Patients diagnosed with neurophysiological conditions that result from an underlying endocannabinoid deficiency may have improved symptom control in response to treatment of the cannabinoid deficiency. However, our findings revealed that IBS-specific readmission rates were similar between the 2 groups. As such, indirect evidence from IBD and the concept of clinical endocannabinoid deficiency cannot fully explain the reduced rate of hospital readmissions for all causes observed among the cannabis users in our study.

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TABLE 3. Independent Predictors of 30-day Irritable Bowel Syndrome-specific Readmission Among Patients With Irritable Bowel Syndrome and Without and With Cannabis Use

	Univariate Logistic Regression		Multivariate Logistic Regression	
Characteristics	**Odds Ratio (95% CI)**	***P***	**Adjusted Odds Ratio (95% CI)**	***P***
Patients who did not use cannabis				
Female	0.83 (0.40-1.72)	0.62		
Mean age	0.99 (0.97-1.01)	0.27		
Median income				
Lowest quartile	Reference			
Second quartile	1.59 (0.62-4.02)	0.33		
Third quartile	**2.77 (1.15-6.67)**	**0.02**	**2.77 (1.15-6.67)**	**0.02**
Highest quartile	1.79 (0.72-4.44)	0.21		
Insurance				
Medicare	Reference			
Medicaid	1.26 (0.54-2.94)	0.59		
Private	1.45 (0.72-2.91)	0.29		
Self-pay	*			
Disposition				
Routine	Reference			
Transfer to short term	*			
Other transfer	0.40 (0.05-2.88)	0.36		
Home health care	0.93 (0.32-2.69)	0.89		
Against medical advice	*			
Charlson Comorbidity Index	0.90 (0.69-1.16)	0.41		
Length of stay	1.00 (0.99-1.02)	0.67		
Hospital bed size				
Small	Reference			
Medium	0.63 (0.25-1.57)	0.32		
Large	0.63 (0.28-1.38)	0.25		
Hospital status				
Metropolitan nonteaching	Reference			
Metropolitan teaching	0.97 (0.47-2.02)	0.94		
Nonmetropolitan hospital	0.89 (0.19-4.18)	0.88		
Patients who used cannabis				
Female	0.57 (0.08-4.13)	0.58		
Mean age	**1.04 (0.99-1.09)**	**0.15**	0.99 (0.97-1.01)	0.44
Median income				
Lowest quartile	Reference			
Second quartile	*			
Third quartile	1.51 (0.09-25.7)	0.78		
Highest quartile	1.76 (0.11-29.3)	0.69		
Insurance				
Medicare	Reference			
Medicaid	**0.25 (0.03-1.83)**	**0.17**	0.96 (0.38-2.38)	0.93
Private	*			
Self-pay	*			
Disposition				
Routine	Reference			
Transfer to short term	*			
Other transfer	*			
Home health care	**12.1 (1.09-134.7)**	**0.04**	1.06 (0.38-2.98)	0.91
Against medical advice	*			
Charlson Comorbidity Index	0.99 (0.53-1.84)	0.97		
Length of stay	0.95 (0.71-1.29)	0.76		
Hospital bed size				
Small	Reference			
Medium	1.04 (0.09-12.0)	0.98		
Large	0.21 (0.01-3.61)	0.29		
Hospital status				
Metropolitan nonteaching	Reference			
Metropolitan teaching	0.89 (0.09-8.77)	0.92		
Nonmetropolitan hospital	*			

Statistically significant *P*-values are bolded, $P < 0.05$.
*Sample size is too small for meaningful analysis.
CI indicates confidence interval.

TABLE 4. Independent Predictors of 30-day All-cause Readmission Among Patients With Irritable Bowel Syndrome and Without and With Cannabis Use

	Univariate Logistic Regression		Multivariate Logistic Regression	
Characteristics	**Odds Ratio (95% CI)**	***P***	**Adjusted Odds Ratio (95% CI)**	***P***
Patients who did not use cannabis				
Female	0.81 (0.61-1.07)	0.14	0.80 (0.61-1.06)	0.13
Mean age	**1.01 (1.00-1.01)**	**0.10**	0.99 (0.98-1.00)	0.05
Median income				
Lowest quartile	Reference			
Second quartile	1.23 (0.88-1.72)	0.22		
Third quartile	1.09 (0.81-1.47)	0.56		
Highest quartile	1.01 (0.74-1.37)	0.97		
Insurance				
Medicare	Reference			
Medicaid	0.88 (0.63-1.23)	0.45	0.86 (0.58-1.27)	0.44
Private	**0.55 (0.42-0.72)**	**< 0.05**	**0.55 (0.40-0.76)**	**< 0.01**
Self-pay	0.57 (0.32-1.00)	0.05	0.56 (0.31-1.03)	0.31
Disposition				
Routine	Reference			
Transfer to short term	0.06 (0.06-4.22)	0.53	0.38 (0.04-3.40)	0.40
Other transfer	1.50 (0.95-2.39)	0.08	1.33 (0.84-2.10)	0.22
Home health care	**2.20 (1.56-3.09)**	**< 0.05**	**1.91 (1.34-2.72)**	**< 0.01**
Against medical advice	1.43 (0.58-3.55)	0.44	1.42 (0.57-3.50)	0.45
Charlson Comorbidity Index	**1.17 (1.09-1.26)**	**< 0.01**	**1.13 (1.05-1.21)**	**< 0.01**
Length of stay	1.02 (−0.96 to 1.08)	0.54		
Hospital bed size				
Small	Reference			
Medium	1.24 (0.88-1.76)	0.23		
Large	1.21 (0.86-1.70)	0.28		
Hospital status				
Metropolitan nonteaching	Reference			
Metropolitan teaching	1.03 (0.81-1.31)	0.80		
Nonmetropolitan hospital	0.84 (0.52-1.33)	0.45		
Patients who used cannabis				
Female	1.71 (0.61-4.84)	0.31		
Mean age	1.00 (0.96-1.03)	0.81		
Median income				
Lowest quartile	Reference			
Second quartile	1.08 (0.24-4.86)	0.92		
Third quartile	1.96 (0.51-7.58)	0.33		
Highest quartile	2.41 (0.62-9.45)	0.21		
Insurance				
Medicare	Reference			
Medicaid	1.09 (0.29-4.18)	0.90		
Private	0.43 (0.08-2.32)	0.33		
Self-pay	*			
Disposition				
Routine	Reference			
Transfer to short term	*			
Other transfer	*			
Home health care	2.95 (0.32-27.6)	0.34		
Against medical advice	**25.2 (5.03-126.5)**	**< 0.01**	**25.2 (5.03-126.5)**	**< 0.01**
Charlson Comorbidity Index	0.50 (0.17-1.54)	0.23		
Length of stay	1.09 (0.93-1.28)	0.29		
Hospital bed size				
Small	Reference			
Medium	1.29 (0.27-6.05)	0.75		
Large	0.71 (0.17-2.96)	0.64		
Hospital status				
Metropolitan nonteaching	Reference			
Metropolitan teaching	0.75 (0.24-2.41)	0.63		
Nonmetropolitan hospital	2.79 (0.50-15.3)	0.24		

Statistically significant *P*-values are bolded, $P < 0.05$.
*Sample size is too small for meaningful analysis.
CI indicates confidence interval.

We presented readmission rates that were IBS-specific and those resulting from all causes to highlight the overall complexity of this issue. An evaluation of IBS-specific readmission rates alone permits us to draw several important, albeit indirect conclusions regarding disease-specific symptom control. This focus also facilitates an evaluation that could control for possible residual confounding factors associated with differences in baseline characteristics that were not captured in our regression models. However, IBS-specific readmission fails to capture the full impact of IBS on the health care system, as it does not include the costs and resource utilization incurred by the same patients who were readmitted for issues that were not specifically related to IBS. However, given the relatively low readmission rate for IBS-specific diagnoses, we recognize that our finding of no effect of cannabinoid on IBS-specific readmission rates may also be a beta-error. Further studies with larger event rates will be needed to evaluate this possibility.

It is interesting to note that the 5 most common reasons for 30-day hospital readmission rates for all causes differed significantly between patients who reported cannabis use and those who did not. Two of the readmission principal diagnoses for patients who did not report cannabis use were infection-related (ie, enterocolitis because of *C. difficile* and sepsis). By contrast, readmission of patients with IBS who reported cannabis use was most frequently associated with GI motility and pain (ie, cyclical vomiting, IBS with diarrhea, right upper quadrant abdominal pain, and nausea with vomiting). Of note, motility-related symptoms and pain are clinical markers of IBS flares and may also be adverse events associated with cannabis use. Among these adverse events, cannabis withdrawal syndrome can occur upon cessation of heavy; prolonged cannabis use; and is associated with irritability, nervousness, difficulties with sleep, reduced appetite, restlessness, depressed mood, and generalized physical discomfort.[20] Use of synthetic cannabis has also been associated with severe cyclical nausea and vomiting.

Cannabis use was associated with lower adjusted mean total hospitalization costs and charges among patients with IBS who were admitted for IBS-specific reasons. In contrast, among patients with IBS who were readmitted for any cause, cannabis use had no effect on resource utilization as measured in this study. Similar adjusted mean LOS between the 2 groups during all-cause readmission is surprising because patients who reported cannabis use left the hospital against medical advice more frequently than those who did not. However, as this rate was only 3.3%, its contribution to an overall hospital stay in the cohort was probably not significant. The lower adjusted mean total hospitalization costs and charges during IBS-specific readmissions cannot be explained by the distribution of IBS subtypes, as both cannabis users and nonusers were diagnosed primarily with the diarrhea-predominant form of this disorder (IBS-D), at 49.9% versus 42.1%, respectively ($P = 0.08$). However, these differences might be explained by the severity of illness, given that age, comorbidity burden, and other important determinants of LOS were adjusted for in the analysis. A similar association between cannabis use and shorter LOS and lower total hospitalization charges was reported previously in studies of patients with IBD.[30,31] These findings further highlight the complexity of the issues involved when assessing the impact of hospital readmission on resource utilization. Although this study was not designed to explore the reasons for these differences, our results do indicate that they were not because of any differences in LOS, which were similar between patients who reported cannabis use and those who did not in IBS-specific and in all-cause readmissions.

By consensus of those involved in cost analysis and health care economics, the cost of care is reported from the patient's perspective. The NRD includes 2 specific cost measurements: total hospitalization charges and total hospitalization costs. The total hospitalization charge is the amount that the patient is billed for a hospital stay. This variable does not reflect the true cost of care primarily because it does not reflect the amount of money that is remitted by the patient. Some patients may ultimately pay nothing at all if they are uninsured and unable to pay the hospital bill. Others may pay only a portion of the charges, as in cases in which insurance denies the full amount billed and instead pays a lower prenegotiated amount. By contrast, total hospitalization costs reflect the cost of care from the hospital's perspective and include expenses incurred by the hospital when providing specific services to the patient. This value may also not represent the full cost of care. Notably, the patient will in all cases be billed an amount that is higher than the true cost of care, otherwise, the hospital will not make any profits. Although it is important to present and to discuss both values, the total hospitalization charges, rather than the total hospitalization costs, represent a better estimate of the cost of care from the patient's perspective.

Although we evaluated numerous patient- and hospital-based variables, we were unable to identify meaningful predictors of IBS-specific readmission. The value of median income estimates based on the patient's residential zip code and its use as a predictor for IBS-specific readmission among patients who did not report cannabis use must be interpreted carefully and within the context of the study limitations. This is of particular concern given that no other variable was found to be significantly associated with IBS-specific readmission in this patient population, and as such, we were unable to construct a multivariate regression model. By contrast, we found that leaving the hospital against medical advice was the only independent predictor of hospital readmission for all causes among the patients who reported cannabis use (OR, 25.2; 95% CI, 5.03-126.5; $P < 0.05$). This is not surprising, as earlier studies have reported that patients who leave against medical advice have both higher 30-day readmission and mortality rates.[32] We believe that the relatively small sample size led to a beta-error rather than a true absence of any associations between the factors tested and readmission rates, evidenced by the wide confidence interval. Among those who did not use cannabis, we identified private insurance as an independent predictor for lower readmission rates for all causes, whereas disposition to home with home health care was a predictor of higher readmission rates. These findings highlight the impact of socioeconomic factors on hospital readmission rates. The Charlson comorbidity index was also an independent predictor of hospital readmission. It is interesting to note that hospital characteristics were not important determinants of hospital readmission. Once we have a clear understanding of the factors that can be modified together with those that are independently associated with readmission rates, we will be in a position to implement directed quality improvement measures.

Our study has several limitations. First, this is a retrospective study of an administrative database that relies on ICD-10-CM codes to identify patients with IBS and those who report and cannabis use. This methodology may include inaccurate or missed codes. This issue is especially true for cannabis use as patients may not be fully forthcoming with this information. Interestingly, if the case group including only those patients who were forthcoming regarding their cannabis, the significance of the positive results would be even stronger. Second, because of limitations inherent in the database studies, we

could not assess the duration, mode of administration, or dosage of cannabis used by each patient, nor could we perform any follow-up of patients included in the study cohort. Third, the NRD does not include a patient medication history; as such, we were unable to consider the impact of prescription and nonprescription medications on the study outcomes. Finally, it was not possible to determine whether differences in the IBS subtype observed among patients who were readmitted were because of the use of cannabis or lack of available data.

This study also has several strengths. To the best of our knowledge, this is the first large-scale national study that was designed to evaluate the impact of cannabis use on 30-day readmission rates and hospital resource utilization among patients diagnosed with IBS. For this study, we utilized the largest publicly available all-payer readmission database in the United States of critical importance, the NRD is representative of the nation as a whole and includes patients admitted to small, medium, and large hospitals in 27 states, including those designated as teaching and nonteaching facilities and those that are rural versus urban, privately owned versus publicly owned, and for-profit and not-for-profit. As such, the results of this study are more likely to be generalizable to patients with IBS throughout the United States. The NRD also provides the larger sample size needed to define risk factors; this is typically a limitation of single-center cohort studies. Furthermore, the unique variables tabulated in the NRD permitted us to explore factors such as estimates of household income, hospitalization costs, and hospital-related factors that are not commonly available in single-center studies.

In conclusion, the results from our study revealed that cannabis use is associated with reduced 30-day hospital readmission rates for all causes among patients diagnosed with IBS; cannabis use was also associated with less resource utilization both during the index admission and IBS-specific readmissions. The most common reasons for readmission among patients reporting the use of cannabis were GI pain and motility issues, whereas GI inflammation and infection were chief causes of readmission for patients who were not using cannabis. More research will be needed to understand the mechanisms underlying these interesting and important observations and to elucidate the critical therapeutic applications of cannabis specifically for those diagnosed with IBS. Cannabis remains a schedule I drug in many states, and its clinical use is limited because of its psychoactive properties.[4] Furthermore, given the many adverse effects that have been associated with cannabis, its use for treating GI and other diseases remains controversial. Cannabis is currently regarded as adjuvant therapy that can be used in a subset of patients with digestive diseases. The risks and benefits of cannabis use need to be clarified before it emerges as a conventional treatment for IBS.

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Randomized Pharmacodynamic and Pharmacogenetic Trial of Dronabinol Effects on Colon Transit in Irritable Bowel Syndrome-Diarrhea

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Abstract

Background—Genetic variation in endocannabinoid metabolism is associated with colonic transit in irritable bowel syndrome (IBS) with diarrhea (IBS-D). The nonselective cannabinoid (CB) receptor agonist, dronabinol (DRO), reduced fasting colonic motility in nonconstipated IBS. *FAAH* and *CNR1* variants influenced DRO's effects on colonic motility. Our aims were: 1) To compare dose-related effects of DRO to placebo (PLA) on gut transit in IBS-D; and 2) To examine influence of genetic variations in CB mechanisms on DRO's transit effects.

Methods—36 IBS-D volunteers were randomized (double-blind, concealed allocation) to twice daily PLA (n=13), DRO 2.5mg (n=10), or DRO 5mg (n=13) for two days. We assessed gastric, small bowel, and colonic transit by validated radioscintigraphy and genotyped the single nucleotide polymorphisms *CNR1* rs806378 and *FAAH* rs324420. Data analysis utilized a dominant genetic model.

Key Results—Overall treatment effects of DRO on gastric, small bowel, or colonic transit were not detected. *CNR1* rs806378 CT/TT was associated with a modest delay in colonic transit at 24h compared to CC (p=0.13 for differential treatment effects on post- minus pre-treatment changes in colonic transit by genotype). No significant interaction of treatment with *FAAH* rs324420 was detected.

Conclusions/Inferences—Overall, DRO 2.5mg or 5mg twice daily for two days had no effect on gut transit in IBS-D. There appears to be a treatment-by-genotype effect whereby DRO preferentially delays colonic transit in those with the *CNR1* rs806378 CT/TT genotypes. Further study of CB pharmacogenetics may help identify a subset of IBS-D patients most likely to benefit from CB agonist therapy.

Keywords

cannabinoid; anandamide; FAAH; motility; nonselective; receptor; gastric; small bowel

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Cannabinoid receptors type 1 (CB_1) are identified in colonic mucosa and neuromuscular layers[1–3]; they are also expressed in plasma cells and influence mucosal inflammation[4]. The endocannabinoid system consists of CB_1 and CB_2 receptors; the ligands of these receptors are anandamide and 2-arachidonyl glycerol (2-AG), and their respective ligand-inactivating enzymes are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGLL)[5–8]. Activation of CB_1 receptors coupled to cholinergic motor neurons inhibits excitatory nerve transmission in human colonic circular muscle in vitro[9]. In vivo, endocannabinoids acting on myenteric CB_1 receptors tonically inhibit colonic propulsion in mice[10]; they also inhibit gastric and small intestinal transit without altering intraluminal pressure or basal tone in rodents[11,12].

We have previously shown that dronabinol (DRO), a nonselective CB receptor agonist, inhibits gastric emptying and colonic motility in healthy humans[13,14]. The effects on colonic tone and phasic motility were observed with 7.5mg dronabinol, which also induced side effects of drowsiness, lightheadedness, and dizziness[13]. The 5mg dronabinol dose was more tolerable among healthy participants[14]. In patients with irritable bowel syndrome (IBS) with diarrhea (IBS-D), genetic variation in endocannabinoid metabolism in the fatty acid amide hydrolase (*FAAH*) gene was associated with symptoms and colonic transit[15]. In another prior study of non-constipated IBS patients consisting of both patients with IBS-D and IBS with alternating bowel habit (IBS-A), DRO 5mg reduced fasting colonic motility[16].

We hypothesized that dronabinol inhibits colonic transit in IBS, and that these inhibitory effects are modulated by variations in the genes for the CB_1 receptor (*CNR1*) and for *FAAH*, the rate-limiting enzyme in degradation of the endocannabinoid anandamide. Our specific aims were: 1) to compare effects of two consecutive days of twice daily administration of oral placebo, DRO 2.5mg, and DRO 5mg on gastric, small bowel, and colonic transit in cannabinoid-naive IBS-D patients; and 2) to examine potential influences of genetic variations in *CNR1* and *FAAH* on the transit effects of dronabinol treatment.

MATERIALS AND METHODS

Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group study (registered at ClinicalTrials.gov, identifier NCT01253408) of the pharmacodynamic effects of DRO on gastric, small bowel, and colonic transit of otherwise healthy participants with IBS-D by Rome III criteria. Their ages were between 18 and 69 years, and body mass indices between 21 and 56 kg/m^2, with 2 subjects with BMI>40kg/m^2. The study was conducted in the Clinical Research Unit at Mayo Clinic in Rochester, MN (NIH CTSA grant RR0024150), where the full trial protocol is kept; the study began on October 2008 and was completed on April 2011. The study was approved by Mayo Clinic Institutional Review Board, and a data safety monitoring plan was established prior to starting the study.

Participants

All participants were recruited from a database of patients with IBS who reside within 150 miles of Rochester, MN. Participants completed a validated bowel disease questionnaire (BDQ, including questions that correspond to Rome III criteria)[17] and the Hospital Anxiety and Depression Inventory (HAD)[18]. Potential participants who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. All candidates were screened by history and by review of their medical records to ensure they were cannabinoid-naïve. All females of childbearing potential had to have a negative pregnancy test within 48 hours of study. The trial flow is summarized in Figure 1.

Experimental Design

Thirty-six participants with IBS-D were enrolled and completed most studies as in the protocol with measurements over 48 hours. Participants were randomized to oral administration of matching placebo, dronabinol 2.5mg, or dronabinol 5mg, taken with water twice daily for two days, with the morning dose ingested at the study center under supervision of study staff.

Randomization to treatment group was conducted by computer program. Allocation was concealed, and participants and investigators were blinded to all treatment assignments. The research pharmacist ensured participants were assigned to the appropriate group, in accordance with the random allocation sequence. At study completion, the randomization code was communicated to the study statistician by the research pharmacist.

Pharmacology of Dronabinol

Dronabinol is a synthetic delta-9-tetrahydrocannabinol (Δ^9-THC). It is a cannabinoid agonist that is non-selective, with affinity for both CB_1 and CB_2 receptors. It is highly (~95%) absorbed after a single oral dose[19]; however, due to high first pass hepatic metabolism (primarily by microsomal hydroxylation) and lipid solubility, only 10–20% of administered oral doses reach the systemic circulation. The onset of action is at 0.5 to 1 hour after oral administration, and the peak effect is at 2 to 4 hours. The elimination phase follows a two-compartment model, with an initial half-life of ~4 hours and a terminal half-life of 25–36 hours. Biliary excretion is the major route of elimination. The rapid onset and peak effect of the medication and the experimental nature of the study with potential for adverse effects (mental, dizziness etc…) led us to choose an experimental design that required only two days of treatment to observe the acute effects of DRO, rather than 7–10 days of treatment which would be required for drug levels to reach steady state. Given the well-published pharmacokinetic results[19] and the prior observations of pharmacological effects of DRO using this acute administration design[13–14,16], we did not conduct any blood measurements for drug levels.

Experimental Procedure

All participants underwent the following procedures: documentation of eligibility, screening questionnaires, and physical examination within the prior month. The physical examination included standard rectal and pelvic floor examinations[20] to exclude rectal evacuation disorder. This was deemed necessary to ensure the diarrhea was not secondary to “retention of stool with overflow”. Participants then underwent baseline colonic transit measurement (GC 24 and GC 48 hours), off treatment. Treatment days corresponded to the scintigraphic transit testing days (days 1 and 2) with participants receiving the medication to which they were randomized. Scintigraphic measurements of gastric, small bowel, and colonic transit were conducted, using a previously validated method (see below) on days 1 and 2, and were completed with a fasting 48-hour scan on day 3 when no medication was administered.

On days 1 and 2, the morning dose of medication was ingested in the research lab, with the participant fasting. On day 1, the morning dose of medication was administered together with the delayed release capsule containing ^{111}In-labeled activated charcoal used to measure colonic transit. On day 2, the morning dose of medication will be given after the 24-hour scan. The evening doses on days 1 and 2 were ingested by participants at bed time in their homes. This timing was selected to reduce the potential for adverse effects such as drowsiness and dizziness which we previously observed in humans who were administered similar doses.

With appropriate consent, a venous blood sample was obtained from all participants, except one from whom a blood sample could not be drawn despite multiple unsuccessful venipuncture attempts, for DNA extraction and pharmacogenomics studies.

Selection of Candidate Endocannabinoid Genetic Polymorphisms

To address the impact of pharmacogenetics on the transit response to dronabinol, we selected two genetic variants, based on the findings in our prior studies[15,16] and the minor allele frequencies observed in our database. FAAH and CB_1 receptor expressions have been localized to myenteric neurons[21].

A. *CNR1* is the gene coding for the CB_1 receptor. *CNR1* rs806378 (CC vs. CT/TT) showed potential effect on fasting proximal left colonic motility in IBS-D and IBS-A patients[16]. The T allele of *CNR1* polymorphism rs806378 is associated with altered nuclear protein binding in an electrophoretic mobility shift assay, suggesting that rs806378 is a functional polymorphism[22]. We chose to study rs806378 (whose nearest gene on the chromosome is *CNR1*), since we previously demonstrated association of this variant with gastric motor functions. In a study by Vazquez-Roque et al.[23], rs806378 CC genotype was associated with reduced fasting gastric volume, as well as a modest, non-significant association with gastric emptying of solids compared to the CT/TT group.

B. FAAH is the rate-limiting enzyme for metabolism of the endocannabinoid, anandamide. The 385C-to-A allelic variant of rs324420 in the human *FAAH* gene leads to a Pro129Thr amino acid change, which decreases expression of the FAAH protein secondary to reduced protein stability[24]. The prevalence of the A allele is 16–25% in studies of Caucasians in the NCBI database. Our laboratory previously confirmed the A allele frequency to be 25% in our sample population of healthy controls and IBS patients in southeastern Minnesota[15]. Reduction in FAAH protein level and activity compromises inactivation of the endocannabinoid anandamide. This leads to higher synaptic concentrations of anandamide and, hypothetically, a greater effect of the exogenously administered cannabinoid, dronabinol, via activation of CB_1 and CB_2 receptors.

Genotyping

DNA was extracted from whole blood, as previously described[24]. Genotyping of *FAAH* rs324420 and *CNR1* rs806378 was performed using Taqman™ SNP Genotyping assays (Applied Biosystems, Inc., Foster City, CA) in accordance with manufacturer instructions.

Gastrointestinal and Colonic Transit

A validated scintigraphic method was used to measure gastric, small bowel, and colonic transit. A methacrylate-coated capsule that dissolves in the alkaline pH of the distal ileum was used to release ^{111}In-labeled activated charcoal particles to evaluate colonic transit on sequential scans[25]. Orally ingested ^{99m}Tc-labeled egg meal allows measurement of gastric and small bowel transit. The method has been shown to detect accelerated or delayed transit. These measurements of colonic transit are associated with altered stool frequency and consistency and are predictive of response to therapy for bowel dysfunction [26–29]. Three standard meals were ingested during day 1, and patients were instructed to eat their normal diet on day 2.

The primary endpoint for analysis was colonic transit geometric center at 24 hours. Secondary endpoints were colonic transit geometric center at 48 hours, ascending colon emptying $T_{1/2}$; gastric emptying $T_{1/2}$; and colonic filling at 6 hours (a surrogate for small bowel transit time).

Sample Size Assessment

Table I (in Supplementary Materials) shows the coefficients of variation (COV) and effect sizes demonstrable with approximately 80% power, assuming an average n=12 per group, using a two-sample t-test with a two-sided α level of 0.05.

Statistical Analysis

The entire research team was blinded to treatment allocation until all studies had been completed. All subjects randomized were included in the analysis under the intention-to-treat (ITT) paradigm. Subjects with missing data had the corresponding values imputed using the overall mean for the remaining subjects. An analysis of covariance (ANCOVA) was used to assess treatment effects on colonic transit incorporating BMI and the corresponding "baseline" value as covariates. An adjustment in the error degrees of freedom was made (subtracting one for each missing value imputed) to adjust the estimates of error variance in the ANCOVA models. In the pharmacogenetic ANCOVA models that explored gene-by-treatment interactions, one patient randomized to DRO 2.5mg was excluded as she did not consent to provide a DNA sample.

RESULTS

Participants and Compliance with Medication

The trial flow is shown in Figure 1. Forty-six patients were assessed for eligibility. Thirty-six IBS volunteers meeting the entry criteria were screened, randomized, and completed the study. A total of 13 volunteers randomly received placebo BID, 10 received DRO 2.5mg BID, and 13 received DRO 5mg BID. One patient in the DRO 5mg group discontinued medication due to an adverse event, and those data were imputed in accordance with the statistical analysis plan (see above). The table within Figure 2 summarizes patient demographics by treatment groups. No clinically important differences in age, sex, and body mass index were observed between treatment groups.

Pharmacodynamic Effects of Dronabinol on Gastric, Small Bowel and Colonic Transit

There were no overall or dose–related treatment effects on gastric (p= 0.88), small bowel (p=0.76), and colonic (overall p=0.23; 2.5mg DRO vs placebo, p=0.16; 5mg DRO vs placebo p=0.53) transit (Figures 3A and 3B).

Pharmacogenetics: Treatment by Genotype Interaction Effects for the Entire IBS Group

In the CC *FAAH* rs324420 genotype group the baseline values were fairly similar. There were no qualitative differences for changes (Post-Pre) in colonic transit from pre-treatment baseline values following placebo or DRO treatment (Figure 4A). However, the baseline GC 24 hour values in the CA/AA subgroup were rather dissimilar. In this subgroup, although there appear to be differential treatment effects (e.g. placebo vs. 2.5mg or 5mg doses), a statistically significant treatment-by-gene interaction was not detected (p=0.46).

CNR1 rs806378 CC genotype was associated with numerical post-treatment changes in colonic transit GC24 from pre-treatment that were qualitatively similar in the three treatment groups (Figure 4B). In contrast, the CT/TT genotype subgroup showed slowing of colonic transit post-treatment with both 2.5mg and 5mg doses, in contrast to the placebo group which showed a slight acceleration post-treatment. The statistical analysis revealed no significant differences to suggest a gene-by-treatment dose interaction.

Given the similarity in the slowing effects of the DRO 2.5mg and 5mg doses in the *CNR1* rs806378 CT/TT genotype group, we examined potential differential treatment effects

associated with genotype comparing placebo with the combined DRO dose groups. As illustrated in Figure 5, the numerical slowing of colonic transit at 24 hours (indicated by individual patient data in Figure 5A, and by the post-pre change in colonic transit at 24 hours in Figure 5B) was confirmed in the CT/TT genotype group, relative to placebo. While this was not statistically significant (p=0.14 for delta GC 24), the unexpected lack of correlation in pre- vs. post-treatment GC 24 values resulted in larger than anticipated variation for changes in colonic transit

Analysis of *FAAH* rs324420 genotype for differential treatment effects on post-treatment minus pre-treatment colonic transit at 24 hours was not significant (test for gene–by-treatment interaction, p=0.47).

Adverse Effects

The observed adverse effects (Table II in Supplementary Materials) were not significantly different among the three treatment groups.

DISCUSSION

Cannabinoid receptors are located on cholinergic neurons in the brain stem, stomach and colon. Their activation by the nonselective cannabinoid receptor agonist, dronabinol, inhibits gastrointestinal and colonic muscle excitation by inhibiting cholinergic neurons in the central and enteric nervous systems[30]. Our overall hypothesis was that cannabinoid receptor modulation is a potential target for therapy in diseases associated with accelerated transit[27], as in the increased colonic motor function observed in patients with IBS-D[31,32]. About 48% of patients with IBS-D have accelerated colonic transit at 24 or 48 hours compared to healthy controls[27]. Given the effects of CB_1 receptor modulation on colonic functions[13,16] and the association of *FAAH* genetic variation with diarrheal symptoms and colonic transit in IBS-D patients[24], we conducted a pharmacogenetic analysis exploring the influence of genetic variations in the CB_1 receptor and in the rate-limiting catabolic enzyme for anandamide (FAAH) in humans.

This study demonstrates that nonselective cannabinoid CB receptor stimulation with DRO 2.5mg or 5mg b.i.d. does not significantly alter overall gastric, small bowel, or colonic transit in patients with IBS-D, of whom the vast majority (34/36) in the current study was female. In a previous study of gastrointestinal and colonic transit in 30 healthy volunteers (7 males and 8 females randomized in each of two groups to DRO and placebo), we had evaluated the effects of DRO 7.5mg b.i.d and observed significant delay of gastric emptying in females[14], but no significant effects on small bowel or colonic transit in either gender[13]. Therefore, the effect of DRO in IBS-D patients on the primary endpoint of interest (overall colonic transit) is consistent with the effect observed in healthy human subjects. The absence of an effect on gastric emptying in IBS-D patients in the current study may reflect the lower dose of DRO used (5mg b.i.d. instead of 7.5mg b.i.d.).

The current study results do not conform with the observed reduction in intraluminally measured colonic motility and compliance observed with dronabinol treatment of patients with non-constipated IBS[16]; however, it is worth noting that the 5mg dronabinol inhibited fasting colonic phasic pressure activity and colonic compliance, and there was no demonstrated effect on postprandial colonic tone or phasic pressure activity[16]. Overall, the two studies question whether a non-selective CB agonist that has potential for central adverse effects can be dosed at sufficient high levels to replicate colonic motor inhibitory effects observed with 7.5mg DRO b.i.d. Clearly peripherally-selective, CB1 modulating agents are required to explore the role of cannabinoid mechanisms in the control or modulation of colonic motor function.

On the other hand, the pharmacogenetic component of the study shows that, even with the small numbers of patients involved in the genotype subgroups, some patients who carry the *CNR1* rs806378 CT/TT genotype may show notable delays in colonic transit with DRO treatment.

In the current study, we elected to use the lower maximum dose of 5mg DRO b.i.d. because of the central side effects of drowsiness and dizziness observed in our prior study with a single dose of 7.5mg dronabinol in healthy subjects [13]. In contrast, a single 5mg dose in IBS patients did not increase stress or arousal in another previous study in our laboratory[14]. We perceived that it was important to limit the maximum dose to 5mg DRO b.i.d., as this was associated with tolerable central effects in prior studies[14], and it had previously been shown that a single 5mg dose of DRO acutely increased colonic compliance and reduced fasting colonic motility in the subgroups of IBS-D and IBS-A patients[16]. The same 5mg DRO dose also increased colonic compliance and decreased colonic motility and tone in healthy male and female volunteers[13]. In fact, the differential effect of DRO (combined 2.5 and 5mg groups) relative to placebo treatment on median colonic transit is about 0.80 geometric center units at 24 hours in the *CNR1* rs806378 CT/TT genotype group. This difference in GC24 with DRO relative to placebo is consistent with the magnitude of effects of other agents that significantly affect bowel function, such as linaclotide in patients with IBS-C[33] or alosetron in IBS-D patients, in terms of the difference between post- and pre-treatment colonic transit[34].

The lack of demonstrable effects of genetic variation in *FAAH* (rs324420) on transit in response to DRO is not known. However, in contrast to the significant modulation of the effect of DRO by changes in the function of the CB_1 receptor due to variation in *CNR1,* it is conceivable that the *FAAH* alteration results in only a small additional variation in the level of endocannabinoids at the synapse. In accordance with this hypothesis, the variation in endocannabinoids is not sufficient to modify the overall or combined effects of CB agonist (DRO) and the endocannabinoids reaching the CB_1 receptors.

Our study illustrates the potential for cannabinoid agents to modulate colonic function in IBS-D, though this may only pertain to a subgroup of patients, based on a variation in the gene for the CB_1 receptor. It is possible that greater peripheral selectivity of the CB_1 agonist may have greater effects on transit, and that selection of IBS patients based on *CNR1* rs806378 CT/TT genotype may enhance the effects of agents acting on CB_1 receptors. The potential for cannabinoids to change gastrointestinal and colonic transit is illustrated by the effects of experimental, more peripherally selective agents. Thus, in vivo studies in mice by Storr et al.[35] demonstrated that the inverse CB agonist, AM251, accelerated upper gastrointestinal transit and whole gut transit, while the neutral CB antagonist, AM4113, also increased upper gastrointestinal transit. Regional effects of cannabinoid antagonists also differ in mice, with reduced colonic expulsion with both AM251 and AM4113; whereas, whole gut transit is accelerated by both agents at specific dose levels[35]. Although there are data suggesting that cannabinoid modulation with the CB_1 and CB_2 receptor antagonists[36] and the FAAH inhibitor, AM3506[37], may affect visceral sensation in inflammation models[36] or gastrointestinal transit and colonic fecal output in mice exposed to endotoxin[37], the effects on pain or visceral sensation in human studies have been disappointing[38,39].

The strengths of our study include the validated methods measuring gastrointestinal and colonic transit, the clinical significance (number and consistency of bowel movements) of the measurement used as primary endpoint (that is colonic GC24), and inclusion of pharmacogenetic analysis to assess whether DRO's effects may be influenced by genetic variations in cannabinoid signaling or metabolism.

The weaknesses of this study include assessment of only four doses of DRO over two days and the nonselective nature of dronabinol for CB_1 and CB_2 receptors. Importantly, our study had insufficient power to detect gene-by-treatment interactions. We conducted a post-hoc analysis of the statistical power of the study based on the variation in the primary response measure (GC at 24 hours), the sample sizes of each group based on specific genotypes, and the pattern of delta GC24 hour data among the four gene-by-drug combinations. Using the dominant genetic model (homozygous major versus combined heterozygous plus homozygous minor groups), treatment group categorized as placebo compared to the combined 2.5 and 5 mg groups, and the pattern of median values in Figure 5B, there would have been approximately 80% power to detect gene-by-treatment interactions of a magnitude illustrated in Table III (in Supplementary Materials), if the variation in delta (post-pre) GC24 values would have been the same as the variation in baseline GC24 values (SD=1.04). Unfortunately the observed variation in delta GC24 values was greater (SD=1.44) and, as a result, there was insufficient power to detect a potential gene-by-treatment interaction. In fact, the usual advantage gained from using baseline GC24 as a covariate did not manifest itself in this study. In summary, the analysis for differential drug effects depending on genotype was limited both by the sample sizes, as well as by the larger than expected observed variation in delta GC24. Thus, there was only 52% power to detect the “interactions” illustrated by the patterns in Table III (in Supplementary Materials), given the observed variation in delta GC24.. To achieve 80% power with the observed SD in GC24 of 1.44, we would require approximately 40 patients per treatment arm assuming a similar distribution of genotypes in each arm (Table III, Supplementary Material). This information is helpful to plan future studies.

Therefore, the pharmacogenetic results in particular are to be viewed as hypothesis-generating. However, the individual responses in the patients who carry the *CNR1* rs806378 CT/TT genotype suggest that inclusion of pharmacogenetics in drug appraisal is relevant, at least at the proof-of-concept stage with quantifiable endpoints.

In summary, our study shows that the nonselective cannabinoid receptor agonist, DRO, does not significantly affect colonic transit; however, DRO may inhibit colonic transit in a subset of IBS-D patients, based on a specific genetic variation in CB_1. A selective CB_1 agonist may have potential as therapy in diarrhea-predominant IBS patients. Further studies to assess the therapeutic role of selective cannabinoid receptor agonists in IBS are warranted. Clinical trials may be enhanced by inclusion of stratification based on *CNR1* rs806378 genotype or use of the genotype variation as a covariate in the analysis of results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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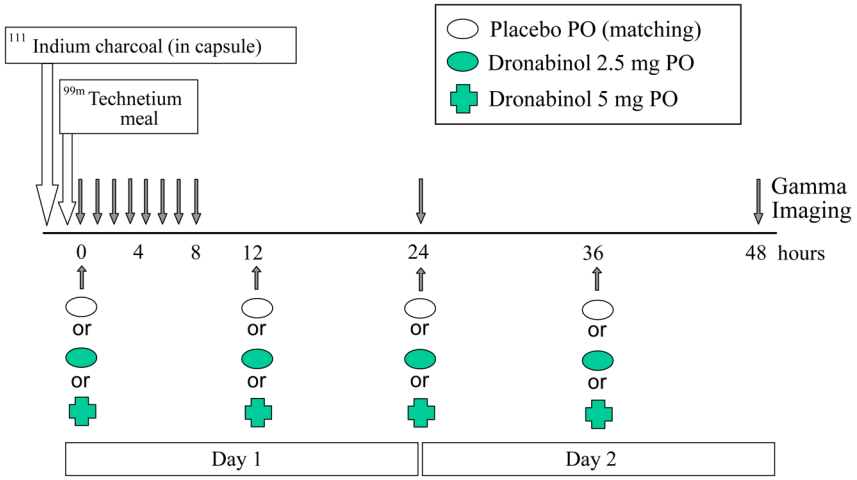
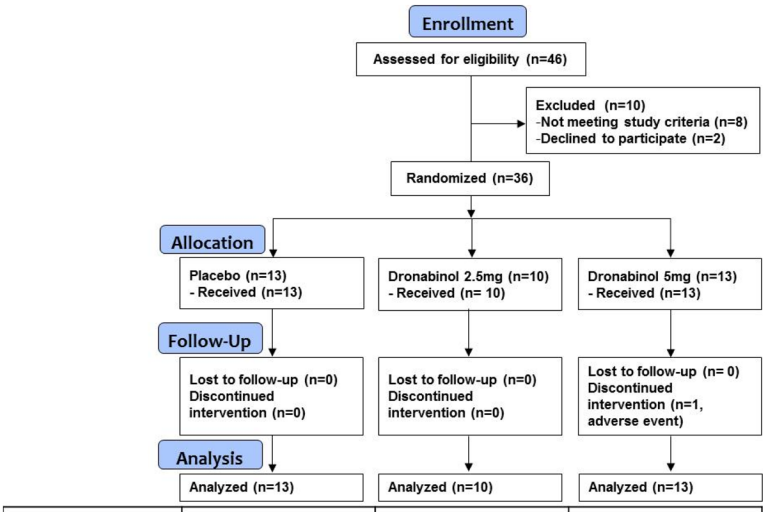


Figure 1.
Experimental design showing timing of study medications and scintigraphic transit measurements.



Age (years)	36.7 ± 3.1	47.7 ± 7.9	42.3 ± 4.5
# Females:Males	13:0	10:0	11:2
BMI (kg/m^2)	30.8 ± 1.8	28.7 ± 1.5	31.6 ± 3.9

Figure 2.
Trial flow chart and baseline characteristics of study participants (mean ± SEM, unless otherwise noted).

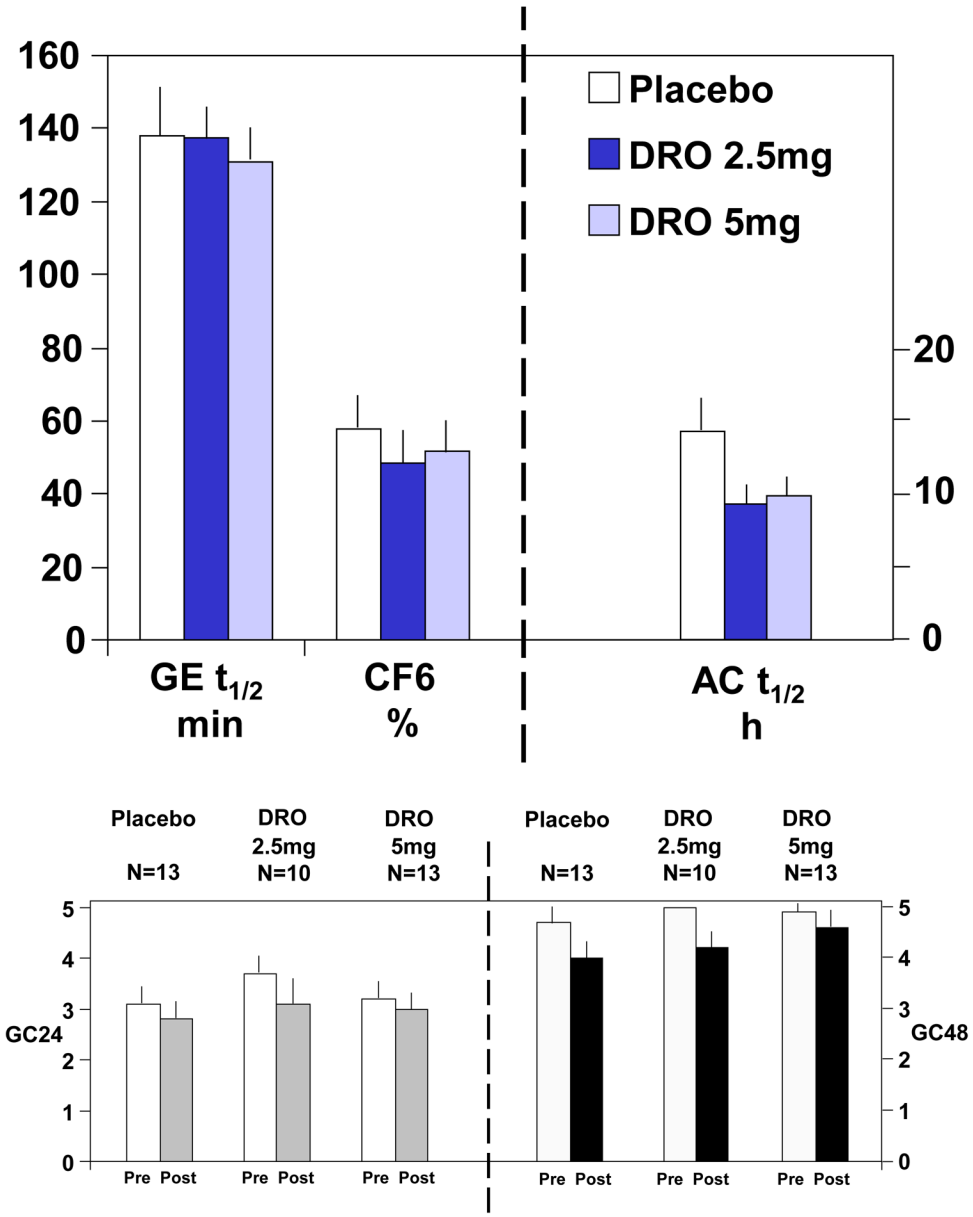


Figure 3.

Figure 3A. Effect of dronabinol on gastric emptying, colonic filling, and ascending colon emptying $t_{1/2}$. Data show mean ± SEM.

Figure 3B. Effect of dronabinol on colonic transit expressed as geometric center at 24 and 48 hours (GC24 and GC48, respectively). Data show mean ± SEM. The pre-drug GC48 for DRO 2.5mg has no SEM bar because all measurements reached a maximum of 5 GC units.

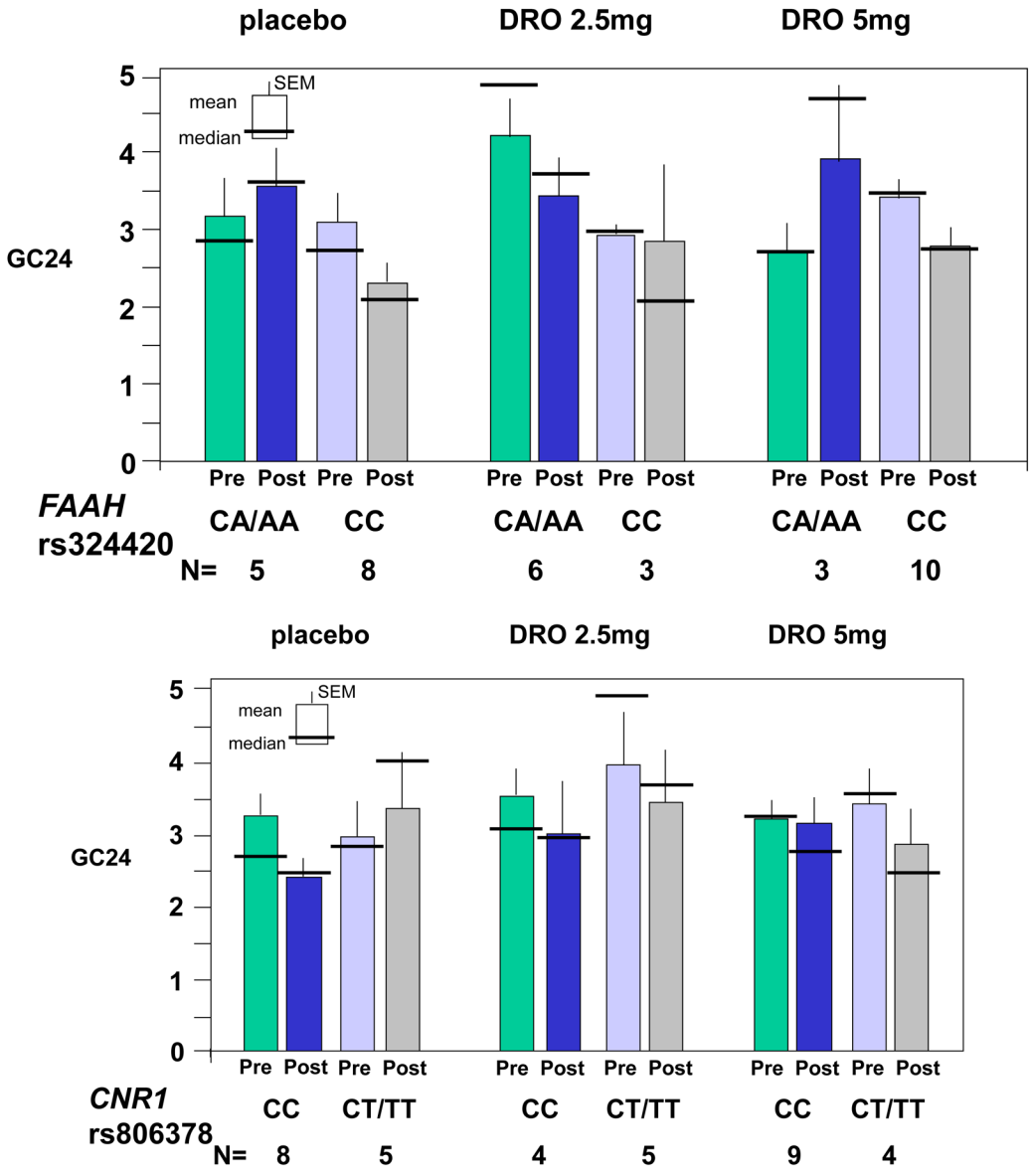


Figure 4.

Figure 4A. Pharmacogenetics of *FAAH* rs 324420 and effects of the two doses of dronabinol and placebo on colonic transit at 24 hours (GC24). Data show mean, SEM, and median.

Figure 4B. Pharmacogenetics of *CNR1* rs806378 and effects of the two doses of dronabinol and placebo on colonic transit at 24 hours (GC24). Data show mean, SEM, and median.

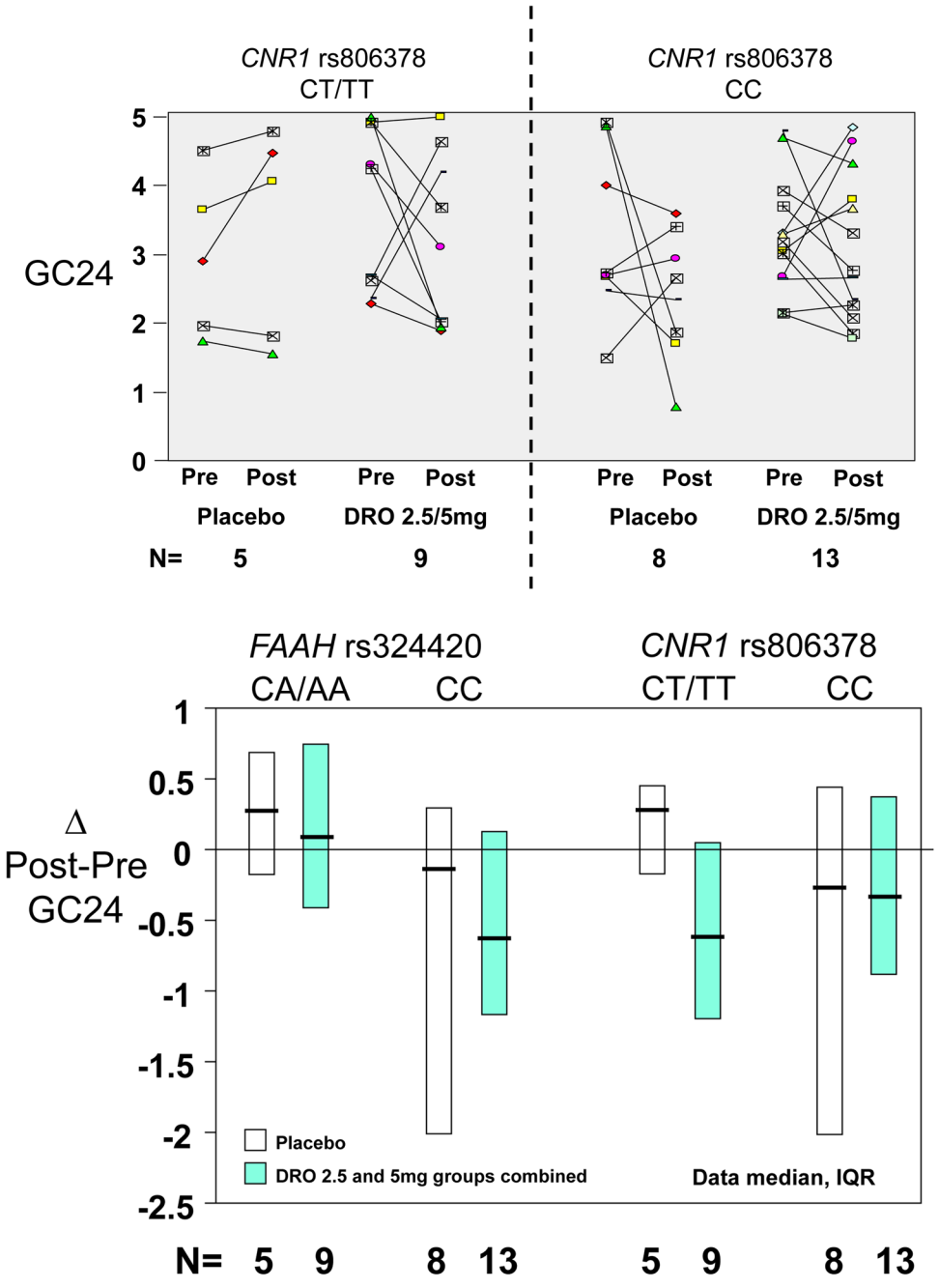


Figure 5.

Pharmacogenetics of *FAAH* rs 324420 and *CNR1* rs806378 on pre- and post-treatment colonic transit GC24 for each individual participant (Figure 5A) and the change in colonic transit at 24 hours (Figure 5B) for the combined dronabinol treatment group compared to placebo.

CLINICAL AT

Pharmacogenetic Trial of a Cannabinoid Agonist Shows Reduced Fasting Colonic Motility in Patients With Nonconstipated Irritable Bowel Syndrome

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BACKGROUND & AIMS: Cannabinoid receptors are located on cholinergic neurons. Genetic variants that affect endocannabinoid metabolism are associated with colonic transit in patients with irritable bowel syndrome (IBS) with diarrhea. We compared the effects of dronabinol, a nonselective agonist of the cannabinoid receptor, with those of placebo on colonic motility and sensation in patients with IBS, and examined the effects of IBS subtype and specific genetic variants in cannabinoid mechanisms. **METHODS:** Seventy-five individuals with IBS (35 with IBS with constipation, 35 with IBS with diarrhea, and with 5 IBS alternating) were randomly assigned to groups that were given 1 dose of placebo or 2.5 mg or 5.0 mg dronabinol. We assessed left colonic compliance, motility index (MI), tone, and sensation during fasting and after a meal. We analyzed the single nucleotide polymorphisms *CNR1 rs806378*, fatty acid amide hydrolase *(FAAH) rs324420*, and *MGLL rs4881*. **RESULTS:** In all patients, dronabinol decreased fasting proximal left colonic MI compared with placebo (overall $P = .05$; for 5 mg dronabinol, $P = .046$), decreased fasting distal left colonic MI (overall $P = .08$; for 5 mg, $P = .13$), and increased colonic compliance ($P = .058$). The effects of dronabinol were greatest in patients with IBS with diarrhea or IBS alternating (proximal colonic MI, overall $P = .022$; compliance, overall $P = .03$). Dronabinol did not alter sensation or tone. *CNR1 rs806378* (CC vs CT/TT) appeared to affect fasting proximal MI in all patients with IBS ($P = .075$). Dronabinol affected fasting distal MI in patients, regardless of *FAAH rs324420* variant (CA/AA vs CC) ($P = .046$); the greatest effects were observed among IBS with constipation patients with the *FAAH* CC variant ($P = .045$). Dronabinol affected fasting proximal MI in patients with IBS with diarrhea or alternating with the variant *FAAH* CA/AA ($P = .013$). **CONCLUSIONS: In patients with IBS with diarrhea or alternating, dronabinol reduces fasting colonic motility; *FAAH* and *CNR1* variants could influence the effects of this drug on colonic motility.**

Keywords: Sensory; Motor; Clinical Trial; Drug Metabolism.

The effects of cannabinoids are mediated primarily through cannabinoid receptors. Two types of G-protein-coupled cannabinoid receptors, CB_1 and CB_2, have been identified and cloned.[1-3] There may be a third as yet uncloned cannabinoid receptor.[4] CB_1-immunoreactivity is located on normal colonic epithelium, smooth muscle, and the myenteric plexus, whereas both CB_1 and CB_2 receptors are expressed in plasma cells.[5] The endocannabinoid system consists of CB_1 and CB_2 receptors; the ligands of these receptors are anandamide and 2-arachidonyl glycerol, and the ligand-inactivating enzymes are monoacylglycerol lipase (MGLL) and fatty acid amide hydrolase (FAAH).[6-9]

The activity of the endocannabinoid system varies between species and in different regions of the gastrointestinal tract within the same species. On the other hand, activation of CB_1 receptors coupled to cholinergic motor neurons inhibits excitatory nerve transmission in human colonic circular muscle[10] in vitro. In mice, endocannabinoids acting on myenteric CB_1 receptors tonically inhibit colonic propulsion.[11] In rodent models, activation of enteric cannabinoid CB_1 receptors inhibits gastric and small intestinal transit without altering intraluminal pressure or basal tone.[12,13] In a prior study in healthy volunteers, we have shown that dronabinol, a nonselective CB receptor agonist, inhibits gastric emptying and colonic motility in healthy humans.[14,15] The effects on colonic tone and phasic motility were observed with 7.5 mg dronabinol, which was shown to induce drowsiness, lightheadedness, and dizziness.[15] The 5-mg dronabinol dose was more tolerable among healthy participants in our previous study. CB receptors are also involved in mediating nociception[16,17] and inflammation.[18]

In this study, we assessed the effects of 5 mg dronabinol on colonic sensory and motor functions in patients with irritable bowel syndrome (IBS) who were cannabinoid-naïve. We hypothesized that dronabinol inhibits colonic

Abbreviations used in this paper: FAAH, fatty acid amide hydrolase; IBS-A, irritable bowel syndrome alternating; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; MGLL, monoacylglycerol lipase; MI, motility index; VAS, visual analogue scale.

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motility and sensation in IBS, and that these inhibitory effects are affected by genetic variations in the CB_1 receptor and in rate-limiting enzymes of endocannabinoid degradation.

Our specific aims were to compare the effects of single administrations of oral placebo, dronabinol 2.5 mg and dronabinol 5 mg, on colonic motility and sensation in cannabinoid-naïve IBS patients; and to examine potential influences of IBS subtypes and genetic variations in cannabinoid mechanisms on the effects of dronabinol treatment. In the latter aim, we examined the effects of variations in critical genes for CB signaling (CBR type1), genes involved in metabolic breakdown of anandamide and 2-acylglycerol, FAAH, and MGLL, respectively, and *CYP2C9*3*, which significantly alters the metabolism of dronabinol on colonic motor and sensory functions observed in response to treatment with dronabinol in IBS patients.

Methods

Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group study (ClinicalTrials.gov identifier NCT01253408) of the pharmacodynamic effects of dronabinol on colonic sensory and motor functions of otherwise healthy human volunteer participants with IBS (aged between 18 and 67 years, and body mass index between 18 and 47). The study was conducted in the Clinical Research Unit at Mayo Clinic in Rochester, MN (National Institutes of Health Clinical and Translational Science Awards grant RR0024150); the study started October 2008 and was completed November 2010. The study was approved by Mayo Clinic Institutional Review Board, and a data safety monitoring plan was established prior to starting the study.

Participants

All participants were recruited from a database of ~1000 patients with IBS who reside within 120 miles of Rochester, MN. Participants filled in a validated bowel disease questionnaire (including questions to correspond to Rome III criteria)[19] and the Hospital Anxiety and Depression Inventory.[20] The bowel disease questionnaire also included a somatic symptom checklist intended to identify somatization. All candidates were screened to ensure they were cannabinoid-naïve, and those who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. The trial flow is summarized in Supplementary Figure 1.

Ultimately, 75 otherwise healthy participants with IBS were enrolled, and 72 completed most studies characterizing the intermediate phenotypes. All females of childbearing potential had to have a negative pregnancy test within 48 h of study. Participants were randomized to 1 oral administration of placebo, dronabinol 2.5 mg, or dronabinol 5 mg, taken with water at the study center under supervision of study staff.

Randomization with 24 per treatment group was conducted by computer program. Allocation was concealed, and participants and investigators were blinded to all treatment assignments. The research pharmacist ensured the random allocation sequence was followed and that participants were assigned to the appropriate group. At study completion, the randomization code was communicated to the study statistician by the research pharmacist.

Pharmacology of Dronabinol

Dronabinol is a synthetic Δ-9-tetrahydrocannabinol. It is a nonselective cannabinoid agonist with affinity for both CB_1 and CB_2 receptors; 90%-95% of the dose is absorbed after a single oral dose.[21] Because of high first-pass hepatic metabolism (primarily by microsomal hydroxylation) and lipid solubility, only 10%-20% of the administered oral dose reaches the systemic circulation. The onset of action after oral administration is at 0.5 to 1 h, and the peak effect is at 2 to 4 h. The elimination phase follows a 2-compartment model with an initial half-life of ~4 h and a terminal half-life of 25-36 h. Biliary excretion is the major route of elimination.

Experimental Protocol

After overnight bowel preparation using a standard polyethylene glycol-containing electrolyte solution (GoLytely; Braintree Laboratories, Inc., Braintree, MA) and a 12-h fast to induce cleansing, a balloon-manometry assembly was placed in the mid-descending or upper sigmoid colon of each participant with the aid of unsedated left-side colonoscopy, guide-wire placement and fluoroscopy. Details of the catheter, barostat, and conduct of sensation and motility testing are provided in Supplementary Figure 2 and the Supplementary Materials and Methods, and followed the procedures in prior studies.[22,23]

The study medication was ingested and 1 h later the same colonic functions were assessed in the fasting state: the 30-min post-drug tone first, followed by a second visual analogue scale (VAS) scale to assess the levels of tension, relaxation, energy, and drowsiness, and then the compliance and randomly ordered phasic distensions as previously done predrug. Subsequently, colonic tone and phasic pressure activity were measured for 30 min before and 1 h after a standard 1000-kcal liquid meal (750 mL chocolate milkshake, 53% fat, 35% carbohydrate, 12% protein). When the recording was finished, the balloon was deflated and the tube was removed by gentle traction.

Data Analysis and Outcome Measures

Colonic compliance. We used a validated linear interpolation method to estimate compliance of the colon, summarized as the pressure at half-maximum volume ($PR_{50\%}$ or PR_{50}).[24]

Colonic motor function. Colonic tone was assessed operationally as the intracolonic balloon volume measured at the operating pressure. Tone was calculated by the baseline colonic volumes measured with the same intraballoon operating pressure throughout the period of interest during fasting (before and after drug) or after the meal.[25,26] Using computer-based 10-min mean volumes for the periods of interest and using the mean of each 10-min observation in those periods, changes in colonic tone were calculated as absolute volume changes during fasting in response to the study medication and as the symmetric percent change in volume postprandially.[23]

Colonic manometry. The same computer program was used to measure the postprandial phasic motor activity in the proximal and distal 3 manometric sensors. Because of variation in the location of the barostat balloon in the upper or lower descending colon, the phasic activity was summarized in each individual for the 3 sensors that were located in the distal descending and sigmoid colon. Data for the fasting period were compared with the two 30-min periods after the 1000-kcal meal

was ingested. Colonic phasic pressure activity was summarized as a motility index (MI), where MI = $\log_e$ (sum of amplitudes × number of contractions + 1).

Colonic sensation. We recorded the pressure thresholds at which participants reported first perception, gas, and pain during the assessment of colonic compliance (ramp distention), and the intensity ratings recorded for gas and pain on 100-mm VAS scales that were averaged over the 4 phasic pressure distensions (termed the *mean sensation rating*). We assessed stress and arousal scores while we assessed the effects of treatment on sensation. As there were no significant effects noted based on the scores of tension, relaxation, energy, and drowsiness, the sensation results are provided without adjusting for these measurements.

Genotyping

DNA was extracted from whole blood as described previously.[27] The selection of candidate endocannabinoid genetic polymorphisms is included in the Supplementary Materials and Methods. Genotyping of *FAAH* rs324420, *CNR1* rs806378, and *MGLL* rs4881 was performed using Taqman SNP Genotyping assays (Applied Biosystems, Inc., Foster City, CA) in accordance with manufacturer's instructions. In addition, we screened patients for the *CYP2C9* rs1057910 polymorphism (A1075C; Ile359Leu), also known as *CYP2C9*3*, because this variant significantly alters the metabolism of orally administered dronabinol,[28] with a 3-fold increase in plasma dronabinol levels in CC homozygotes, but only a modest increase in heterozygotes compared to wild-type AA homozygotes.

Sample Size Assessment

Supplementary Table 1 shows the coefficients of variation and effect sizes demonstrable with n = 24 per group, based on pretreatment data or post-treatment placebo group data of motor and sensory end points for the participants in this study, using 80% power with a 2-sided α of .05 in a 2-sample t test.

Statistical Analysis

The study statistician and the entire research team were blinded to treatment allocation until all analyses of motor and sensory end points had been completed. All subjects randomized were included in the analysis under the intention to treat paradigm. Subjects with missing data had the corresponding values imputed using the overall subjects mean (or median). An analysis of covariance was used to assess treatment effects on colonic tone, compliance, and VAS sensation rating scores, incorporating sex, body mass index, and the corresponding baseline or predrug value as covariates. An adjustment in the error degrees of freedom was made (subtracting 1 for each missing value imputed) to adjust the estimates of error variance in the analysis of covariance models. In the overall analyses of treatment effects (ie, ignoring IBS subgroup and genotype) and in the assessment of potential differential treatment effects among IBS subgroups, 4-7 missing values were imputed, depending on the particular quantitative trait or end point assessed (eg, distal MI was missing in 7, and PR_{50} was missing in 4). In the pharmacogenetic analyses, 73 (*CNR1*), 71 (*FAAH*), and 72 (*MGLL*) of the 75 subjects had genotype status identified. Among the genotyped subjects, 1 to 4 missing values for the intermediate phenotype endpoints were imputed.

For the analysis of VAS sensation scores, analyses of the scores at the 40 mm Hg distension level and, separately, for the corresponding postdrug average (over all 4 distensions) were examined. The overall average baseline sensory rating score during the predrug study was the corresponding baseline value used as a covariate in these analyses.

A proportional hazards regression analysis was used to assess treatment effects on sensation thresholds, incorporating sex, body mass index, and the corresponding pretreatment sensory threshold value as covariates.

The analyses were repeated including IBS subgroup (combining IBS with diarrhea [IBS-D] and IBS alternating [IBS-A], because the latter have been shown to have accelerated transit at 48 h, similar to IBS-D)[29] and, separately, the *CNR1*, *FAAH* and *MGLL* genotypes (dominant genetic model grouping the minor allele homozygotes together with heterozygotes) as covariates, along with the corresponding treatment by subgroup interaction terms. Due to the small minor allele frequency of the *MGLL* rs4881 single nucleotide polymorphism, for both the *CNR1* rs806378 and *FAAH* rs324420 single nucleotide polymorphisms, we assessed potential differential drug vs placebo treatment effects by combining the 2.5 and 5 mg dronabinol doses. Finally, exploratory analyses incorporating IBS subtype and each genotype subtype (separately) were also examined to check for potential differential treatment effects by IBS subtypes and candidate genotypes.

Results

Participants and Compliance With Medication

The trial flow is shown in Supplementary Figure 1. Seventy-five IBS volunteers meeting the entry criteria were screened and randomized, with a total of 72 completing the study. A total of 27 volunteers randomly received placebo, 24 received dronabinol 2.5 mg, and 24 received dronabinol 5 mg. The table in Supplementary Figure 1 summarizes patient demographics by treatment groups. No clinically important differences in age, sex, body mass index, barostat operating pressure, or predrug fasting colonic tone were observed between treatment groups.

CYP2C9 Polymorphism

Genotyping of our study cohort for *CYP2C9* rs1057910 revealed 62 participants with AA and the remaining 10 with CA genotypes. Subjects were equally distributed by genotype across the 3 treatment groups. As there were no CC homozygotes, who would be expected to have different blood levels of dronabinol in contrast to heterozygotes who had minimal changes in blood levels,[28] we did not expect clinically significant variations in plasma dronabinol levels or in median area under the concentration curve across treatment groups. Therefore, there would be no impact of individual metabolism of dronabinol on the study end points.

Effects of Dronabinol on Colonic Compliance in Overall and Patient Subgroups

There was overall borderline treatment effect on colonic compliance (P = .058), which was most pronounced in the dronabinol 5 mg group (Table 1). The reduction in Pr_{50} reflects an increase in compliance of the colon in response to dronabinol. In addition, the effect on compliance was prominent in the IBS-D/A subgroup (P =

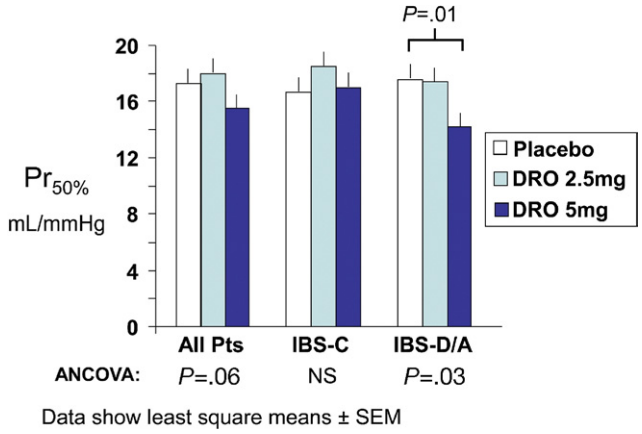

Figure 1. Effect of dronabinol on colonic compliance. The *error bars* are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups from the analysis of covariance) divided by the subgroup sample size.

.03 unadjusted for 2 subgroup comparisons, that is, IBS-C and IBS-D/A). Similarly, the effect on compliance within the IBS-D/A subgroup was most robust with the 5-mg dronabinol dose (Figure 1).

Effects of Dronabinol on Fasting and Postprandial Colonic Tone

Fasting pretreatment colonic tone was not significantly different among the 3 groups (Supplementary Figure 1). There were no significant effects of dronabinol treatment on fasting or postprandial colonic tone (Table 1).

Effects of Dronabinol on Phasic Colon Contractile Activity

Phasic contractility during fasting and postprandially was compared for the upper 3 pressure sensors corresponding to the upper descending colon (henceforth called proximal left colon) and separately for the lower 3 pressure sensors corresponding to the junction of descending colon, sigmoid and rectum (henceforth called distal left colon) as recorded in all individuals. Before treatment, fasting colonic motility was not different among the 3 treatment groups (data not shown).

Dronabinol significantly reduced proximal left colon MI (overall effect $P = .05$) and tended to reduce postdrug colon MIs (overall effect, $P = .08$, Table 1 and Figure 2). In each case, the effect was predominantly attributed to the dronabinol 5 mg dose (proximal colon, $P = .046$ [adjusted] and distal colon, $P = .13$ [adjusted]).

Overall treatment effects on proximal colon MI were significant in patients with IBS-D/A ($P = .044$, after adjustment for 2 tests for the 2 IBS subgroups), but not in IBS-C (Figure 2), with the predominant effect observed with the dronabinol 5 mg dose.

Effects on Colonic Sensory Function During Phasic and Ramp Distensions

Sensation thresholds for gas and pain during ramp distensions were not different among the treatment

Table 1. Effect of Dronabinol on Colonic Compliance, Proximal and Distal Left Colon Motility Index, Fasting and Postprandial Change in Colonic Tone, and Sensation Ratings in Response to Distensions

Parameter	Placebo			Dronabinol 2.5 mg			Dronabinol 5 mg		
	All IBS	IBS-C	IBS-D/A	All IBS	IBS-C	IBS-D/A	All IBS	IBS-C	IBS-D/A
CYP2C9*3: n with CA/AA genotype[a]	3/22	1/8	2/14	3/19	2/10	1/9	3/20	1/10	3/10
Compliance Pr_{50}, *mL/mm Hg*	17.3 ± 0.9	16.6 ± 1.4	17.6 ± 1.0	18.0 ± 1.0	18.5 ± 1.1	17.4 ± 1.4	15.5 ± 1.0	17.0 ± 1.3	14.2 ± 1.2
Fasting tone, *mL*	105.3 ± 4.8	98.8 ± 7.3	107.1 ± 5.3	107.6 ± 5.2	110.0 ± 6.0	100.3 ± 7.4	109.9 ± 5.3	107.7 ± 7.1	109.1 ± 6.2
PP relative Δ tone (0–30 in)/ fasting	30.0 ± 5.0	31.7 ± 7.7	27.1 ± 5.6	32.8 ± 5.5	32.8 ± 6.3	32.5 ± 7.8	32.0 ± 5.5	27.3 ± 7.5	35.9 ± 6.6
Fasting proximal left colon MI	9.0 ± 0.5	8.7 ± 0.8	9.3 ± 0.6	8.9 ± 0.6	8.1 ± 0.6	10.0 ± 0.8	7.6 ± 0.6	7.7 ± 0.8	7.7 ± 0.7
Fasting distal left colon MI	8.0 ± 0.6	7.4 ± 0.9	8.3 ± 0.6	8.3 ± 0.7	7.6 ± 0.8	8.9 ± 0.9	6.8 ± 0.7	5.9 ± 0.9	7.5 ± 0.8
Mean pain sensation VAS, *mm*	42.5 ± 3.5	45.8 ± 5.4	40.6 ± 3.9	42.8 ± 3.9	44.8 ± 4.5	39.6 ± 5.5	46.1 ± 3.9	44.1 ± 5.2	47.9 ± 4.6
Mean gas sensation VAS, *mm*	40.0 ± 3.6	42.5 ± 5.6	38.5 ± 4.0	39.9 ± 4.0	41.5 ± 4.6	37.3 ± 5.7	43.1 ± 4.0	41.9 ± 5.4	44.0 ± 4.8

NOTE. Values are least square mean ± standard error of mean.
PP, postprandial.
[a]Note there were no homozygous CC participants for *CYP2C9* rs1057910 in the entire study; data based on total 75 subjects randomized.

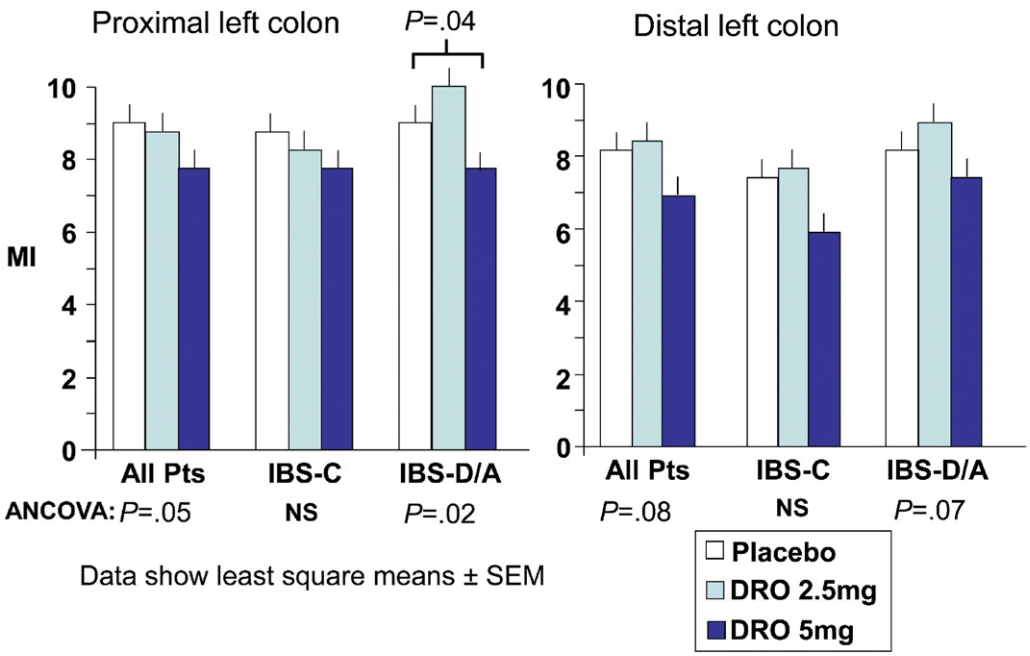

Figure 2. Effect of dronabinol on colonic phasic pressure activity. The *error bars* are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups from the analysis of covariance) divided by the subgroup sample size.

groups over the entire range of pressures tested (data not shown).

Sensation scores for pain and gas in response to high distension pressures were not significantly different among treatment groups (Table 1). No overall treatment effects on mean post-drug VAS sensation rating scores were detected for sensation of gas ($P = .67$) or pain ($P = .60$).

Effect on Central Arousal and Stress

Supplementary Table 2 shows effects on states of tension, relaxation, energy, and drowsiness, which illustrate the lack of significant central effects of the 2.5 and 5 mg dronabinol doses.

Pharmacogenetics: Treatment by Genotype Interaction Effects for the Entire IBS Group

***CNR1* rs806378.** In the CT/TT genotype (in contrast to the CC genotype), somewhat higher sensation ratings of gas and pain were observed in response to dronabinol vs placebo (Supplementary Table 3, which shows effects of 2.5 and 5 mg doses of dronabinol separately). However, significant differential treatment effects were not detected ($P = .39$ for gas sensation and $P = .43$ for pain sensation with the pooled analyses of effects of 2.5 and 5 mg dronabinol).

In addition, in the CC genotype (but not CT/TT), a more pronounced dronabinol-induced reduction in fasting proximal colon MI was observed ($P = .11$ for CC vs $P = .99$ for CT/TT). The effects of *CNR1* rs806378 genotype and dronabinol dose interaction on main sensation and motility end points are shown in Table 2.

No differential treatment effects on compliance associated with *CNR1* status were detected (interaction, $P = .93$; treatment effects in CC, $P = .59$; treatment effects in CT/TT, $P = .63$).

Table 2. Effects of *CNR1* rs806378 Genotype and Dronabinol Dose Interaction on Main Sensation and Motility End Points

Effect	Gas sensation ratings, mean	Pain sensation ratings, mean	Proximal fasting MI	Distal fasting MI
Gene by treatment (interaction effect)	.40	.56	.48	.44
CC (n = 18 on PLA) overall treatment effect	.53	.62	.037[a]	.038[b]
2.5 mg DRO (n = 12) vs PLA	.48	.59	.85[a]	.34[b]
5 mg DRO (n = 14) vs PLA	.60	.59	.016[a]	.064[b]
CT/TT (n = 8 on PLA) overall treatment effect	.56	.60	.67	.79
2.5 mg DRO (n = 11) vs PLA	.29	.36	.68	.98
5 mg DRO (n = 10) vs PLA	.46	.38	.69	.58

NOTE. Sensation ratings are averaged over the different levels of distension. Total of 73 participants had this genotyping. *P* values (unadjusted) from analysis of covariance models examining differential treatment effects (placebo [PLA], 2.5 mg and 5 mg dronabinol [DRO]).

[a]When the 2.5 and 5 mg doses are pooled, these 3 *P* values "collapse" to .11.

[b]When the 2.5 and 5 mg doses are pooled, these 3 *P* values "collapse" to .52.

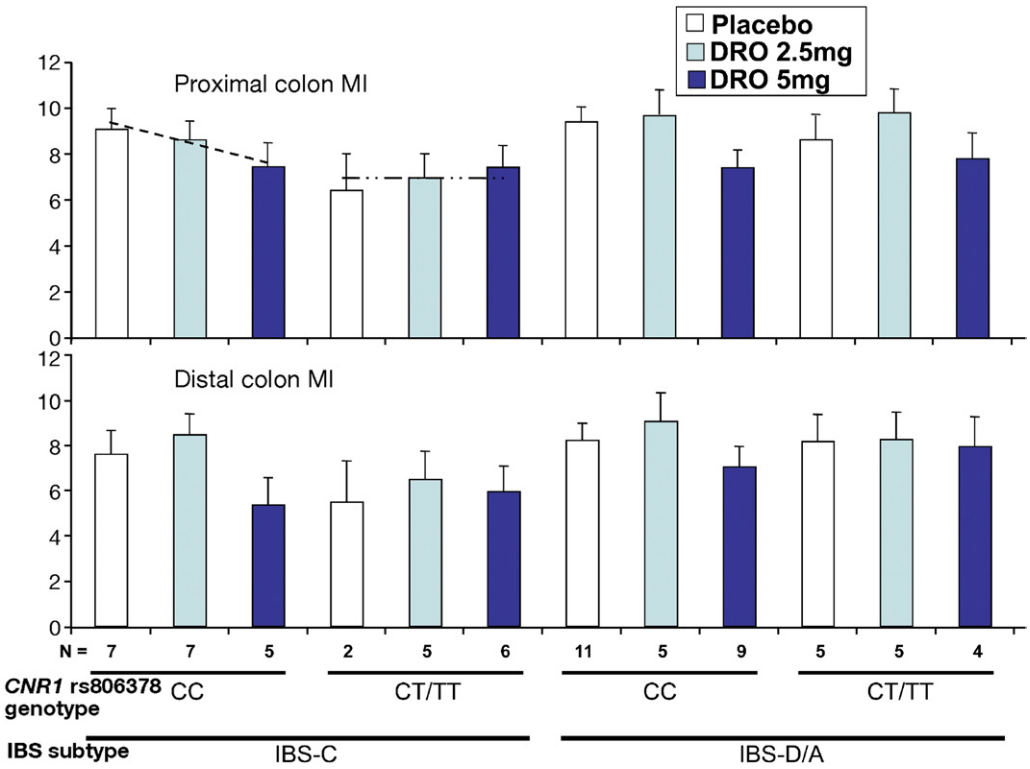

Figure 3. Pharmacogenetics of *CNR1* rs806378 and colonic motility index. Treatment effects were most prominently suggested in IBS-D/A and the *CNR1* rs806378 genotype CC for proximal left colon MI ($P = .075$). Data reported are least squares (LS) means and standard errors (SEM). The *error bars* are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups from the analysis of covariance) divided by the subgroup sample size.

***FAAH* rs324420.** In the CC genotype, a reduced postprandial tone response was observed during treatment with dronabinol, while in the CA/AA genotype, increased postprandial tone (calculated as the relative change in colonic tone, fasting compared to fed tone) was observed in response to dronabinol (test for drug by genotype interaction, $P = .10$).

No other differential treatment effects by *FAAH* genetic status were noted (Supplementary Table 3).

***MGLL* rs4881.** No differential treatment effects on motor or sensory functions by *MGLL* rs4881 genotype status were detected.

Treatment by IBS Subgroup by Genotype Interactions

***CNR1* rs806378.** Treatment effects were suggested with genotype CC in IBS-D/A for compliance ($P = .066$) and proximal left colon MI ($P = .075$, Figure 3).

Differential treatment effects among *CNR1* rs806378 genotypes (CC vs CT/TT) and IBS subtypes were observed for fasting colon tone ($P = .047$) (see Supplementary Tables 4 and 5), with the most pronounced treatment effects observed with the CC genotype in IBS-C ($P = .09$).

Although the overall test for treatment group by IBS subgroup by *CNR1* genotype interaction was not significant ($P = .11$), overall treatment effects (ie, differences among the 3 treatment groups) on postprandial (relative change from fasting) tone were borderline significant ($P = .084$, unadjusted) within the IBS-C and CT/TT subgroup, but not for any of the other subtype/genotype combinations.

***FAAH* rs324420.** Differential treatment effects among *FAAH* rs324420 genotypes (CC vs CA/AA) and IBS subtypes (Figure 4) were observed for proximal left colon MI ($P = .09$), most pronounced in IBS-D/A and CA/AA ($P = .013$), and for distal left colon MI ($P = .046$), most pronounced in IBS-C and CC ($P = .045$).

***MGLL* rs4881.** The analyses for MGLL did not detect any striking "differential" treatment effects, but the minor allele frequency was rather low (1 CC, 12 CT, and 59 TT). There were some suggestions of differential treatment effects for mean VAS gas scores ($P = .12$), mean VAS pain scores ($P = .08$), and a possibly higher pain sensation threshold in CT/CC subjects on drug; however, there were only 6 in this subgroup. There also appeared to be an "overall" (irrespective of treatment) modest association of *MGLL* subtype, with relative change in colonic tone and proximal fasting (postdrug) MI.

No other differential treatment effects were associated with IBS and genotype subgroups.

Adverse Effects

The most frequent adverse effects were drowsy/tired 23%; flushing/hot 19%; headache 13%; dizzy/lightheaded 11%; loopy/foggy thinking 11%; elevated heart rate 11%; relaxed/dream-like state 9%; nausea 8%, dry mouth

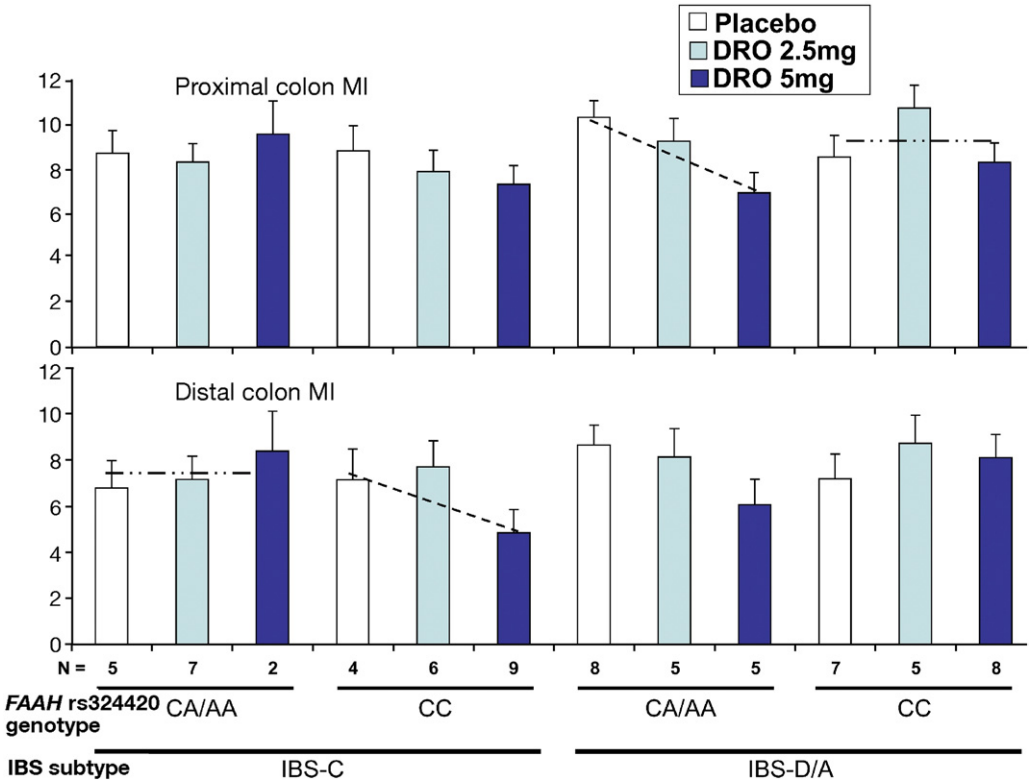

Figure 4. Pharmacogenetics of *FAAH* and colonic motility index. Differential treatment effects among *FAAH* rs324420 genotypes (CC vs CA/AA) and IBS subtypes were observed for proximal left colon MI ($P = .09$) and were most pronounced in IBS-D/A and CA/AA ($P = .013$). Differential treatment effects were also observed for distal left colon MI ($P = .046$) and were most pronounced in IBS-C and CC ($P = .045$). Data reported are least squares (LS) means and standard errors (SEM). The *error bars* are based on the square root of the ratio: pooled estimate of residual error variance (across all subgroups from the analysis of covariance) divided by the subgroup sample size.

and eyes 7%. The adverse effects are broken down by group in Supplementary Table 6. The only adverse effect that was more common with dronabinol than placebo was loopy/foggy thinking ($P = .009$ by Fisher exact test).

Discussion

This study demonstrates cannabinoid modulation of colonic compliance and fasting colonic motility in patients with IBS; specifically, a single dronabinol dose of 5 mg acutely increased colonic compliance and reduced fasting colonic motility in the subgroups of IBS-D and IBS-A patients. Previously, dronabinol had been demonstrated to increase colonic compliance and to inhibit colonic motility and tone in healthy male or female volunteers.[14] Dronabinol also delayed gastric emptying in female but not male healthy subjects.[15] Our current study involving >90% female IBS patients characterizes dronabinol's effects on colonic motor and sensory functions.

Using a barostat-manometry assembly, we observed an increase in colonic compliance and a decrease in proximal left colon phasic motility index with dronabinol treatment. These 2 effects are internally consistent and reflect the inhibition of tonic excitatory motor or activation of inhibitory neural mechanisms by the nonselective cannabinoid agonist. In contrast to dronabinol's effects on colonic motor function observed with the 7.5-mg dronabinol dose in healthy volunteers,[14] the 5-mg dose of dronabinol in this study did not significantly inhibit fasting colonic tone or the motor response to feeding in IBS patients. The drug dose is clearly critical, because the 2.5-mg dose in this study had no effect, while the 7.5-mg dose used previously[14] inhibited colonic tone, increased colonic sensations, and induced central effects, such as lightheadedness consistent with known responses to the cannabinoid receptor agonist.[14] The observed effects of a single administration of 5 mg dronabinol, together with the known expression of cannabinoid receptors on cholinergic neurons in the brain stem, stomach, and colon, are consistent with the hypothesis that dronabinol may be inhibiting colonic muscle excitation via cholinergic neurons in the central and enteric nervous systems.[30] Cannabinoid receptor modulation is a potential target for therapy in diseases associated with accelerated transit[29] or increased colonic motor function in patients with IBS-D.[31,32]

In contrast to the effects of a single dose of 7.5 mg dronabinol noted in healthy subjects, a single 5-mg dose in IBS patients did not increase stress, arousal, or colonic sensations of gas and pain measured as either sensory thresholds or VAS ratings in response to random-order phasic distensions. Identification of a peripheral effect on colonic motor function without increasing unwanted sen-

sations of gas or pain, as well as alterations in affect or arousal is critically important to the development of cannabinoid agents as potential therapy in IBS. In agreement with a recent study on dronabinol's effects on visceral perception to rectal balloon distension,[33] our study also did not show any potentially beneficial changes in visceral perception to balloon distension in the left colon.

Our data show that significant effects of dronabinol on colonic compliance and motility were predominantly observed with the 5-mg dose in those IBS patients who experience diarrhea (IBS-D and IBS-A). Of note, about 48% of patients with IBS-D have accelerated colonic transit at 24 or 48 h and, as a group, patients with IBS-A have accelerated transit at 48 h compared to healthy controls.[29] Inhibition of colonic motility by dronabinol may provide potential benefit to those IBS-D and IBS-A patients with accelerated transit.

Given the effects of CB_1 receptor modulation on colonic functions[14] and the association of *FAAH* genetic variation with diarrhea and colonic transit in IBS-D patients,[34] we conducted a pharmacogenetic analysis exploring the influence of genetic variation in the CB_1 receptor and in the rate-limiting catabolic enzymes for anadamide (FAAH) and 2-acylglycerol (MAGL), the 2 primary endocannabinoids in humans. Our data suggest that effects of dronabinol on colonic compliance and proximal colonic motility may be influenced by genetic variations in *FAAH* and *CNR1*. We did not observe any significant modulation by variation in *MGLL*, but our analysis of *MGLL* was compromised by the low minor allele frequency of rs4881. Overall, our pharmacogenetic data lend support to the hypothesis that a genetic basis accounts for differences in effects on colonic functions by drugs targeting cannabinoid receptors or the metabolism of anadamide. Therefore, future studies of more selective cannabinoid receptor agonists or antagonists may be more informative if pharmacogenetic analysis is included to help identify individuals more likely to benefit from cannabinoid or anti-cannabinoid medications.

Cannabidiol analogs devoid of the central effects on cannabinoid receptor activation have been proposed as therapy for diarrheal diseases.[35,36] In contrast, a cannabinoid receptor antagonist may oppose the inhibition of cholinergic mechanisms by endogenous cannabinoids, which may relieve constipation via acceleration of colonic transit and enhancement of intestinal secretion. Izzo et al showed in a mouse model that the CB_1 antagonist, rimonabant (also known as SR141716A, 0.1-5 mg/kg, intraperitoneally), increased defecation, gastrointestinal transit, and fluid accumulation in the colon. These effects were inhibited by atropine (1 mg/kg, intraperitoneally), but not by the ganglion-blocking agent hexamethonium, or by antagonists of NK_1 and NK_2 receptors.[37] Interestingly, in clinical trials of rimonabant used in aiding nicotine cessation or in treating obesity, diarrhea was 2 to 2.4 times more frequent among those treated with the drug than with placebo, suggesting accelerated colonic transit and/or enhanced mucosal secretion resulting from CB_1 blockade.[38,39]

We did not observe increase in sensation with the 5-mg dronabinol dose in IBS, in contrast to the effects of the 7.5-mg dose in healthy subjects. This is relevant because any beneficial effects on colonic motor function could potentially be negated by increased sensations of gas or pain. Increased awareness of surroundings was reported more frequently in patients receiving Δ-9-tetrahydrocannabinol.[40] On the other hand, Sanson et al[17] suggested that cannabinoid effects on increasing sensation during colonic distension in rats with inflamed colon were mediated peripherally. Importantly, the increased compliance induced by dronabinol did not compromise our assessment of sensory effects because our study used pressure-based distensions to avoid the erroneous interpretation of sensory changes as would occur with sensory ratings measured using volume-based distensions. Further studies are needed to explore the effects of cannabinoid receptor modulation in the sensory neuraxis in humans after repeated administrations of cannabinoid agents.

The strengths of our study include our research team's extensive experience with methods measuring colonic motility and sensation, and the trial generalizability as shown by sample size with adequate power to detect clinically meaningful effects on primary end points, multiple medication doses studied, analysis by IBS subgroups based on predominant bowel function, and inclusion of pharmacogenetic analysis to assess whether dronabinol's effects may be influenced by genetic variations in cannabinoid signaling or metabolism.

The weaknesses of this study include assessment of a single administration of dronabinol and the nonselective nature of dronabinol for CB_1 and CB_2 receptors. Our study had sufficient power to detect treatment effects on motor and sensory responses based on 24 patients per group; the power was lower for symptom subgroups of IBS and for subgroups based on genotypes, where the number of participants in each group divided according to genotype ranged from 2 to 11. Our study also had limited power to detect differences in sensation thresholds due to the large coefficient of variation in these end points when compared to the coefficients for MIs and sensation ratings. Therefore, the pharmacogenetic results, in particular, are to be viewed as only hypothesis-generating. In addition, knowing the blood levels of dronabinol may also have enhanced the interpretation of the associations of the genetic variations of the effects of dronabinol.

Conclusions

Our study shows that the nonselective cannabinoid receptor agonist, dronabinol, inhibits fasting colonic motility and enhances colonic compliance in IBS, particularly in patients with IBS-D and IBS-A. These effects may be better harnessed with selective cannabinoid receptor

agonists and antagonists. A selective CB_1 agonist, in particular, may have potential as therapy in diarrhea-positive IBS patients. Further studies to assess the therapeutic role of dronabinol and other cannabinoid receptor agonists in IBS are warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi:10.1053/j.gastro.2011.07.036.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Materials and Methods

Colonic Motility and Sensation Testing

The catheter incorporated 6 manometric, water-perfused point sensors 5 cm apart and a polyethylene balloon (10-cm long cylinder with a maximum volume of 600 mL; MVI Scientific, Ontario, Canada). Supplementary Figure 2 outlines the experimental protocol. The final position of the barostatically controlled balloon was confirmed fluoroscopically and was in the upper or lower descending colon in 52 participants (35 assigned to dronabinol, 17 to placebo) and in the sigmoid colon in 20 patients (12 dronabinol, and 8 placebo).

The catheter was connected to a rigid-piston barostat (Mayo Clinic, Rochester, MN) by means of a double-lumen tube for balloon distention and intraballoon pressure and volume measurement. A pneumobelt was placed around the abdomen at the level of the lower costal margin to identify and exclude artifact during movement and coughing.

After an initial inflation to a volume of 75 mL to ensure unfolding of the balloon, it was deflated. Previous studies have shown that an initial "conditioning" distension to 20 mm Hg renders subsequent assessments of compliance and perception more reproducible (reference 18 in main article). Therefore, a conditioning distention from 0 to 20 mm Hg in increments of 4 mm Hg every 15 seconds was performed over a period of 75 seconds. After an equilibration period of 10 minutes, a VAS (0 = none; 10 = maximum) was used to assess the level of tension, relaxation, energy, and drowsiness experienced by each subject because it has been shown previously to be a potentially significant covariate in the assessment of visceral sensation scores (reference 23 in main article). Colonic compliance was then assessed by increasing intraballoon pressure in a ramp-like procedure in 4-mm Hg increments at 60-second intervals. The last 30 seconds of the interval is averaged for the mean volume calculation. During the assessment of colonic compliance, participants were asked to report the threshold pressures at which they had first perception, gas and pain, as in prior studies (references 22 and 23 in main article).

Operating pressure was determined by reinflating the balloon in 2 mm Hg increments of pressure. The operating pressure was defined as 2 mm Hg above the minimal distension pressure at which respiratory excursions were clearly recorded from the barostat tracing. After a 10-minute equilibration period, randomly ordered phasic distensions were then applied at 16, 24, 32, and 40 mm Hg above the operating pressure to measure the sensation ratings of gas and pain using a 100-mm VAS. Each distention lasted 1 minute and was followed by an equilibration period at the operating pressure for 2 minutes. After an equilibrium period of 10 minutes, predrug fasting tone was measured for 30 minutes. Thus, colonic compliance, fasting tone, pressure thresholds for first perception, gas, and pain, and VAS sensation rating scores of gas and pain during phasic distensions were measured.

Selection of Candidate Endocannabinoid Genetic Polymorphisms

One of the aims of the study was to assess whether the magnitude of physiologic response to dronabinol reflects genetic differences in the CB_1 receptor, FAAH, or MCLL.

CNR1 (the gene for CB_1 receptor) has 2 synonymous single nucleotide polymorphisms (SNPs), rs35057475 and rs1049353. Allelic frequency of rs35057475 has been reported in only 24 European Caucasians (A/G = 0.026, G/G = 0.974), while that of rs1049353 has been reported in only 38 African Americans (A/G = 0.458; G/G = 0.542) in NCBI. For both variants, there were initially no reported homozygotes of the minor alleles. More recently, rs1049353's minor allele frequency was reported to be 0.26, and an association was reported for this SNP with reduced susceptibility to developing ulcerative colitis.[1] Because rs1049353 is a synonymous SNP, it does not alter the CB_1 receptor amino acid sequence.

There is an $(AAT)_n$ repeat at the 3′ end of *CNR1*, 18,000 bases downstream from the start site of exon 4 of *CNR1*. The literature shows that the number of repeats is highly variable and, although associations with psychiatric disease, intravenous drug use, and response to antipsychotics has been described,[2-6] the functional significance of this genetic variation remains unclear.

The T allele of *CNR1* polymorphism rs806378 is associated with altered nuclear protein binding in an electrophorectic mobility shift assay, suggesting that rs806378 is a functional polymorphism.[7] We chose to study rs806378 (whose nearest gene on the chromosome is *CNR1*), because we had demonstrated association of this genotype with gastric motor functions. In a study by Vazquez-Roque et al,[8] rs806378 CC genotype was associated with reduced fasting gastric volume ($P = .031$), as well as a modest, nonsignificant association with gastric emptying of solids ($P = .17$) compared to the CT/TT group.

FAAH is the rate-limiting enzyme for metabolism of the endocannabinoid anandamide. FAAH and CB_1 receptor expressions have been localized to myenteric neurons.[9] The 385C to A allelic variant of rs324420 in the human *FAAH* gene leads to a Pro129Thr amino acid sequence change, which decreases expression of the FAAH protein due to reduced protein stability (reference 27 in main article). The prevalence of the A allele is 16%–25% in studies of Caucasians in the National Center for Biotechnology Information database. Our laboratory has previously confirmed the A allele frequency to be 25% in our sample population of healthy controls and IBS patients in southeastern Minnesota (reference 34 in main article). Reduction in FAAH protein level and activity

compromises inactivation of the endocannabinoid anandamide, which leads to higher synaptic concentrations of anandamide and, hypothetically, a greater effect of the exogenously administered cannabinoid, dronabinol, via activation of CB_1 and CB_2 receptors.

The *MGLL* gene encodes the rate-limiting enzyme, MGLL, for metabolism of the endocannabinoid, 2-arachidonyl glycerol. There are 2 nonsynonymous SNPs in *MGLL*, whereas other known SNPs in this gene are synonymous or within introns up- or downstream from the gene. The 2 nonsynonymous SNPs are rs11538700 and rs1804711. In the NCBI database, there are no data on allelic distribution for rs1804711. For rs11538700, the published frequencies of 58 European Caucasians, 44 Asians, and 58 sub-Saharan Africans showed no allelic changes with all subjects having the TT genotype (reference 5 in the main article). Given the lack of information or low minor allele frequency of the nonsynonymous SNPs in *MGLL*, we chose to study rs4881, the only synonymous *MGGL* variant with a minor allele frequency >10% that could conceivably allow us to detect significant pharmacogenetic effects.

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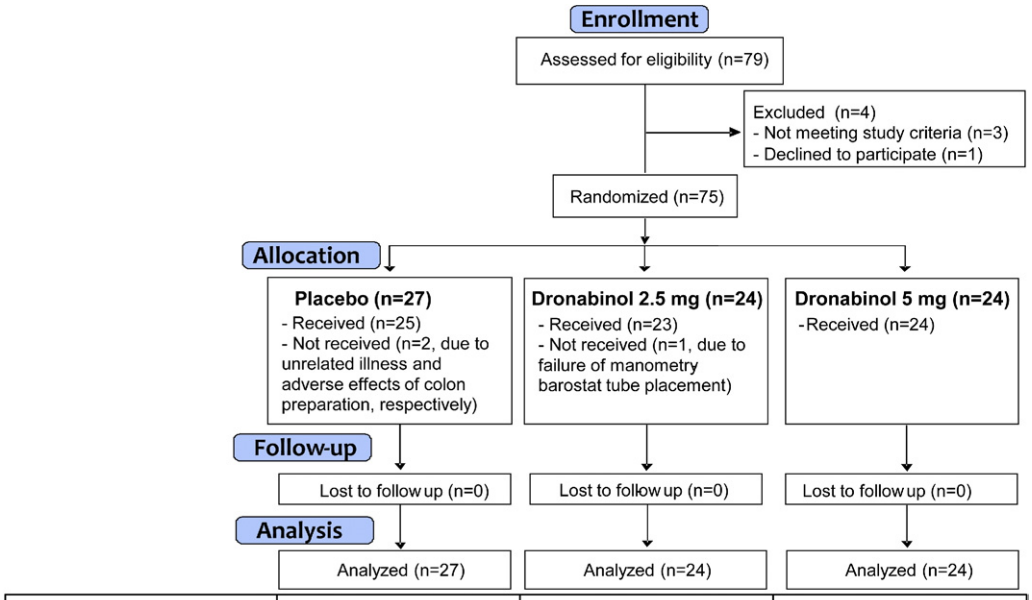
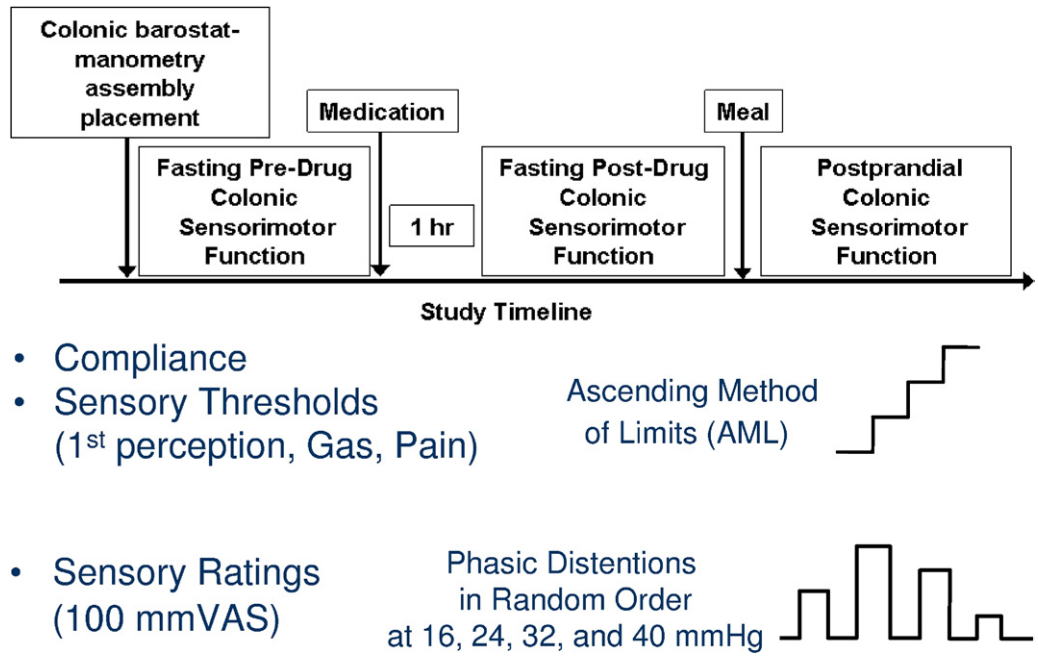


Age (years)	43.2 ± 2.5	36.1 ± 2.5	43.7 ± 2.1
# Females: Males (%)	24: 3 (89%: 11%)	22: 2 (92%: 8%)	23: 1 (96%: 4%)
BMI (*kg/m²*)	28.9 ± 1.2	26.7 ± 1.0	29.7 ± 1.1
# IBS-D /-A /-C subtype	14 / 2 / 9	10 / 0 / 13	10 / 3 / 11
Operating pressure (*mmHg*) *	13.4 ± 0.5	12.9 ± 0.5	13.2 ± 0.4
Pre-drug fasting tone (*ml*) *	105.6 ± 4.4	98.5 ± 4.5	100.6 ± 6.3

** Based on data available in 25 and 23 patients respectively in the placebo and dronabinol 2.5mg groups*

Supplementary Figure 1. Trial flow chart and baseline characteristics of study participants (mean ± standard error of mean, unless otherwise noted).



Supplementary Figure 2. Experimental protocol. Stepwise distension during ascending method of limits was used to appraise thresholds and compliance, and random-order phasic distensions to obtain sensory ratings. Motor function was tested before drug, after drug, and after meal ingestion.

Supplementary Table 1. Statistical Power and Effect Sizes Demonstrable With n = 24/Group (Based on Pretreatment Data or Post-Treatment Placebo Data)

Response	Mean	SD	COV, %	Effect size[a] detectable with 80% power, %
Colonic compliance (Pr 1/2), *mm Hg*	19.6	6.3	32	26
Postprandial colonic tone, *mL*[b]	82	21	26	22
Postprandial proximal colonic MI[b]	10.7	2.5	23	19
Postprandial distal colonic MI[b]	10.5	1.7	16	13
Pain ratings at 32 mm Hg, *mm VAS*	43	25	58	48
Pain ratings at 40 mmHg, *mm VAS*	50	25	50	41
Mean pain rating, *mm VAS*	42	19	45	37
Pain threshold, *mm Hg*[c]	43	16	37	31
Gas threshold, *mm Hg*[d]	21	11	78	64

COV, coefficient of variation; SD, standard deviation.
[a]Difference in group mean values as a percentage of overall mean value listed.
[b]Placebo data only.
[c]Includes 16 values censored at 60 mm Hg.
[d]Includes 3 values censored at 60 mm Hg.

Supplementary Table 2. Stress and Arousal Effects of Placebo and Dronabinol Treatment (mm VAS)

	Placebo	Dronabinol 2.5 mg	Dronabinol 5 mg
Tense	29.3 ± 4.0	22.4 ± 4.5	25.4 ± 4.5
Relax	70.9 ± 4.4	72.7 ± 4.9	73.6 ± 4.9
Energy	31.9 ± 4.4	30.3 ± 4.9	22.1 ± 4.8
Drowsy	65.8 ± 3.9	66.4 ± 4.3	69.4 ± 4.4

NOTE. Values are mean ± standard error of mean.

Supplementary Table 3. Modulation of Effect of Treatment on Colonic Motor and Sensory Functions by *CNR1* and *FAAH* SNPs in Overall IBS Group

SNP	*CNR1* rs806378						*FAAH* rs324420					
Genotype	CC			CT/TT			CC			CA/AA		
Drug	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg
Compliance	17.2 ± 1.0	18.3 ± 1.2	15.2 ± 1.2	17.0 ± 1.5	17.2 ± 1.4	15.4 ± 1.4	17.0 ± 1.5	18.3 ± 1.5	15.2 ± 1.3	17.3 ± 1.2	17.2 ± 1.3	15.8 ± 1.6
Fasting proximal left colon MI	9.25 ± 0.57	9.11 ± 0.68	7.41 ± 0.67	7.98 ± 0.85	8.39 ± 0.78	7.59 ± 0.79	8.72 ± 0.83	9.27 ± 0.81	7.79 ± 0.70	9.73 ± 0.66	8.81 ± 0.71	7.72 ± 0.85
Fasting distal left colon MI	8.10 ± 0.65	8.95 ± 0.80	6.52 ± 0.76	7.58 ± 0.98	7.60 ± 0.90	6.96 ± 0.92	7.41 ± 0.94	8.44 ± 0.95	6.49 ± 0.83	7.99 ± 0.77	7.84 ± 0.84	6.82 ± 0.99
Fasting colonic tone	104 ± 5	108 ± 6	110 ± 6	111 ± 8	108 ± 7	112 ± 7	100 ± 8	99 ± 8	109 ± 7	104 ± 6	109 ± 7	103 ± 8
Postprandial colonic tone	79 ± 6	74 ± 7	77 ± 7	83 ± 8	82 ± 8	78 ± 8	65 ± 8	69 ± 8	70 ± 7	82 ± 6	76 ± 7	76 ± 8
Sensory ratings for pain	44 ± 4	41 ± 5	47 ± 5	42 ± 6	48 ± 5	47 ± 5	40 ± 6	45 ± 6	47 ± 5	45 ± 5	43 ± 5	46 ± 6
Sensory ratings for gas	42 ± 4	38 ± 5	44 ± 5	37 ± 6	44 ± 5	42 ± 6	37 ± 6	41 ± 6	43 ± 5	42 ± 5	40 ± 5	44 ± 6

NOTE. Values are least squares adjusted mean ± standard error of mean.

Supplementary Table 4. Modulation of Effect of Treatment on Colonic Motor and Sensory Functions by *CNR1* and *FAAH* SNPs in IBS-D/A Group

SNP	*CNR1* rs806378						*FAAH* rs324420					
Genotype	CC			CT/TT			CC			CA/AA		
Drug	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg
Compliance	17.5 ± 1.2	17.3 ± 2.0	13.5 ± 1.4	17.2 ± 1.9	17.0 ± 2.0	15.0 ± 2.0	16.9 ± 1.8	17.6 ± 2.0	13.8 ± 1.7	17.7 ± 1.4	16.6 ± 2.0	14.4 ± 1.9
Fasting proximal left colon MI	9.41 ± 0.66	9.69 ± 1.07	7.40 ± 0.78	8.63 ± 1.06	9.80 ± 1.05	7.80 ± 1.13	8.57 ± 0.97	10.78 ± 1.05	8.33 ± 0.87	10.36 ± 0.75	9.27 ± 1.05	6.94 ± 0.94
Fasting distal left colon MI	8.23 ± 0.76	9.06 ± 1.25	7.06 ± 0.90	8.17 ± 1.21	8.26 ± 1.21	7.96 ± 1.31	7.18 ± 1.06	8.72 ± 1.21	8.09 ± 1.01	8.64 ± 0.86	8.12 ± 1.22	6.06 ± 1.09
Fasting colonic tone	105 ± 6	87 ± 10	109 ± 7	108 ± 10	110 ± 10	105 ± 10	101 ± 9	90 ± 10	108 ± 9	105 ± 7	101 ± 10	103 ± 9
Postprandial colonic tone	79 ± 6	61 ± 10	74 ± 8	91 ± 10	81 ± 10	71 ± 11	65 ± 9	65 ± 10	62 ± 9	85 ± 7	62 ± 10	75 ± 9
Sensory ratings for pain	41 ± 5	33 ± 8	50 ± 6	39 ± 7	46 ± 7	45 ± 8	39 ± 7	45 ± 8	48 ± 6	42 ± 6	35 ± 8	48 ± 7
Sensory ratings for gas	40 ± 5	30 ± 8	46 ± 6	35 ± 8	44 ± 8	40 ± 8	36 ± 7	41 ± 8	43 ± 7	37 ± 6	33 ± 8	44 ± 7

NOTE. Values are least squares adjusted mean ± standard error of mean.

Supplementary Table 5. Modulation of Effect of Treatment on Colonic Motor and Sensory Functions by *CNR1* and *FAAH* SNPs in IBS-C Group

SNP	*CNR1* rs806378						*FAAH* rs324420					
Genotype	CC			CT/TT			CC			CA/AA		
Drug	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg	PLA	DRO 2.5 mg	DRO 5 mg
Compliance	16.5 ± 1.7	19.2 ± 1.5	17.9 ± 1.9	16.0 ± 2.9	17.2 ± 1.9	15.7 ± 1.8	16.6 ± 2.2	18.8 ± 1.9	16.3 ± 1.7	16.2 ± 2.0	17.8 ± 1.6	18.5 ± 2.9
Fasting proximal left colon MI	9.08 ± 0.91	8.63 ± 0.82	7.46 ± 1.05	6.43 ± 1.59	6.98 ± 1.05	7.41 ± 0.98	8.84 ± 1.14	7.91 ± 0.97	7.33 ± 0.86	8.74 ± 1.03	8.34 ± 0.84	9.60 ± 1.50
Fasting distal left colon MI	7.61 ± 1.06	8.46 ± 0.95	5.37 ± 1.21	5.49 ± 1.84	6.50 ± 1.24	5.95 ± 1.14	7.13 ± 1.33	7.69 ± 1.13	4.83 ± 1.01	6.77 ± 1.19	7.14 ± 1.01	8.37 ± 1.73
Fasting colonic tone	94 ± 8	116 ± 7	101 ± 10	104 ± 15	96 ± 10	109 ± 9	89 ± 11	99 ± 10	105 ± 9	97 ± 10	114 ± 8	95 ± 15
Postprandial colonic tone	75 ± 9	79 ± 8	78 ± 10	56 ± 16	79 ± 10	78 ± 10	53 ± 11	64 ± 10	70 ± 9	70 ± 10	84 ± 8	69 ± 15
Sensory ratings for pain	47 ± 6	45 ± 6	40 ± 7	43 ± 11	47 ± 7	48 ± 7	41 ± 9	45 ± 7	45 ± 6	50 ± 8	47 ± 6	41 ± 11
Sensory ratings for gas	44 ± 7	42 ± 6	41 ± 8	39 ± 12	43 ± 8	42 ± 7	37 ± 9	39 ± 8	41 ± 7	45 ± 8	45 ± 7	42 ± 11

NOTE. Values are least squares adjusted mean ± standard error of mean.

Supplementary Table 6. Adverse Effects

Adverse effects	All groups (n = 75), %	Placebo (n = 27), %	Dronabinol 2.5 mg (n = 24), %	Dronabinol 5 mg (n = 24), %	*P* value
Drowsy/tired	23	19	21	29	.70
Flushing/hot	19	15	25	17	.66
Headache	13	15	17	8	.76
Dizzy/light-headed	11	4	8	21	.16
Loopy/foggy thinking	11	0	8	25	.009
Elevated heart rate	11	19	8	4	.26

NOTE. Data are percent of group reporting each adverse effect. *P* values are by Fisher exact test.

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Association Between Cannabis Use and Healthcare Utilization in Patients With Irritable Bowel Syndrome: A Retrospective Cohort Study

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Abstract

Introduction

Irritable bowel syndrome (IBS) is a frequent cause of abdominal pain and altered bowel habits, which is associated with significant healthcare utilization. The effects of the active compound of cannabis, Δ9-tetrahydrocannabinol (THC), on gut motility and tone have been studied in several experimental models. It is unknown whether these effects correlate with improved healthcare utilization among cannabis users. The purpose of this study is to evaluate the impact of cannabis use on inpatient length of stay and resource utilization for patients with a primary discharge diagnosis of IBS.

Methods

Data were extracted from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database from 2010 to 2014 for all patients with a primary discharge diagnosis of IBS. Cannabis users (n=246) and non-users (n=9147) were directly compared for various clinical outcomes.

Results

Cannabis users were less likely to have the following: upper gastrointestinal endoscopy (17.9% vs. 26.1%; adjusted odds ratio [aOR]: 0.51 [0.36 to 0.73]; p<0.001) and lower gastrointestinal endoscopy (21.1% vs. 28.7%; aOR: 0.54 [0.39 to 0.75]; p<0.001). Additionally, cannabis users had shorter length of stay (2.8 days vs. 3.6 days; p=0.004) and less total charges (US$20,388 vs. US$23,624). There was no difference in the frequency of CT abdomen performed.

Conclusions

Cannabis use may decrease inpatient healthcare utilization in IBS patients. These effects could possibly be through the effect of cannabis on the endocannabinoid system.

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Introduction

Irritable bowel syndrome (IBS) is a frequent cause of abdominal pain and altered bowel habits worldwide. Per the Rome IV criteria, the disorder is characterized by recurrent abdominal pain associated with defecation or changes in stool frequency or form [1]. Patients are subtyped based on predominant symptoms of diarrhea (IBS-D) versus constipation (IBS-C) or may be categorized to have mixed (IBS-M) or unclassified IBS. IBS is estimated to affect 10 to 15% of the worldwide population and is among the most frequent digestive diagnoses in ambulatory care settings in the United States [2,3]. Despite being predominantly treated in outpatient settings, IBS patients with severe symptoms are occasionally admitted to the hospital [4]. Consequently, these hospitalizations contribute approximately 25% to 30% of total health expenditures from the illness [4]. The syndrome is not a significant cause of mortality, yet it is associated with substantial healthcare utilization and reduction in quality of life [4]. The cost of IBS has been estimated to be US$949.8 million (direct) and US$57.5 million (indirect), accounting for more than one billion dollars in economic burden [5]. Health-related quality of life (HRQoL) data suggest physical impairment similar to patients with diabetes and a greater degree of impairment than those with depression and gastroesophageal reflux disease [6].

The exact pathophysiology of IBS remains unclear. Proposed mechanisms include gut motility dysregulation, altered microbiomes, visceral hypersensitivity, and altered brain-gut interaction [1,7]. Other factors include infectious exposures, inflammatory triggering, genetic susceptibility, and psychological states [7,8].

Corresponding with the heterogeneity of the disorder's pathophysiological mechanisms and manifestations, a variety of pharmacological agents are used in the treatment of IBS. Treatments are aimed at an individual's predominant symptoms (e.g. diarrhea vs. constipation) and include antispasmodics, antidiarrheals, and intestinal secretagogues. Cognitive behavioral therapy and antidepressants are also often used in clinical practice to help alter central pain processing related to the illness [1,9].

Cannabis and other cannabinoids have emerged as therapeutics for gastrointestinal disorders with symptoms similar to IBS, including inflammatory bowel disease and chemotherapy-related nausea; thus, they may be potential agents for symptom reduction in IBS [10]. The use of cannabis in the past has been limited by factors such as federal prohibition, cultural attitudes, and lack of randomized controlled trial data [11-13]. However, in the recent two decades, there has been a decline in negative public perceptions regarding its harms [13]. As of March 2020, 33 states and Washington D.C. have passed laws allowing the use of cannabis for medicinal purposes [14].

Cannabis is thought to act in the gastrointestinal tract through Δ9-tetrahydrocannabinol (THC), which binds to G-protein coupled cannabinoid receptors, CB1 and CB2. These alter gut motility and colonic tone by lowering the presynaptic release of excitatory neurotransmitters, primarily acetylcholine and substance P, from myenteric neurons [11,15]. Placebo-controlled studies have shown that the use of dronabinol, a synthetic form of THC, is associated with reduced fasting colonic motility and tone in IBS patients [10].

Despite proven effects on gastrointestinal regulation, it is uncertain whether cannabis use is associated with favorable clinical outcomes and resource utilization in patients with IBS. Our study used the Nationwide Inpatient Sample database to evaluate the impact of cannabis use on inpatient length of stay and resource utilization for patients with a primary discharge diagnosis of IBS.

Materials And Methods

Cohort and variables

This study used a population-based cohort database based on the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) dataset. We extracted five years of data (calendar years 2010 through 2014). The NIS is a yearly survey of 20% of total admissions from more than 4,000 hospitals across more than 30 U.S. states and the District of Columbia. The NIS has been validated in several studies to provide reliable estimates of disease and co-morbidity prevalence among inpatient admissions in the United States [16].

In this study, we analyzed the inpatient data for a cohort of patients with IBS identified through the following primary diagnosis code: 564.1. Cannabis use was defined by ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes 304.3, 304.3x, and 305.2x as either mild (non-dependent use) or moderate/severe (dependent use), which has also been used in previous studies [17-19].

For each dataset, we extracted demographic factors (gender, age, race), hospital-level characteristics (hospital size, teaching status [teaching vs. non-teaching], and geographic location [region of the United States and rural vs. urban]), health insurance, and income status. Co-morbidity burden was collected and quantified using the Elixhauser Comorbidity Index [20]. Patients with a concomitant diagnosis of inflammatory bowel disease or with missing variables were excluded from the sample population. Our clinical outcomes were lower gastrointestinal endoscopy (LGIE), upper gastrointestinal endoscopy (UGIE), CT of the abdomen, length of stay, and total charge.

Statistical analysis

Cannabis users were compared directly with non-users using the Student t-test, Wilcoxon rank-sum test, or Kruskal-Wallis test to compare continuous variables as guided by the statistical test for normal distributions. Depending on cell size, we used the chi-square test or Fisher exact test to compare categorical variables.

To evaluate the statistical significance of differences in the aforementioned clinical end-points, we built forward stepwise multivariable logistic regression models to establish adjusted odds ratios (aORs) for cannabis use on the rates of LGIE, UGIE, and CT of the abdomen. The selection criteria for entry into the model was a p-value of <0.2, and for retention in the model, it was a 0.1. All statistical analyses were performed using STATA Version 14.0 (StataCorp., College Station, TX, USA). All p-values were two-tailed; p-values of <0.05 were considered to be statistically significant.

Results

Cohort characteristic and direct comparison

A total of 9,393 adult patients were admitted with a diagnosis of IBS during the study period, among which 246 (2.6%) were coded as cannabis users. Compared with patients without recognized cannabis use, cannabis users were significantly younger (mean age 34 years vs. 51 years; p<0.001), more likely to be male (37.4% vs. 19.2%; p<0.001), African American (26.6% vs. 11.5%; p<0.001), in the lowest quartile of median household income (34.6% vs. 26.6%; p<0.004), and more likely to use alcohol (8.9% vs. 2.0%; p<0.001). Comparison of hospital characteristics revealed significant differences between users and non-users as cannabis users more likely had Medicaid as their expected primary payer (32.5% vs. 16.6%; p<0.001) and less likely to list private insurance as their expected primary payer (22.0% vs. 35.4%; p<0.001) (Table *1*).

A direct comparison of co-morbidity profile between users and non-users showed a

significantly lower prevalence of selected disease among cannabis users, including congestive heart failure, diabetes, and hypothyroidism, but a significantly higher rate of concurrent psychiatric diseases (Table *1*).

	Cannabis exposed	Non-cannabis exposed	p-Value‡
Observations, n	246	9147	
Sex, female	62.6	80.8	<0.001
Race, %*			<0.001
Caucasian	60.1	76.6	
Black	26.6	11.5	
Hispanic	10.3	8.6	
Asian or Pacific Islander	0	0.9	
Native American	0.4	0.4	
Other	1.9	2.6	
Age, mean (SD), years†	34.3 (11)	50.9 (19)	<0.001
Co-morbidities, %*			
AIDS	0.4	0.2	0.571
Alcohol abuse	8.9	2.0	<0.001
Deficiency anemia	11.0	14.9	0.089
Arthritis	2.9	4.8	0.163
Blood loss anemia	0.0	0.8	0.157
Congestive heart failure	1.2	4.4	0.015
Chronic lung disease	17.1	20.2	0.233
Coagulopathy	0.4	2.1	0.062
Depression	27.2	24.6	0.350
Diabetes	5.7	13.8	<0.001
Diabetes with chronic complications	2.9	3.0	0.907
Hypothyroidism	3.3	12.9	<0.001
Hypertension	24.8	42.5	<0.001
Liver	6.5	5.6	0.542
Electrolyte derangement	34.6	36.4	0.544

Metastatic cancer	0.0	0.3	0.360
Neurological disorders	3.7	6.4	0.085
Obesity	7.7	12.4	0.028
Paralysis	1.2	0.7	0.298
Peripheral vascular disease	1.2	3.9	0.031
Psychosis	17.1	9.9	<0.001
Pulmonary circulation disorders	0.0	1.1	0.106
Renal failure	2.4	5.2	0.052
Tumor	0.0	0.7	0.206
Valvular heart disease	2.0	2.9	0.408
Elixhauser index score, %*			
0-1	17.9	34.5	<0.001
2-3	54.4	41.5	<0.001
≥4	27.6	24.1	0.197
Hospital bed size, %*			0.002
Small	12.2	14.8	
Medium	37.6	27.3	
Large	50.2	58.0	
Hospital location, %*			0.036
Rural	6.9	9.6	
Urban non-teaching	38.4	43.7	
Urban teaching	54.7	46.7	
Hospital regions, %*			<0.001
Northeast	16.3	19.5	
Midwest	26.4	24.6	
South	31.3	39.9	
West	26.0	16.0	
Expected primary payer, %*			<0.001
Medicare	13.8	35.7	
Medicaid	32.5	16.6	

Private	22.0	35.4	
Others	30.6	12.1	
Median household income (in quartiles), %*			0.004
Q1	34.6	26.6	
Q2	22.9	25.8	
Q3	28.3	25.7	
Q4	14.2	21.9	

TABLE 1: Descriptive statistics of patients admitted with a primary discharge diagnosis of irritable bowel syndrome

n, number; SD, standard deviation

‡p-Values obtained using the Kruskal-Wallis test for continuous values and the chi-square test or Fisher exact test for categorical variables.

*Categorical variables presented as frequency.

†Continuous variables presented as mean value and standard deviations.

When we evaluated clinical end-points, we found that among cannabis users, there was less LGIE (21.1% vs. 28.7%; p<0.010), less UGIE (17.9% vs. 26.1%; p<0.040), shorter lengths of stay (2.8 days vs. 3.6 days; p=0.004), and less total charges (US$20,388 vs. US$23,624) (Table *2*). There was no difference in the frequency of CT of the abdomen performed (Table *2*).

	Cannabis exposed	Non-cannabis exposed	p-Value‡
Observations, n	246	9147	
Hospital course†			
Median total charge (USD)	20,388	23,624	<0.001
Median length of stay (days)	2.8	3.6	0.004
Investigation, %*			
LGIE	21.1	28.7	0.010
UGIE	17.9	26.1	0.040
CT of the abdomen	2.8	3.1	0.755

TABLE 2: Descriptive statistics of healthcare utilization among patients with a primary diagnosis of irritable bowel syndrome

USD, U.S. dollars; CT, computed tomography; LGIE, lower gastrointestinal endoscopy; UGIE, upper gastrointestinal endoscopy

‡p-Value obtained using the Kruskal Wallis test for continuous values and the chi-square test or Fisher exact test for categorical variables.

†Continuous variables presented as median.

*Categorical variables presented as percentage.

Univariate and multivariate logistic regression

In the multivariable logistic regression analysis, cannabis use remained associated with a reduced prevalence of the following outcomes: UGIE (aOR: 0.51 [0.36 to 0.73]; p<0.001) and (LGIE (aOR: 0.54 [0.39 to 0.75]; p<0.001) (Table *3*).

	Cannabis exposed vs. non-cannabis exposed			
Odds of having	Unadjusted OR (95% CI)	Unadjusted p-value	Adjusted* OR (95% CI)	Adjusted* p-value
LGIE	0.67 (0.49-0.91)	0.010	0.54 (0.39-0.75)	<0.001
UGIE	0.63 (0.46-0.88)	0.006	0.51 (0.36-0.73)	<0.001
CT of the abdomen	0.89 (0.42-1.90)	0.760	0.97 (0.44-2.14)	0.948

TABLE 3: Univariate and multivariate logistic regression of clinical outcomes

OR, odds ratio; CI, confidence interval; LGIE, lower gastrointestinal endoscopy; UGIE, upper gastrointestinal endoscopy

*Adjusted for age, gender, race, median income quartile, Elixhauser Comorbidity Index score, comorbidities, and hospital and insurance characteristics.

Discussion

Our study is the first nationwide cohort study to evaluate the association between cannabis use and healthcare utilization in patients with IBS. We have found that cannabis use is associated with a lower use of endoscopic procedures, lower length of stay, and lower median total cost of hospitalization. We posit that the lower use of endoscopy in cannabis users - and hence lower cost of hospitalization - may be due to a lower symptomatic burden when compared to non-users [9]. These findings may be attributable to the well-studied effects of cannabis' active compound, THC, on the endocannabinoid system of the gastrointestinal tract. While cannabis itself has not been well-studied in IBS, several studies have evaluated the effects of dronabinol, a synthetic THC oral agent, on intestinal motility and compliance and on visceral perception in IBS patients and healthy volunteers.

A randomized control trial by Wong et al. in 2011 studied the effect of dronabinol on colonic motility and sensation in patients with IBS. They found that dronabinol was associated with reduced fasting colonic motility index in the proximal left colon and distal left colon. Additionally, it was found that colonic compliance was increased. The effects were most pronounced in those with IBS-D and IBS with alternating symptoms [21]. A follow-up study by the same group in 2012 investigated the effect of dronabinol on colonic transit time in patients with IBS-D. This study found that patients with a specific cannabinoid receptor 1 genotype, rs806378 CT/TT, demonstrated a delay in colonic transit when receiving dronabinol compared with the control group. This effect was not seen in patients with other genotypes studied [22]. This suggests that the effects of THC on colonic motility may depend on an individual's specific cannabinoid receptor genotype. On the contrary, Klooker et al in 2011 conducted a study to assess the effect of dronabinol on sensitivity to rectal distension in 12 healthy volunteers and 10 IBS patients (IBS-D, 4 IBS-C, and 1 IBS alternating based on Rome II criteria). They did not find significant differences in visceral perception after rectal distension, with and without sigmoid stimulation, between the dronabinol and placebo groups [23]. This finding was consistent in both healthy volunteers and IBS patients.

As elucidated above, the existing clinical research regarding THC and IBS is mostly limited to its effects on short-term symptoms and physiological parameters. Even so, these studies support a potential therapeutic role of THC containing agents in IBS. While the pharmacokinetic profiles and route of administration of dronabinol and cannabis differ, we

believe that data on dronabinol may be cautiously extrapolated to cannabis given that their pharmacological effects are posited to be driven by THC.

Our study adds to the literature on IBS and cannabis by presenting data related to in-hospital resource utilization, which may be related to therapeutic effects of cannabis use. Existing data suggest that healthcare costs associated with IBS are driven by diagnostic testing, invasive procedures, and operations [6]. This is consistent with our findings that cannabis users required less lower and upper gastrointestinal endoscopies, with concomitant lower lengths of hospitalizations and lower total costs of care. This could be explained by cannabis users having less symptomatic presentations, hence requiring fewer investigative modalities and inpatient services.

Our study used data from one of the largest databases of hospitalized patients in the United States. However, our study has limitations. First, the time of diagnosis and severity of illness and the concurrent therapeutic regimens of the studied population could not be ascertained from the dataset. Second, ICD-9 coding standards do not stratify patients with IBS by predominant symptom (e.g. IBS-D, IBS-C, IBS-M, or IBS alternating). This is important as THC's effects on IBS have been shown to be most pronounced in patients with IBS-D, as discussed above. Third, NIS data are only generalizable to the hospitalized populations in the United States, and outcomes following discharge could not be delineated. Fourth, cannabis use may be underestimated given that data were extracted from coded diagnoses and not from direct interview, which may explain a lower prevalence of cannabis use in our study when compared with previous research [24,25]. Cannabis use may additionally be underreported in clinical settings given its federal prohibition. Furthermore, our study lacks data on methods, routes, and dosing of cannabis. Additionally, side effects of cannabis could not be ascertained from the dataset given reliance on coded diagnoses. Despite the aforementioned limitations, the large nationwide cohort, scientific rationale, and methodological rigor of our study provide a unique addition to the literature on the effect of cannabis use on IBS. Our results should be interpreted cautiously at this time but warrant further validation with prospective randomized controlled trials.

Conclusions

Our study provides evidence to suggest that cannabis use may decrease healthcare utilization and costs among hospitalized patients with IBS. These findings are likely attributable to the effects of cannabis' active compound, THC, on gastrointestinal motility and colonic compliance. The role of cannabis in the treatment for IBS has potential for significant impact at the individual and population level given the burden of IBS on individual quality of life and healthcare expenditures.

Appendices

Variables	ICD-9 codes
Irritable bowel syndrome	564.1
Cannabis abuse	
Dependent	304.3, 304.3x
Non-dependent	305.2x
Procedures	
Lower gastrointestinal endoscopy	45.24, 48.23, 45.23, 45.25, 45.22, 48.24
Upper gastrointestinal endoscopy	42.23, 42.24, 44.13, 44.14, 45.13, 45.14, 45.16
CT of the abdomen and pelvis	88.01

TABLE 4: ICD-9-CM Codes for identifying irritable bowel syndrome, cannabis use (dependent and non-dependent)

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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DEPARTMENT OF HEALTH

News Release

Nov. 30, 2022

Contact information

Minnesota's medical cannabis pro new qualifying medical condition

The Minnesota Department of Health (MDH) will add irritable bowel syndrome an to the list of qualifying medical conditions for participation in Minnesota's medica law, the new qualifying conditions will take effect Aug. 1, 2023.

"We are adding the new qualifying conditions to allow patients more therapy opt debilitating," said Minnesota Commissioner of Health Jan Malcolm.

Irritable bowel syndrome (IBS) is a disorder characterized by abdominal pain or d movements that can result in diarrhea, constipation, both diarrhea and constipat compulsive disorder (OCD) is characterized by recurring, intrusive thoughts that c distress and anxiety. This can lead to behaviors that the affected person feels com distress. Research has shown that people who suffer from these conditions can se cannabis to treat their symptoms.

As in past years, MDH conducted a formal petition process to solicit public input c conditions and delivery methods for medical cannabis. Minnesotans submitted p Following that, the process moved into a public comment period and a review pa

No petitions for new delivery methods were submitted this year. Petitions for gas disorder were not approved. Gastroparesis, or delayed gastric emptying, was not because research indicates that cannabis can make the condition worse. As for op from medical and mental health providers who recommended against approving qualifying medical condition due to lack of evidence for its effectiveness and the medications for treatment.

Under state rules, patients certified for new qualifying medical conditions will be state's medical cannabis program on July 1, 2023, and receive medical cannabis f medical cannabis manufacturers starting Aug. 1, 2023. As with other qualifying co certification from a participating Minnesota health care provider. More informatic Medical Cannabis Patient [LINK http://www.health.state.mn.us/people/cannabis/patients/regist

When the Minnesota Legislature authorized the creation of the state's medical can nine conditions that qualified a patient to receive medical cannabis. With the new conditions will be 19. Under state rules, the commissioner of health each year con conditions and delivery methods.

For a list of qualifying medical conditions, go to Medical Cannabis Qualifying Med Conditions [LINK http://www.health.state.mn.us/people/cannabis/patients/conditions.html] .

-MDH-

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Last Updated: 11/30/2022

To whom it may concern,

My name is Dr. John Dunne. I am an Occupational Medicine Physician practicing in a multi-disciplinary rehabilitation setting and have been recommending medical marijuana to a wide range of qualified patients, many of whom suffer from co-morbidities including IBS. Patients often report symptom and functional improvement in certain co-morbidities in addition to their qualified conditions as serendipitous outcomes, including IBS symptoms.

I support the proposal to add irritable bowel syndrome as a qualifying condition for medical marijuana under Ohio's Medical Marijuana Control Program.

Patients suffering from IBS are encouraged to implement lifestyle changes such as regular exercise and increasing dietary fiber intake. Many patients are prescribed medications to assist with managing troublesome symptoms which have a severe impact on quality of life such as bloating, cramping, and irregular bowel movements. Such medications are not without their risks. Alosetron, a drug used to address gastric motility issues and diarrhea, actually carries a black box warning from the FDA due to its potential to cause ischemic colitis.

Recent studies have suggested that dysregulation of the endocannabinoid system in the gut may be implicated in the pathophysiology of IBS. The body's endocannabinoid system contains CB1 and CB2 receptors in high density in the GI tract where they play a large role in modulating communications along the gut-brain axis and appear to play a role in regulating gastric motility.

Through the agonist properties of THC at the CB1 receptor, medical marijuana may improve quality of life and reduce the symptoms of IBS linked to dysregulated gastric motility and secretions. Treatment with medical marijuana therefore offers a therapy targeting a currently unutilized pathophysiologic pathway with success highlighted in the briefings coming from Minnesota Department of Health, which recently added IBS as an approved condition under its medical marijuana program.

Please feel free to call me if you have any questions!

Kind regards, **John L. Dunne, DO**