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 *
Caroline	Henry	caroline@buckeyerelief.com
Address *	**City ***	**State ***
33525 Curtis Boulevard	Eastlake	OHIO
Zip Code *	**County ***	**Specific Disease or Condition ***
44095	LAKE	Obsessive-Compulsive Disorder

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

See attached response from the Ohio Medical Cannabis Industry Association (OMCIA)

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
OMCIA Response #1_OCD.pdf	575.86 kB

Links will not be reviewed

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

See attached response from the Ohio Medical Cannabis Industry Association (OMCIA)

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
OMCIA Response #2_OCD.pdf	2.31 MB

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

See attached response from the Ohio Medical Cannabis Industry Association (OMCIA).

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
OMCIA Response #3_OCD.pdf	10.03 MB

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 *

See attached response from the Ohio Medical Cannabis Industry Association (OMCIA)

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
OMCIA Response #4_OCD.pdf	1.30 MB

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. *

See attached response from the Ohio Medical Cannabis Industry Association (OMCIA)

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
OMCIA Response #5_OCD.pdf	152.99 kB

OMCIA
OHIO MEDICAL CANNABIS INDUSTRY ASSOC.

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

The National Alliance on Mental Illness defines Obsessive-Compulsive Disorders as the following:

"Obsessive-compulsive disorder (OCD) is characterized by repetitive, unwanted, intrusive thoughts (obsessions) and irrational, excessive urges to do certain actions (compulsions). Although people with OCD may know that their thoughts and behavior don't make sense, they are often unable to stop them.

Symptoms typically begin during childhood, the teenage years or young adulthood, although males often develop them at a younger age than females. 1.2% of U.S. adults experience OCD each year.

Symptoms

Most people have occasional obsessive thoughts or compulsive behaviors. In an obsessive-compulsive disorder, however, these symptoms generally last more than an hour each day and interfere with daily life.

***Obsessions** are intrusive, irrational thoughts or impulses that repeatedly occur. People with these disorders know these thoughts are irrational but are afraid that somehow they might be true. These thoughts and impulses are upsetting, and people may try to ignore or suppress them.*
Examples of obsessions include:

- *Thoughts about harming or having harmed someone*
- *Doubts about having done something right, like turning off the stove or locking a door*
- *Unpleasant sexual images*
- *Fears of saying or shouting inappropriate things in public*

***Compulsions** are repetitive acts that temporarily relieve the stress brought on by an obsession. People with these disorders know that these rituals don't make sense but feel they must perform them to relieve the anxiety and, in some cases, to prevent something bad from happening. Like obsessions, people may try not to perform compulsive acts but feel forced to do so to relieve anxiety.*
Examples of compulsions include:

- *Hand washing due to a fear of germs*
- *Counting and recounting money because a person is can't be sure they added correctly*
- *Checking to see if a door is locked or the stove is off*
- *"Mental checking" that goes with intrusive thoughts is also a form of compulsion*

Causes

The exact cause of obsessive-compulsive disorder is unknown, but researchers believe that activity in several portions of the brain is responsible. More specifically, these areas of the brain may not respond normally to serotonin, a chemical that some nerve cells use to communicate with each other. Genetics are thought to be very important. If you, your parent or a sibling, have obsessive-compulsive disorder, there's around a 25% chance that another immediate family member will have it.

Diagnosis

A doctor or mental health care professional will make a diagnosis of OCD. A general physical with blood tests is recommended to make sure the symptoms are not caused by illicit drugs, medications, another mental illness, or by a general medical condition. The sudden appearance of symptoms in children or older people merits a thorough medical evaluation to ensure that another illness is not causing of these symptoms.

To be diagnosed with OCD, a person must have must have:

- *Obsessions, compulsions or both*
- *Obsessions or compulsions that are upsetting and cause difficulty with work, relationships, other parts of life and typically last for at least an hour each day"*[1]

[1] https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Obsessive-compulsive-Disorder/Treatment (Attachment #1)

ATTACHMENT #1

Obsessive-compulsive Disorder

Obsessive-Compulsive Disorder

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To be diagnosed with OCD, a person must have must have:

- Obsessions, compulsions or both
- Obsessions or compulsions that are upsetting and cause difficulty with work, relationships, other parts of life and typically last for at least an hour each day

Treatment

A typical treatment plan will often include both psychotherapy and medications, and combined treatment is usually optimal.

- **Medication**, especially a type of antidepressant called a selective serotonin reuptake inhibitor (SSRI), is helpful for many people to reduce the obsessions and compulsions.
- **Psychotherapy** is also helpful in relieving obsessions and compulsions. In particular,cognitive behavior therapy (CBT) and exposure and response therapy (ERT) are effective for many people. Exposure response prevention therapy helps a person tolerate the anxiety associated with obsessive thoughts while not acting out a compulsion to reduce that anxiety. Over time, this leads to less anxiety and more self-mastery.

Though OCD cannot be cured, it can be treated effectively. Read more on our treatment page.

Related Conditions

There are related conditions that share some characteristics with OCD but are considered separate conditions.

- **Body Dysmorphic Disorder.** This disorder is characterized by an obsession with physical appearance. Unlike simple vanity, BDD is characterized by obsessing over one's appearance and body image, often for many hours a day. Any perceived flaws cause significant distress and ultimately impede on the person's ability to function. In some extreme cases, BDD can lead to bodily injury either due to infection because of skin picking, excessive exercise, or from having unnecessary surgical procedures to change one's appearance.
- **Hoarding Disorder.** This disorder is defined by the drive to collect a large amount of useless or valueless items, coupled with extreme distress at the idea of throwing anything away. Over time, this situation can render a space unhealthy or dangerous to be in. Hoarding disorder can negatively impact someone emotionally, physically, socially and financially, and often leads to distress and disability. In addition, many hoarders cannot see that their actions are potentially harmful, and so may resist diagnosis or treatment.
- **Trichotillomania.** Many people develop unhealthy habits such as nail biting or teeth grinding, especially during periods of high stress. Trichotillomania, however, is the compulsive urge to pull out (and possibly eat) your own hair, including eyelashes and eyebrows. Some people may consciously pull out their hair, while others may not even be aware that they are doing it. Trichotillomania can create serious injuries, such as repetitive motion injury in the arm or hand, or, if the hair is repeatedly swallowed, the formation of hairballs in the stomach, which can be life threatening if left untreated. A similar illness is excoriation disorder, which is the compulsive urge to scratch or pick at the skin.

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

(excerpt from Natures Reviews Disease Primers July 20, 2020 "Obsessive-Compulsive Disorder" [2]*) Formerly classified as an anxiety disorder under the DSM-4, OCD was recategorized under the DSM-5 as Obsessive-Compulsive and Related Disorders. OCD is characterized by the presence of obsessions and/or compulsions. In addition, the diagnostic criteria for OCD include a clinical significance criterion and a diagnostic hierarchy criterion. The clinical criterion states that a diagnosis of OCD requires obsessions and compulsions that are associated with clinically significant distress or functional impairment, which is important given that intrusive thoughts and repetitive behaviors are common, and that rituals are a normal part of development. The diagnostic hierarchy criterion states that the obsessions and compulsions are neither a manifestation of another mental disorder, nor are they attributable to the physiological effects of a substance (such as a drug of abuse or a medication) or another medical condition. Obsessions and compulsions in patients with OCD fall into a small number of symptom dimensions. Within a particular individual, obsessions and compulsions tend to be stable, with any changes occurring within symptom dimensions.*

OCD should be differentiated from normal health, as well as from a number of other psychiatric conditions. In general, this is typically carried out by a general psychiatric assessment. Intrusive thoughts and repetitive behaviors are common in the general population (such as thoughts of harming oneself or others and double-checking locks), but a diagnosis of OCD should be made only if these thoughts and behaviors are time-consuming (such as taking up more than 1 hour a day) and cause substantial distress or functional impairment. Recurrent thoughts and rituals also occur in a range of OCRDs (such as body dysmorphic disorder, hoarding disorder, trichotillomania and excoriation disorder), somatic symptom disorders (for example, illness anxiety disorder) and eating disorders (such as anorexia nervosa), but in all of these conditions the foci of apprehension and the form of repetitive behaviors are distinct from OCD.

Worries and ruminations that are characteristic of generalized anxiety disorder and depression are typically about real-life concerns and tend to be less irrational and ego-dystonic than in OCD. Compulsions are also not typically seen under these conditions. Substance-related and addictive disorders, as well as the paraphilic disorders, disruptive, impulsive-control and conduct disorders, often have an ego-syntonic, gratifying component, particularly in the short term. Patients with OCD and poor or absent insight have beliefs that are OCD-related, without the additional features of the schizophrenia spectrum and other psychotic disorders, such as thought disorder and hallucinations. Obsessions and compulsions can be difficult to distinguish from the restricted, repetitive, and inflexible activities and interests that are typical of autism spectrum disorders; however, patients with OCD generally do not present with difficulties in social communication or reciprocal social interactions that are typical of autism spectrum disorders.

[2] Nature Reviews Disease Primers July 20, 2020 "Obsessive Compulsive Disorder" Dan J. Stein, et al (Attachment #2)

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ATTACHMENT #2

Obsessive–compulsive disorder

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Abstract

Obsessive–compulsive disorder (OCD) is a highly prevalent and chronic condition that is associated with substantial global disability. OCD is the key example of the ‘obsessive–compulsive and related disorders’, a group of conditions which are now classified together in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and the International Classification of Diseases, 11th Revision, and which are often underdiagnosed and undertreated. In addition, OCD is an important example of a neuropsychiatric disorder in which rigorous research on phenomenology, psychobiology, pharmacotherapy and psychotherapy has contributed

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Author contributions

Introduction (D.J.S.); Epidemiology (D.J.S.); Mechanisms/pathophysiology (O.A.v.d.H.); Diagnosis, screening and prevention (C.L.); Management (E.C.M., D.L.C.C., R.G.S.); Quality of life (Y.C.J.R.); Outlook (H.B.S.); Overview of Primer (D.J.S.).

Competing interests

D.J.S. has received research grants and/or consultancy honoraria from Lundbeck and Sun, and is also on the scientific advisory board of the TLC Foundation for Body-Focused Repetitive Behaviours, the Anxiety and Depression Association of America (ADAA), and the South African Depression and Anxiety Support Group. D.L.C.C. has received consultancy honoraria from Pfizer and Libbs, and a scholarship from Fundação de Amparo à Pesquisa do Estado de Sao Paulo (Sao Paulo State Foundation for Research Support). E.C.M. has received a productivity grant from the Brazilian National Council for Scientific and Technological Development. Y.C.J.R. has been involved in a study on bipolar disorder, supported by GlaxoSmithKline, and is also lead author on clinical guidelines on OCD produced by the Indian Psychiatric Society. R.G.S. has received consultancy honoraria from Lundbeck, and she receives a productivity grant from the Brazilian National Council for Scientific and Technological Development. H.B.S. has received research grants from Biohaven Pharmaceuticals and royalties from UpToDate, Inc. and Cambridge University Press. She is also on the Board of Directors and the Scientific Advisory Board of ADAA, and is an Associate Editor at *JAMA Psychiatry*. All other authors declare no competing interests.

Peer review information

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Publisher’s note

The current state of mobile applications (apps) for DSM-5 obsessive-compulsive disorderSupplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/s41572-019-0102-3.

to better recognition, assessment and outcomes. Although OCD is a relatively homogenous disorder with similar symptom dimensions globally, individualized assessment of symptoms, the degree of insight, and the extent of comorbidity is needed. Several neurobiological mechanisms underlying OCD have been identified, including specific brain circuits that underpin OCD. In addition, laboratory models have demonstrated how cellular and molecular dysfunction underpins repetitive stereotyped behaviours, and the genetic architecture of OCD is increasingly understood. Effective treatments for OCD include serotonin reuptake inhibitors and cognitive–behavioural therapy, and neurosurgery for those with intractable symptoms. Integration of global mental health and translational neuroscience approaches could further advance knowledge on OCD and improve clinical outcomes.

Obsessive–compulsive disorder (OCD) is an important mental disorder owing to its prevalence and associated disability, and because it is a key example of a set of conditions known as obsessive–compulsive and related disorders (OCRDs; FIG. 1). OCD is characterized by the presence of obsessions and/or compulsions. Obsessions are repetitive and persistent thoughts, images, impulses or urges that are intrusive and unwanted, and are commonly associated with anxiety. Compulsions are repetitive behaviours or mental acts that the individual feels driven to perform in response to an obsession according to rigid rules, or to achieve a sense of ‘completeness’. Children might have difficulty in identifying or describing obsessions, but most adults can recognize the presence of both obsessions and compulsions. Cognitive–behavioural theories have long emphasized that obsessions often lead to an increase in anxiety or sense of discomfort, and that compulsions are performed in response to obsessions. However, some evidence indicates that compulsive behaviour is primary and that obsessions occur as a post-hoc rationalization of these behaviours, although this theory requires further study[1]. Most patients with OCD are keenly aware that their compulsive symptoms are excessive and wish that they had more control over them.

Common sets of obsessions and compulsions in patients with OCD include concerns about contamination together with washing or cleaning, concerns about harm to self or others together with checking, intrusive aggressive or sexual thoughts together with mental rituals, and concerns about symmetry together with ordering or counting[2,3] (FIG. 2). Failing to discard items is characteristic of hoarding disorder, but hoarding to prevent harm, for example, can also be seen in OCD. These symptom dimensions have been observed around the world, indicating that in some ways OCD is a seemingly homogenous disorder. Nevertheless, OCD can present with a range of less common symptoms, including scrupulosity, obsessional jealousy and musical obsessions[4–6]. Avoidance is another key feature of OCD; individuals might curtail a range of activities to avoid obsessions being triggered.

The major international classifications of mental disorders, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), have each introduced a chapter on OCRDs[7,8] (FIG. 1). Although there are important overlaps between OCD and the other OCRDs, including intersecting comorbidities and family history[9,10], there are also key differences in their biology, assessment and management[7,8]. This Primer discusses the epidemiology and evaluation of OCD, its

pathogenesis and underlying mechanisms, and its clinical management. In addition, this Primer discusses quality of life (QOL) issues associated with OCD and key outstanding research questions.

Epidemiology

Prevalence and demographics

OCD was initially believed to be quite rare. However, the first rigorous community surveys that used operational criteria for the diagnosis of mental disorders demonstrated that OCD was one of the most prevalent mental disorders[11], and OCD was estimated to make a considerable contribution to the global burden of disease[12]. More recent nationally representative surveys have confirmed that OCD has a lifetime prevalence of 2–3%, although figures vary across regions, and that it is associated with substantial comorbidity and morbidity[13]. Few sociodemographic correlates of OCD or its symptomatology have been demonstrated in epidemiological studies[14,15]. OCD is more common in females than in males in the community, whereas the ratio of females to males is often fairly even in clinical samples. Similarly, OCD is found in individuals across socioeconomic classes, as well as in low-income, middle-income and high-income countries.

OCD typically starts early in life and has a long duration. In the National Comorbidity Survey Replication (NCS-R) study, nearly a quarter of males had onset before 10 years of age[14]. In females, onset often occurs during adolescence, although OCD can be precipitated in the peripartum or postpartum period in some women[16]. Consistent with the early age of onset, the strongest sociodemographic predictor of lifetime OCD is age, with the odds of onset highest for individuals 18−29 years of age[14]. However, a few onsets do occur in individuals older than 30 years of age. Longitudinal clinical and community studies have demonstrated that OCD symptoms can persist for decades, although remission can occur in a considerable number of individuals[17].

The clinical features of OCD are similar in patients in clinical and community studies. In a range of studies in clinical settings, obsessions and compulsions were found to fall into a small number of symptom dimensions, including concerns about contamination (with subsequent cleaning), concerns about harm (with subsequent checking) and concerns about symmetry (with subsequent ordering)[2,3]. Similar symptom profiles in OCD have been observed in community surveys across different countries[13,14]. Although social and cultural factors can certainly impact the expression and experience of obsessive–compulsive symptoms (for example, concerns about contamination could focus on syphilis in one region, and on HIV in another), there is also considerable uniformity of OCD symptoms across the world[18].

Comorbidity and morbidity

OCD is characterized by substantial comorbidity. In the NCS-R, 90% of respondents with lifetime OCD (based on DSM-IV diagnostic criteria) met the diagnostic criteria for another lifetime disorder in DSM-IV; of these disorders, the most common were anxiety disorders, mood disorders, impulse-control disorders and substance use disorders[14] (FIG. 3). Tic

disorders and other OCRDs also commonly co-occur with OCD. In 79.2% of cases, OCD began after the comorbid anxiety disorders, whereas OCD was about equally likely to begin before or after a mood disorder, and began after comorbid impulse-control and substance use disorders in 92.8% and 58.9% of cases, respectively[14]. In addition, some evidence suggests increased comorbidity of general medical disorders in individuals with OCD[19].

OCD is often a seriously impairing disorder, with 65.3% of 12-month cases (that is, individuals with OCD symptoms in the 12 months before assessment) in the NCS-R reporting severe role impairment on the Sheehan Disability Scale[14]. In addition, those in the clinically severe subgroup reported the highest impairment ratings in relationships and social functioning domains. 12-month OCD was associated with an average of 45.7 days out of role in the prior 12 months. Increased mortality has also been observed in OCD[20]. Despite growing awareness of OCD and associated morbidity, this condition is underdiagnosed and undertreated; in the NCS-R, only a minority of severe cases (30.9%) received treatment specifically for OCD[14].

Limitations of epidemiological research

Important limitations of the current epidemiological evidence for OCD should be emphasized. First, many studies use lay interviewer diagnoses of OCD; however, some data question the validity of this method of diagnosis and further work to determine concordance between lay and clinical interview diagnosis is needed[14,21]. In addition, cross-national data on OCD from surveys that have used similar methodologies are sparse[22]. Finally, survey interviews that are commonly used in epidemiological studies, such as the Composite International Diagnostic Interview, have not distinguished rigorously between OCD and other OCRDs (such as body dysmorphic disorder, hoarding disorder, or Tourette syndrome); thus, it is possible that some respondents with OCRDs are diagnosed with OCD, or that these disorders are entirely missed. Additional analyses from the World Mental Health Survey consortium over time could contribute to a better understanding of the prevalence and correlates of OCD across the globe[23].

Risk factors

Twin studies have shed light on the genetic and environmental contributors to OCD[24]. One meta-analysis of twin studies suggested that additive genetic effects accounted for ~40% of the variance, and non-shared environment accounted for ~51% of the variance in obsessive–compulsive symptoms[24]. In addition, an aetiological role of gene–environmental interactions in OCD, and the shaping of obsessive–compulsive symptoms by very general aetiological factors (such as those influencing negative emotionality) have preliminary supporting evidence[24]. Some subtypes of OCD might have a higher heritability than others, including early-onset OCD with tics[25].

Candidate gene studies have suggested a potential role for variants in serotonergic, catecholaminergic and glutamatergic genes in OCD[26,27], but these studies have been underpowered. More recent genome-wide association studies have indicated that OCD is a polygenic disorder with many identified risk loci of small effect, including variants in glutamatergic genes (see Mechanisms/pathophysiology, below)[28]. Investigation of copy

number variants found a 3.3-fold increased burden of large deletions that were associated with other neurodevelopmental disorders in patients with OCD[29]. Notably, half of these deletions were located in 16p13.11, and three 16p13.11 deletions were confirmed de novo. In addition, the overall de novo rate of large CNVs in OCD was 1.4%, which is midway between rates found in healthy controls and autism spectrum disorders[29].

A broad range of environmental factors, including adverse perinatal events such as birth complications, and stressful or traumatic events, have been identified as potential risk factors for OCD[30–32]. However, additional work is needed to assess the relationship between the environome and OCD. In addition, more research is required to carefully delineate the cellular and molecular pathways by which genetic and environmental risk factors influence endophenotypes, and ultimately OCD. Such work, including additional genetic-imaging studies and genome-wide environmental interaction studies, is needed if a precision or personalized medicine approach is to be developed for the prevention and management of OCD[33].

Mechanisms/pathophysiology

Cognitive-affective dysfunction

Studies in the mid-20th century demonstrating that animals could be deconditioned to fear gave rise to clinical research on behavioural therapies, including exposure and response prevention (ERP) for OCD[34,35]. In turn, clinical findings gave impetus to the development of behavioural and cognitive–behavioural models of OCD, with subsequent work suggesting that obsessions can be conceptualized as a noxious stimuli to which individuals fail to habituate[36], that negative interpretations of obsessive thoughts lead to a range of neutralizing behaviours (that is, compulsions) which serve to maintain these interpretations and the obsessive thoughts[37], and that there are deficits in mechanisms that are central to extinction learning[38]. Such models in turn provide a foundation for fear habituation (emphasized in behavioural therapy), belief disconfirmation (emphasized in cognitive therapy), and exposure optimization techniques (to address deficits in extinction learning)[38,39]. Expert consensus has suggested that key belief domains or meta-cognitions in OCD include the overestimation of threat and excessive concern about the importance of controlling one’s thoughts[40].

Similarly, cognitive–affective research paradigms have emphasized dysfunctions in processes that might lead to increased concerns about harm (for example, increased sensitivity to disgust-evoking stimuli and excessive performance monitoring), or that might lead to an inability to control responses to such concerns (for example, impairment in executive functions such as response inhibition and excessive stimulus–response habit formation)[41]. Indeed, a range of impairments in patients with OCD have been observed in neuropsychological studies, including altered executive function (such as altered cognitive flexibility, planning, working memory and response inhibition), and alterations in disgust processing, fear extinction, reward processing and emotion regulation, among others, have been reported in affective studies[42]. However, further work is needed to determine how these cognitive-affective alterations contribute to the symptoms of OCD[43]. Furthermore, although such research has been useful in conceptualizing and researching OCD, cognitive–affective

alterations are not yet sufficiently sensitive or specific to usefully guide clinical practice for OCD.

Neural circuits

The defects in cognitive and affective processing in patients with OCD could be mediated by alterations in specific neural circuits. Early work established that OCD could emerge in individuals with specific neural lesions (BOX 1). Although data from studies using animal models of stereotyped behaviours and grooming have contributed to understanding the neural circuitry of OCD[44,45], advances in functional and structural brain imaging methods have been particularly important in advancing the field and have given impetus to influential models of OCD neurocircuitry. Such models have integrated data from neuroimaging and cognitive–affective studies by hypothesizing the involvement of parallel, partly segregated, cortico–striato–thalamo–cortical (CSTC) circuits that are involved in sensorimotor, cognitive, affective and motivational processes in OCD[46,47] (FIG. 4). Indeed, data from functional and structural imaging studies support this hypothesis by demonstrating alterations in several brain regions that comprise these circuits in patients with OCD compared with healthy individuals. Other models have also implicated alterations in frontolimbic, frontoparietal and cerebellar networks[48,49].

Functional alterations.—The first functional brain imaging studies in OCD used PET and functional MRI (fMRI) to observe changes in brain activation on symptom provocation using disorder-relevant tactile and visual stimuli (often these stimuli were related to contamination fears)[47,48]. An early meta-analysis using activation likelihood estimation combined the results of eight studies and demonstrated increased symptom provocation-induced activation of ventral frontostriatal and temporal regions, including the hippocampus, in patients with OCD compared with controls[50]. A more recent meta-analysis using signal differential mapping demonstrated increased activation in the bilateral amygdala, right putamen, orbitofrontal cortex extending into the anterior cingulate and ventromedial prefrontal cortex, middle temporal cortex, and the left inferior occipital cortex during emotional processing (induced, for example, by exposure to disease-relevant stimuli), particularly in OCD[51]. Of these changes, alterations in the amygdala were most pronounced in unmedicated patients, and those in the right putamen were most prominent in medicated patients.

Other functional imaging studies have investigated brain activation while performing tasks that rely on executive functions, such as working memory, response inhibition, reversal learning and planning[48,49]. Although a number of consistent findings have emerged from these studies, variations in study design, task condition contrasts, and task load, combined with modest sample sizes and lack of control for multiple comparisons, have likely contributed to inconsistencies in the literature. In general, altered frontostriatal and frontoparietal recruitment has been found in these studies, but the extent of hyperactivation or hypoactivation is thought to depend on the participants' capacity to recruit neural circuits to compensate for network inefficiency (which could cause hyperactivation), and on interference with neural circuit recruitment due to limbic activity (which might lead to hypoactivation). Some of the changes reported in patients with OCD are also found in

unaffected siblings, suggesting that genetic factors could contribute to these network alterations[48,49]. Meta-analyses have been useful in summarizing studies evaluating executive function in patients with OCD. Decreased task-relevant activation in the caudate nucleus, putamen, cingulate cortex and prefrontal regions were reported in one meta-analysis of 28 fMRI studies of executive function[52], whereas frontostriatal abnormalities and parietal and cerebellar involvement were reported in another meta-analysis of studies of executive function[53].

More recent studies have focused on the balance between habitual and goal-directed behaviour, and have demonstrated increased habit formation in patients with OCD compared with healthy controls which is associated with hyperactivation of the caudate nucleus[54]. One meta-analysis that combined 54 fMRI studies on both cognitive and affective paradigms in OCD demonstrated differences in brain activation across these paradigms[55]. During emotional processing (an affective paradigm), patients with OCD had overactivation of brain networks involved in salience, arousal and habitual responding, such as the anterior cingulate cortex, insula, head of the caudate nucleus and putamen, and underactivation of regions that have been implicated in cognitive control, such as the medial prefrontal cortex and posterior caudate, compared with healthy controls[55]. In addition, during cognitive paradigms, patients with OCD had increased activation in regions involved in self-referential processing, such as the precuneus and the posterior cingulate cortex, and decreased activation in subcortical regions involved in goal-directed behaviour and motor control, such as the pallidum, ventral anterior thalamus and posterior part of the caudate nucleus[55]. The pattern of alterations in this study is consistent with increased habitual responding and affective processing, and impaired cognitive control in patients with OCD. The exact involvement of various neural circuits likely varies with age and disease stage, and is dependent on symptom characteristics, disease chronicity, and neurocognitive profile (FIG. 5).

Cognitive–affective dysfunctions such as alterations in emotional processing and cognitive control could lack specificity for particular disorders and cut across diagnostic entities[56–58]. The majority of brain imaging studies of OCD compare patients with OCD with healthy controls, without an additional clinical control group consisting of patients with related disorders, except for some studies that have compared patients with OCD with patients with autism spectrum disorder during decision making[59], patients with attention deficit/hyperactivity disorder during temporal discounting (a measure of impulsivity)[60], and patients with panic disorder and hypochondriasis during attention bias and planning[48,49]. Conversely, impairments in inhibitory control could be associated with different network abnormalities in OCD, attention deficit/hyperactivity disorder, and Tourette syndrome[61,62].

Structural alterations.—The development of automated brain imaging analysis techniques, such as voxel-based morphometry (VBM), has facilitated systematic investigation of whole-brain morphometry and has increased the reliability and reproducibility of results. Regional brain volume reflects a combination of grey matter thickness, cortical surface area and cortical folding; cortical surface and folding measurements might be indicative of prenatal neurodevelopmental processes, whereas

cortical thickness changes dynamically across the lifespan as a consequence of development and disease.

Smaller dorsomedial prefrontal, medial orbitofrontal and insular opercular volumes, and larger volumes of the putamen and cerebellum (of which the larger putamen was most pronounced in older patients) was reported in one of the first VBM studies in OCD[63]. This study also demonstrated that the patients with prominent symptoms of aggressive obsessions and checking compulsions had a smaller volume of the right amygdala compared with other individuals with OCD, suggesting that different symptom dimensions might be underpinned by different neural mechanisms. In accordance with these data, other studies have also reported evidence of symptom dimension-specific profiles, with harm-related symptoms associated with a decreased volume of bilateral anterior temporal poles, and contamination symptoms associated with a smaller caudate nucleus[64].

Although such work is important in proposing hypotheses about the neural circuitry of OCD, relatively small sample sizes can lead to false-positive and false-negative findings. Meta-analysis may be useful in synthesizing findings from different studies. The first meta-analysis of brain structure in OCD used signal differential mapping of 12 VBM studies and reported a decreased volume of the dorsomedial prefrontal cortex and an increased volume of the bilateral lenticular nuclei (part of the striatum), consistent with a frontostriatal model of OCD[65]. This decreased dorsomedial prefrontal volume was not specific for OCD and was also observed in other anxiety disorders, whereas the increased volume of the striatum was specific for OCD, with patients with other anxiety disorders showing decreased lenticular volume[66].

A consortium of international sites subsequently undertook a mega-analysis of pooled VBM data from adults with OCD and matched healthy controls (n = 780). This study reported smaller volumes of the dorsomedial prefrontal cortex and the bilateral insular opercular region, and increased volume of the cerebellum in patients with OCD[67]. In line with an earlier study, age-related effects were observed in striatal and limbic regions, with preservation of putamen volume and more pronounced age-related volume decreases in limbic parts of the middle and inferior temporal cortex with increasing age. Most of these findings were replicated using a different analysis technique focusing on cortical thickness[68]. In addition, altered structured covariance between the ventral striatum and insular operculum region was observed predominantly in older patients[69]. Together, these findings suggest that neuroplastic changes occur in patients with OCD, which could occur as a result of disease chronicity and/or long-term effects of medication.

Studies from the ENIGMA-OCD working group aimed to further evaluate changes in neuroanatomical structures associated with OCD over time[70], and demonstrated a decreased volume of the hippocampus and an increased volume of the bilateral putamen in adults with OCD, compared with healthy controls[71]; both changes were more pronounced in medicated patients. In this study, reductions in hippocampus volume were more pronounced in those with comorbid depression, consistent with evidence that hippocampal changes are found in many disorders[72]. In addition, an increased volume of the pallidum was mainly present in the adults with OCD who had child-onset disease, suggesting that the striatal volumetric

changes are a result of disease chronicity and treatment. In children with OCD, a larger volume of the thalamus was found in unmedicated individuals compared with healthy controls. In addition, medicated patients with OCD had thinner cortex in frontal, temporal, parietal, temporal and occipital regions (adult sample) and smaller surface areas in frontal regions (paediatric sample), whereas unmedicated patients with OCD did not differ from controls[73].

Changes in brain white matter have also been reported in patients with OCD. Indeed, widespread white matter abnormalities were reported in one meta-analysis, particularly in the anterior midline tracts (crossing between the anterior parts of cingulum bundle and the body of corpus callosum), and in samples with a higher proportion of medicated patients[74]. In addition, overlapping white matter abnormalities were observed across several affective disorders, including depression, bipolar disorder, OCD, post-traumatic stress disorder and social anxiety disorder, with decreased fractional anistropy in frontotemporal and frontoparietal regions, and the most robust and replicable finding in the superior longitudinal fasciculus[75].

Summary.—In summary, some neurobiological alterations in OCD are common with other psychiatric disorders (such as smaller hippocampus, dorsomedial prefrontal cortex and insular opercular region), whereas others are more specific for OCD (such as larger volume of the basal ganglia, which is most pronounced in older patients and likely related to disease chronicity and/or long-term effects of medication). A larger thalamus in unmedicated children with OCD may reflect altered brain maturation. There is a need for longitudinal studies of OCD and OCRDs with a specific focus on neurodevelopment before onset of the disorder, as well as the long-term effects of pharmacotherapy and other interventions. Advances in high-resolution MRI and improved segmentation of the subregions of the striatum and thalamus may also be useful in delineating the precise neural circuitry in patients with OCD.

Molecular mechanisms

Several key neurotransmitter systems are found within CSTC circuits, including serotonin, dopamine and glutamate, and these might have an important role in underpinning OCD symptoms. The early finding that OCD responds selectively to serotonin reuptake inhibitors (SRIs) has led to substantial attention on the serotonergic system. The involvement of the dopaminergic system was highlighted after patients responded to augmentation of SRIs with dopamine D2 receptor antagonists, among other data, whereas more recent studies have focused on the glutamatergic system.

Although the selective efficacy of the SRIs in patients with OCD gave significant impetus to a serotonin hypothesis, there is surprisingly little evidence of an underlying serotonin deficit that has a primary causal role in OCD[76]. Alterations in levels of serotonin and its metabolites in the cerebrospinal fluid of patients with OCD, with normalization after successful treatment, have been reported in some studies, although evidence is sparse[76]. In addition, associations between variants in serotonergic genes (such as the serotonin transporter) and OCD have been reported in a few studies[26,27], and altered serotonin

transporter receptor binding in areas such as the midbrain has been observed in some studies, although not all data are consistent[77,78].

Dopamine has a key role in stereotypic behaviour, including grooming, in animal models[45]. In addition, dopamine has an important role in a range of cognitive and affective processes including reward processing, which could be altered in OCD. Strong evidence suggests a central role of the dopaminergic system in Tourette syndrome, which many would consider to be one of the key OCRDs[79]. Supporting the role of dopamine in OCD, some studies have reported an association between variants in catecholaminergic genes (including *COMT*) and OCD[26,27], and molecular imaging studies have suggested alterations in specific dopaminergic receptors, such as a decrease in striatal dopamine D2 receptors, in OCD[78,80]. Finally, as discussed below, there might be some therapeutic role for dopamine D2 receptor blockers in OCD[81].

Glutamatergic neurons originating in the prefrontal cortex have a key role in CSTC circuitry, with these neurons projecting to the striatum. Cerebrospinal fluid and magnetic resonance spectroscopy studies have indicated alterations in glutamatergic metabolites, confirming that this system might have a role in OCD, although not all findings are consistent[82,83]. In addition, variants in glutamatergic genes (such as *SLC1A1* and *GRIN2B*) are associated with OCD[84], and meta-analysis of genome-wide association studies in OCD have implicated several glutamatergic system genes (such as *GRID2* and *DLGAP1*)[28]. A different member of the DLGAP family, DLGAP3 (or SAPAP3), is expressed in the striatum and has a key role in a mouse model of OCD, whereby mice with deletion of SAPAP3 have defects in corticostriatal synapses and compulsive grooming behaviour that is decreased by a selective SRI (SSRI)[85]. Although no glutamatergic agent has been registered for the treatment of OCD yet, several have now been studied in randomized controlled trials with promising results[86].

Other neurotransmitters and neuropeptides have been implicated in OCD[76]. The involvement of inflammatory and immune pathways in common mental disorders is increasingly apparent, although findings in OCD remain preliminary[83,87,88]. Molecular studies could ultimately also allow delineation of pathways from genetic and environmental risk factors, through to alterations in brain imaging and other possible endophenotypes, and to different stages and subtypes of OCD[89].

Diagnosis, screening and prevention

Diagnostic criteria

Both DSM-5 and ICD-11 diagnostic criteria for OCD emphasize that OCD is characterized by the presence of obsessions and/or compulsions[8,25]. In addition, the diagnostic criteria for OCD include a clinical significance criterion and a diagnostic hierarchy criterion (BOX 2). The clinical criterion states that a diagnosis of OCD requires obsessions and compulsions that are associated with clinically significant distress or functional impairment, which is important given that intrusive thoughts and repetitive behaviours are common, and that rituals are a normal part of development. The diagnostic hierarchy criterion states that the obsessions and compulsions are neither a manifestation of another mental disorder, nor are

they attributable to the physiological effects of a substance (such as a drug of abuse or a medication) or another medical condition. As previously mentioned, obsessions and compulsions in patients with OCD fall into a small number of symptom dimensions (FIG. 2). Within a particular individual, obsessions and compulsions tend to be stable, with any changes occurring within symptom dimensions[90]. Studies evaluating sex differences in symptom dimensions have not reported consistent differences[91,92].

A range of specifiers and subtypes of OCD have been proposed[25]. The DSM and ICD chapters on OCRDs include specifiers for some of these conditions (BOX 2), such as insight specifiers, which refer to the degree of insight displayed by patients. Three insight specifiers are included in the DSM-5: with good or fair insight, with poor insight, and with absent insight or delusional beliefs. Individuals with OCD and absent insight or delusional beliefs are convinced that their OCD beliefs are true; it is important that this subtype of OCD is recognized and appropriately diagnosed and treated, rather than erroneously diagnosed as a psychotic disorder and inappropriately treated. In addition, the DSM-5 includes a tic specifier that denotes individuals with a current or past tic disorder; this specifier reflects the growing evidence that patients with OCD with or without tics differ in key aspects of phenomenology and psychobiology, and that the evaluation and management of these patients should be tailored accordingly[25]. In addition, this specifier is relevant for appreciating the close relationship between OCD and Tourette syndrome. Males are more likely to have early-onset OCD (that starts before puberty), as well as comorbid tics[91,92]. Other subtypes of OCD, including early-onset OCD and paediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS; BOX 1) have also been investigated by researchers[25].

Differential diagnosis

OCD should be differentiated from normal health, as well as from a number of other psychiatric conditions. In general, this is typically carried out by a general psychiatric assessment. Intrusive thoughts and repetitive behaviours are common in the general population (such as thoughts of harming oneself or others and double-checking locks), but a diagnosis of OCD should be made only if these thoughts and behaviours are time-consuming (such as taking up more than 1 hour a day) and cause substantial distress or functional impairment. Recurrent thoughts and rituals also occur in a range of OCRDs (such as body dysmorphic disorder, hoarding disorder, trichotillomania and excoriation disorder), somatic symptom disorders (for example, illness anxiety disorder) and eating disorders (such as anorexia nervosa), but in all of these conditions the foci of apprehension and the form of repetitive behaviours are distinct from OCD.

Worries and ruminations that are characteristic of generalized anxiety disorder and depression are typically about real-life concerns and tend to be less irrational and ego-dystonic than in OCD. Compulsions are also not typically seen under these conditions. Substance-related and addictive disorders, as well as the paraphilic disorders, disruptive, impulsive-control and conduct disorders, often have an ego-syntonic, gratifying component, particularly in the short term. Patients with OCD and poor or absent insight have beliefs that are OCD-related, without the additional features of the schizophrenia spectrum and other

psychotic disorders, such as thought disorder and hallucinations. Obsessions and compulsions can be difficult to distinguish from the restricted, repetitive, and inflexible activities and interests that are typical of autism spectrum disorders; however, patients with OCD generally do not present with difficulties in social communication or reciprocal social interactions that are typical of autism spectrum disorders.

Assessment

A comprehensive assessment is a first critical step in the diagnosis and management of OCD. The goals of this assessment include making an accurate diagnosis, gaining information on presenting obsessive–compulsive symptoms, determining symptom severity, and assisting with selection of relevant treatment targets. The core of this assessment is taking a detailed psychiatric history and examining the mental status. In addition, a number of well-studied assessment measures with good psychometric properties can be useful for assisting with the diagnosis of OCD, for the identification of symptoms, the measurement of symptom severity, and monitoring of treatment response[93].

Structured diagnostic interviews for diagnosing OCD include the Structured Clinical Interview for DSM-5 (SCID-5 Clinician or Research version) for adults and the Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5), which includes both an adult and a child or parent version. The Mini International Neuropsychiatric Interview (MINI version 7.0) is a shorter instrument, has also been revised in accordance with DSM-5, and is available for use in adults and children or adolescents. A Structured Clinical Interview for OCRDs could be useful in assessing common comorbidities[94].

A number of standardized symptom severity measures are available; of these, the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) and the Children's Y-BOC (CY-BOCS) are widely used, comprise a symptom checklist and a severity scale, and are available in self-report format[95]. The Dimensional Yale-Brown Obsessive–Compulsive Scale (DY-BOCS) allows more detailed assessment of OCD symptom dimensions and their severity[96]. By contrast, the shorter Florida Obsessive–Compulsive Inventory (FOCI) comprises a symptom checklist of common obsessive–compulsive symptoms and only five items to assess symptom severity and impairment[97]. The FOCI has been adapted to address other OCRDs, and is included as a dimensional rating scale in the DSM-5. A range of other measures might be useful for the assessment and monitoring of OCD, including scales that are focused on sensory phenomena, insight, or measures of family accommodation to obsessive–compulsive symptoms (that is, family behaviour that facilitates rather than challenges OCD symptoms — for example, providing reassurance in response to obsessive doubts, assisting the patient with avoidance behaviours, and participating in rituals)[93,98–100].

Prevention

Despite growing attention to the prevention of, and early intervention in, mental disorders, relatively little attention has been paid to such issues in OCD[101]. Targets for OCD primary prevention could potentially include psychoeducation and the reduction of family accommodation in high-risk individuals with subclinical or no symptoms, whereas secondary prevention could include the early identification and management of clinical

OCD[102]. Further work is needed to emphasize the different stages of OCD (ranging from at-risk or prodromal illness to chronic or refractory illness) and to gather data on preventive and early intervention strategies[102].

Management

Treatment of OCD comprises several components, starting with building a therapeutic alliance with the patient and psychoeducation, followed by psychological and/or pharmacological approaches, and, for patients with treatment-resistant OCD, neuromodulation and neurosurgery (FIG. 6). Alternative interventions have also attracted interest but require more evidence[103]. Although general principles of management exist, they need to be individually tailored. Thus, for example, some comorbid conditions (such as depression) respond to first-line OCD pharmacotherapies, whereas others (such as bipolar disorder) might require additional interventions[104]. Although similar pharmacotherapies and psycho therapies are used throughout the lifespan[105–107], key modifications are needed when treating children and adolescents; however, a comprehensive discussion is beyond the scope of this Primer[107].

Psychoeducation

Patients and their family members can experience considerable relief when they are told by a professional that they have a relatively common disorder which is increasingly well understood, and that the available treatments bring at least partial symptom reduction and improved QOL. Factors such as stigma, prejudice, and the role of the family and significant others in aggravating or maintaining OCD (such as family accommodation) should be addressed, so that all involved can contribute to treatment success. For this reason, treatment should include the family whenever possible (and particularly in the case of children or adolescents with OCD).

Substantial delays can occur before patients with OCD seek treatment. Possible reasons for this delay include a lack of knowledge about the disorder, embarrassment about their symptoms, or anxiety about exposure to feared stimuli. Such challenges to engaging with and adhering to treatment can be aggravated in patients with poor insight, and it has been suggested that motivational interviewing techniques can be helpful in such individuals[108,109]. These techniques focus on empathizing with the patient's experience, discussing the benefits of symptoms as well as their costs, and exploring the benefits and costs of symptom reduction. Building a therapeutic alliance is key, as is working with consumer advocacy organizations to decrease stigmatization and to improve health literacy. Fortunately, several such organizations are now available, such as the International OCD Foundation, OCD Action, the South African Depression and Anxiety Group and Astoc St.

Psychotherapy

Cognitive–behavioural therapy (CBT) is the most evidence-based form of psychotherapy for OCD (FIG. 6). Indeed, meta-analyses of randomized controlled trials have consistently demonstrated that CBT significantly improves OCD symptoms in both adults and children[110,111]. CBT comprises two components: cognitive reappraisal and behavioural

intervention. The latter, specifically ERP, is the psychological treatment of choice for OCD. ERP involves gradual and prolonged exposure to fear-provoking stimuli combined with instructions to abstain from the compulsive behaviour. The integration of ERP with cognitive components, such as the discussion of feared consequences and dysfunctional beliefs, can make ERP less aversive and enhance its effectiveness[112], particularly for patients with poor insight and for those who are less tolerant to exposure[113].

Individual and group CBT (that is, ERP with cognitive reappraisal), delivered in-person or by internet-based protocols, are effective for the treatment of OCD[114,115]. The most robust predictor of good short-term and long-term outcome with CBT is patient adherence to between-session homework, such as carrying out ERP exercises in the home environment[116]. CBT can be used as the initial treatment for OCD, particularly if this is the patient's preferred treatment option, if there is access to trained clinicians, and in the absence of comorbid conditions that might require pharmacotherapy[113]. Meta-analyses of randomized controlled trials have indicated that CBT has larger effect sizes than pharmacological therapy for the treatment of OCD. Indeed, one recent review, for example, indicated a number needed to treat of 3 for CBT and 5 for SSRIs as a measure of treatment efficacy[113]. However, such findings do not fully take into account the presence of comorbidities (which can lead to the exclusion of patients with more-severe OCD from CBT trials), the baseline severity of OCD (such as the presence of poor insight, poor functioning or personality traits related to the ability to change), the placebo effect observed in pharmacotherapy trials (which is likely greater than the effect seen in the control arm of CBT studies), and the fact that many CBT trials have included patients who are taking stable doses of SSRIs[113,117,118]. Protocols of intensive CBT (multiple sessions over a few days, often in an inpatient setting) for OCD have been tested not only for severe, treatment-resistant patients, but also as a first-line treatment[119]. Although the number of such trials is still small, the initial findings of intensive approaches suggest that further work in this area might be useful.

Pharmacotherapy

Pharmacotherapy might also be used to initiate treatment of OCD. SSRIs are the first-line pharmacological treatment for OCD based on their evidence of efficacy, tolerability, safety and absence of abuse potential[120]. As a rule, higher doses of SSRIs are used for OCD than for other anxiety disorders or major depression; higher doses of SSRIs are associated with greater treatment efficacy, but also with higher rates of dropout owing to adverse effects (such as initial gastrointestinal symptoms and sexual dysfunction)[121]. Thus, a careful assessment of SSRI adverse effects is crucial when establishing the best dose for each patient. The effect sizes of SSRIs were similar in systematic reviews[120,122]; however, their adverse effects differ and should be taken into account in the choice of a specific SSRI. Other characteristics to consider when choosing between different SSRIs include past treatment response, potential adverse events and drug interactions, presence of comorbid medical conditions, and cost and availability of medication[123].

Clomipramine, a non-selective SRI[124], was the first agent to show efficacy in OCD[125]. Meta-analyses have suggested that clomipramine is more efficacious than SSRIs[113].

However, there are reasons to be sceptical of this finding; for example, clomipramine trials were conducted earlier on fewer treatment-resistant patients with OCD, and head-to-head trials directly comparing clomipramine with SSRIs indicate equivalent efficacy[126–128]. SSRIs have a higher safety and tolerability profile compared with clomipramine, which has advantages for long-term treatment, supporting their use as first-line agents.

OCD treatment guidelines indicate that 8–12 weeks is the optimal duration of an SSRI trial to determine efficacy[120,123,129]. However, in two recent meta-analyses, a significant improvement in OCD symptoms was observed within the first 2 weeks of treatment with SSRIs, with the greatest incremental gains occurring early in the course of treatment[130,131]. Similarly, an open-label trial of fluoxetine in treatment-naive patients indicated that early reduction (such as by 4 weeks) of OCD severity was the best predictor of treatment response at 12 weeks[132]. The recommended maintenance duration of pharmacotherapy is a minimum of 12–24 months after achieving remission[133], but longer treatment might be necessary in many patients owing to the risk of relapse after discontinuing medication[134].

Treatment resistance

Approximately half of patients with OCD who are treated with a first-line treatment fail to fully respond[135,136]. This proportion can be even higher in real-world or pragmatic clinical trials[137]. Several clinical predictors that are associated with a poor response have been identified (BOX 3). Augmentation options for patients with treatment-resistant OCD are outlined in Supplementary Table 1.

Insufficient response after CBT or SSRI monotherapy can also be addressed by combinatorial therapy[46]. In one trial, effect sizes were larger with the augmentation of SSRIs with CBT, compared with augmentation with risperidone (an antipsychotic)[138]. Nevertheless, the combination of SSRIs with CBT is not always feasible, either because CBT is not available[139] or owing to difficulty in tolerating exposure[140]. Valid pharmacological strategies include switching to a different SSRI, using a higher dose of a SSRI than the maximum recommended dose, or a trial of a serotonin–noradrenaline reuptake inhibitor[141–148].

Evidence-based pharmacological SSRI augmentation strategies include the use of antipsychotics, clomipramine (a tricyclic antidepressant), and glutamatergic agents[149–153]. In the only double-blind, randomized controlled trial that compared three pharmacological strategies in patients with SSRI-resistant OCD, fluoxetine plus placebo and fluoxetine plus clomipramine significantly reduced the severity of OCD and were both significantly superior to fluoxetine plus quetiapine (an antipsychotic)[152]. Of note, the effect of time spent on fluoxetine monotherapy (6 months) was the most important factor associated with the response at the endpoint. The greatest concern associated with clomipramine and SSRI combinatorial therapy is the increment in the blood levels of both drugs, which can increase the risk of severe and potentially life-threatening events such as seizures, heart arrhythmia and serotonergic syndrome[154].

The augmentation of SSRIs with antipsychotics is one of the most commonly used pharmacological strategies for patients with SSRI-resistant OCD[149,150]. Indeed, one meta-

analysis provides evidence of efficacy for both risperidone and aripiprazole augmentation[150]. Although other antipsychotics might also be useful, additional studies are needed. However, SSRIs have a moderate effect size in OCD and subsequent antipsychotic augmentation has a smaller effect size, with only one-third of patients with SSRI-resistant OCD showing a clinically meaningful response[149]. Thus, ongoing monitoring of the risk–benefit ratio is needed in patients receiving antipsychotic augmentation of SSRIs, with particular attention on adverse events such as weight gain and metabolic dysregulation[155].

More recently, glutamatergic medications, such as N-acetylcysteine, memantine, lamotrigine, topiramate, riluzole and ketamine, have been evaluated as augmentation agents in patients with treatment-resistant OCD and have demonstrated some evidence of efficacy[156–158]. Of these, N-acetylcysteine augmentation has the largest evidence-base — three out of five randomized controlled trials demonstrated its superiority to placebo in reducing OCD symptoms[158–162]. Memantine augmentation can also be considered in clinical practice, as several trials have demonstrated its efficacy in SSRI augmentation for patients with treatment-resistant OCD[163].

Neuromodulation and neurosurgery

Neuromodulation for OCD includes both noninvasive and invasive approaches, including transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS) (FIG. 7). Ablative procedures have also been used in OCD. Although neuromodulation for OCD has primarily been confined to a research context, the US FDA has approved deep rTMS for the treatment of OCD, which will likely give impetus to greater clinical use.

tDCS involves the application of a weak current to the scalp, with only a fraction of the current entering the brain[164]. Most studies of tDCS in OCD are open-label or case reports, using a range of electrode montages, targeting areas including the supplementary motor cortex and the dorsolateral prefrontal cortex. Initial results from these studies show promise and provide impetus for further research[164,165].

rTMS is a noninvasive technique that modulates neuronal activity via electric currents that are induced by a magnetic coil positioned over the head[166]. rTMS has growing evidence of efficacy for OCD, with targets including the supplementary motor cortex and the dorsolateral prefrontal cortex[165,167,168]. Notably, in the pivotal trial of deep rTMS targeting the medial prefrontal cortex and anterior cingulate cortex, tailored symptom provocation was used in each session to personalize the treatment.

DBS involves the neurosurgical implantation of an electrode that can activate neighbouring neural circuitry[169]. This approach is reserved for very intractable cases (less than 1% of treatment-seeking individuals)[170] (BOX 4). Most studies of DBS target striatal areas, including the anterior limb of the internal capsule, the ventral capsule and ventral striatum, the nucleus accumbens or the ventral caudate nucleus, the subthalamic nucleus, and the inferior thalamic peduncle[171]. Approximately 30–50% of patients with severe refractory OCD respond to these different treatments[171,172]. Preliminary work points also to the

potential of nonstriatal targets, such as the superolateral branch of the medial forebrain bundle[173].

Ablative neurosurgery for OCD has targeted several different brain structures, such as the internal capsule, anterior cingulate cortex and subcaudate white matter, with techniques respectively termed capsulotomy, anterior cingulotomy, and subcaudate tractotomy (limbic leucotomy is a combination of the two last procedures). Ablative methods encompass radiofrequency and radiosurgical ablation, as well as the experimental technique of magnetic resonance-guided focused ultrasonography[174–176]. Approximately 30–60% of patients with intractable OCD can achieve a significant reduction in OCD symptoms after surgery. However, only one method, gamma ventral capsulotomy, has been studied in a double-blind, sham-controlled randomized trial[177]. Using the criterion of response (a 35% reduction in baseline Y-BOCS score plus a Clinical Global Impression change score of 1 or 2), the primary outcome measure did not reach statistical significance 12 months later, although the Y-BOCS score reduction over that same follow-up period was significantly higher in the active treatment group. At the end of the follow-up period (54 months), 7 of 12 (58%) patients who underwent radiosurgery were responders.

Alternative treatments

A range of alternative treatments have been suggested for OCD[103]. These include yogic meditation techniques[178], mindfulness-based CBT[179,180], physical exercise[181,182] and acupuncture[183]. However, further data are needed before these treatments can be routinely recommended as evidence-based interventions.

Quality of life

OCD is associated with considerable comorbidity and morbidity, in addition to significantly reduced QOL, in both adults and children[184–188]. QOL refers to an individual's subjective perception of well-being, which is affected by the person's psychological status, physical health, social relationships, role (such as work) functioning as well as sense of life satisfaction. In patients with OCD, QOL is significantly decreased in all domains (such as work, family, and social activities)[184–188] and, furthermore, the relatives and caregivers of individuals with OCD also have lower QOL than healthy controls[189,190]. Comparisons of QOL in OCD and major depression are inconsistent, but QOL in OCD has been reported to be similar to that in patients with schizophrenia[184–187].

Several demographic factors including age, gender, marital status, employment status, socioeconomic status, education attainment and lack of social support have been associated with QOL in OCD, although findings are somewhat inconsistent[184–187]. The severity of illness, presence of comorbid depression, and certain symptom dimensions (such as hoarding) have been more consistently associated with decreased QOL and increased functional impairment[184–187]. A number of studies have indicated that depressive symptoms mediate the relationship between OCD and impaired QOL, emphasizing the need to treat both OCD and depression when they are comorbid.

Treatment with efficacious pharmacotherapy and psychotherapy has been demonstrated to improve QOL in patients with OCD[184–188]. Indeed, a correlation between improvement in symptoms and improvement in QOL has been demonstrated in most studies[184–188]. In two large trials of SSRIs, QOL was higher in treatment responders and in those who did not relapse, suggesting a relationship between symptomatic and functional improvement[191]. In addition, some evidence suggests an ongoing improvement in QOL with continued active treatment[192]. As in the case of depression, there has been increased awareness of the potential value of aiming not only for treatment response in OCD, but also for symptom remission. Certainly QOL is a useful outcome measure in randomized controlled trials of OCD.

A major limitation of studies on QOL in OCD is the lack of an OCD-specific measure of QOL. One study used a 69-item OCD-specific QOL measure and identified four domains specific to OCD: depression and OCD; restrictions in activities due to symptoms or avoidance; difficulties with partner and/or family due to OCD symptoms or avoidance; and self-concept or coping with own illness[193]. Systematically examining the relationship of symptom dimensions, comorbid conditions, and family measures (such as family accommodation) with QOL in large samples is still required. Furthermore, the data on QOL in OCD are mostly cross-sectional; studies examining the relationship between QOL and longitudinal course and outcome are needed.

Outlook

Although knowledge about OCD has greatly advanced, several obstacles remain. With regards to mechanism, most imaging studies have been single-site studies with relatively small sample sizes, and replication of findings has been variable. This issue could be due to heterogeneity in the OCD samples selected, differences in imaging methods, or both factors. Moreover, although brain abnormalities are presumed to lead to dysfunction in specific neural processes that then lead to OCD symptoms, strong links between brain abnormalities, dysfunction in these neural processes, and specific OCD clinical profiles still need to be made. Ultimately, most imaging studies are correlational; they cannot identify whether the observed brain abnormalities cause OCD symptoms or are the result of these symptoms[57]. This issue has spurred the development of experimental animal systems to examine causality[44,45]; however, the relevance of these animal systems to human OCD is debated (for example, whether repetitive grooming in a mouse is a valid phenotype for human OCD). Finally, even if brain abnormalities cause OCD symptoms, this does not address what caused these abnormalities. To understand why an individual developed OCD, the field must develop a far greater understanding of how genetic risk and resilience, environmental factors, and developmental trajectory interact in humans.

With regards to diagnosis, OCD is often missed in routine clinical practice (for example, because clinicians do not ask or patients do not tell their clinician about their symptoms) or misdiagnosed and mistreated (such as being diagnosed as a psychotic disorder and treated with antipsychotic monotherapy). Improved education of the public and of front-line clinicians is needed to address this problem. Moreover, the diagnosis of OCD relies on self-report, and developing objective tests that confirm self-report of symptoms would advance

the field; for example, for brain dysfunction using imaging or neurocognitive tasks, or for behaviours using passive sensing technology. These tests may most profitably focus not on the categorical diagnosis of OCD, but on component behaviours such as intrusive thoughts, repetitive behaviours, and anxiety.

Finally, although the first-line treatments for OCD help up to 50% of patients achieve minimal symptoms after acute treatment, access to evidence-based care varies around the world, particularly for CBT. How to best harness technology to increase access to CBT (such as via the internet or smartphone applications[194]) deserves further study. At the same time, because patient adherence (to either SRIs or CBT) strongly predicts good outcome and relapse can occur once treatment stops, methods for increasing patient adherence and decreasing relapse also deserve further study. How SRIs and CBT precisely work on the brain also requires more research[195]. The answers could help to explain why these treatments work for only some patients.

Ultimately, better (and preferably faster) treatments are needed to help more individuals with OCD achieve wellness. To meet this challenge, researchers are examining new classes of medications (such as glutamate modulators and cannabinoids), different modes of neuromodulation (such as rTMS, tDCS and DBS), new forms of psychotherapy (such as acceptance and commitment therapy), and new ways for using technology to both increase access to treatments like CBT that are already known to work and to objectively monitor treatment outcomes[194] (TABLE 1). Ideally, such treatments would capitalize on emerging knowledge about genetic and environmental risk factors as well as the neural processes underlying obsessions and compulsions, enabling the treatment to be tailored to an individual's disease process[196]. The ultimate goal will be to intervene as early and as precisely as possible to alleviate individual suffering and reduce the public health burden of this disabling illness.

One approach to address some of the issues raised above is to identify reproducible brain signatures of OCD behaviours. These brain signatures will likely reveal disease dimensions that cut across traditional diagnostic categories, potentially changing how we conceptualize mental illnesses like OCD and advancing nosology. Longitudinal studies can then chart the development of these brain signatures, potentially revealing the best time to intervene to disrupt the disease process. These brain signatures will also provide new treatment targets and could pave the way to precision psychiatry, whereby individual brain signatures can help guide specific treatment choices. The NIH have funded such a study (RO1 MH113250). A collaboration between five expert OCD sites in the United States, Brazil, India, the Netherlands and South Africa will be the first international multimodal imaging and neurocognitive study in OCD to use harmonized clinical, neurocognitive and imaging methods. The short-term goal is to identify robust brain signatures of OCD cognitive and clinical profiles, leveraging these five sites to recruit a large sample of unmedicated patients and to test the reproducibility of the signatures across countries and cultures. The long-term goal is to accelerate discovery and help transform how OCD is conceptualized, diagnosed and treated around the world. International collaborations have already played an important role in advancing our knowledge of OCD and improving clinical outcomes, and further work

integrating global mental health and translational neuroscience perspectives holds great promise for the future[197,198].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1 |

Neurological insults and OCD

Certain neurological lesions can cause obsessive–compulsive disorder (OCD). For example, after the influenza epidemic in the first part of the 20th century, obsessive–compulsive symptoms were noted in patients with encephalitis lethargica and basal ganglia lesions[199]. In addition, subsequent research has identified obsessive–compulsive symptoms in patients with neurological conditions that affect the basal ganglia, including Sydenham chorea and neuroacanthocytosis[200]. OCD can also be a sequela of neurological lesions that affect other areas, such as the frontal lobe, suggesting that frontostriatal circuitry could play a role in OCD pathogenesis[201].

Some of the most interesting literature at the intersection of OCD and neurology is that describing obsessive–compulsive symptoms that are precipitated by streptococcal infection — so-called paediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS)[202]. The recognition of PANDAS was given impetus by early work that demonstrated the presence of obsessive–compulsive symptoms in Sydenham chorea (which is caused by childhood streptococcal infection)[203] and, later, in individuals with rheumatic fever[204]. Advances have been made in formulating diagnostic criteria for PANDAS, in investigating the relevant autoimmune mechanisms, and in developing specific treatments for this disorder[205,206]. However, research has shifted from PANDAS to a broader disorder — paediatric acute-onset neuropsychiatric syndrome — which is characterized by the sudden onset of obsessive–compulsive symptoms that can occur in response to a range of infections and other insults[205,206].

Box 2 |

DSM-5 diagnostic criteria for OCD[207]

The presence of obsessions, compulsions, or both:

- Obsessions are defined by the following:
  - Recurrent and persistent thoughts, urges, or impulses that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
  - The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (that is, by performing a compulsion).
- Compulsions are defined by the following:
  - Repetitive behaviours (for example, hand washing, ordering or checking) or mental acts (for example, praying, counting or repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
  - The behaviours or mental acts[a] are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

The obsessions or compulsions are time-consuming (for example take >1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The obsessive–compulsive symptoms are not attributable to the physiological effects of a substance (for example, a drug of abuse or a medication) or another medical condition.

The disturbance is not better explained by the symptoms of another mental disorder (for example: excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania (hair-pulling disorder); skin picking, as in excoriation (skin-picking) disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behaviour, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behaviour, as in autism spectrum disorder).

Specify if:

- With good or fair insight: the individual recognizes that OCD beliefs are definitely or probably not true or that they may or may not be true
- With poor insight: the individual thinks OCD beliefs are probably true
- With absent insight/delusional beliefs: the individual is completely convinced that OCD beliefs are true Specify if:
- Tic-related: the individual has a current or past history of a tic disorder

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OCD, obsessive–compulsive disorder. [a]Young children may not be able to articulate the aims of these behaviours or mental acts.

Box 3 |

Factors associated with poor treatment outcome in OCD

Clinical characteristics

- More severe obsessive–compulsive disorder (OCD)
- Greater functional impairment
- Sexual, religious and hoarding symptoms
- Poor insight
- Higher number of comorbidities
- Comorbid major depression, agoraphobia or social anxiety disorder
- Lower willingness to fully experience unpleasant thoughts
- Greater resistance to change
- Lower adherence to treatment

Sociodemographic characteristics

- Male sex
- Single relationship status
- Lower socioeconomic status
- Lower educational level

Other characteristics

- Family history of OCD
- Poor therapeutic alliance
- Greater family accommodation
- Absence of early response to selective serotonin reuptake inhibitor treatment

Box 4 |

Selection criteria for neurosurgery for intractable OCD[177]

Inclusion criteria

- Obsessive–compulsive disorder (OCD) must be the main diagnosis
- Yale-Brown Obsessive–Compulsive Scale score ≥28 (or ≥14 if only obsessions or only compulsions are present)
- 5 years of severe OCD symptoms despite adequate treatment trials
- Independent confirmation of refractoriness to treatment
  - 3 adequate[a] trials with a serotonin reuptake inhibitor (at least one with clomipramine)
  - 2 adequate augmentation strategies (such as antipsychotics or clomipramine)
  - 20 hours of OCD-specific cognitive–behaviour therapy (such as exposure and response prevention)[b]
- Age 18–75 years[c]
- Ability to provide informed consent
- Appropriate expectations of the outcomes of surgery

Exclusion criteria

- Comorbid mental or substance use disorder that may impair treatment (for example, severe personality disorder or psychosis)
- Clinically meaningful condition affecting brain function or structure
- Intellectual disability
- Past history of head injury with post-traumatic amnesia
- Recent suicide attempt or active suicidal ideation

[a]Minimum duration of 8 weeks at the maximum recommended or tolerated dose. [b]Participation for shorter times may be permitted if nonadherence is due to symptom severity rather than to noncompliance. [c]Increasing age is a relative contraindication.

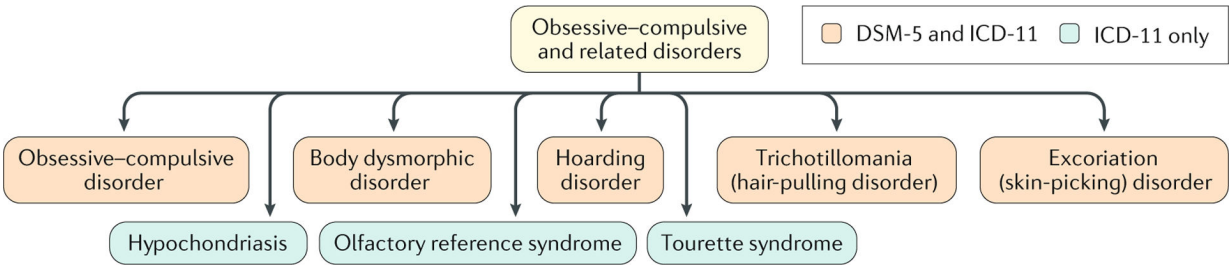

Fig. 1 |. Obsessive–compulsive and related disorders.

The obsessive–compulsive and related disorders (OCRDs) chapter in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) includes obsessive–compulsive disorder (OCD; previously classified as an anxiety disorder), body dysmorphic disorder (previously classified as a somatoform disorder) and trichotillomania (previously classified as an impulse control disorder), as well as hoarding disorder and excoriation (skin-picking) disorder (both of which are new to the classification system). In the International Classification of Diseases, 11th Revision (ICD-11), this chapter also includes Tourette syndrome (also classified as a neurodevelopmental disorder), hypochondriasis (also classified as an anxiety disorder) and olfactory reference syndrome (which is new to the classification system). Similar to OCD, the OCRDs are often prevalent but under-recognized conditions that are characterized by repetitive and unwanted thoughts or behaviours. Some OCRDs include preoccupations and compulsive behaviours (such as body dysmorphic disorder), but others have predominantly motoric or behavioural symptoms (such as trichotillomania). Sensory phenomena, including premonitory urges and ‘just right’ perceptions (where a patient continues their compulsions until there is a feeling that things are ‘just right’ and they can stop), can be present in some OCRDs, including OCD and Tourette syndrome[208].

Dimension	Obsessions	Compulsions
Contamination symptoms	Concerns about dirt and germs, among others	Washing, showering or cleaning
Harm-related symptoms	Concerns about harm	Checking
Unacceptability symptoms	Intrusive aggressive, sexual or religious thoughts	Mental rituals or praying
Symmetry symptoms	Symmetry concerns	Ordering, straightening, repeating or counting
Hoarding symptoms	Hoarding concerns	Hoarding behaviours

Fig. 2 |. OCD symptom dimensions.

Studies using a factor-analytic approach have consistently supported a four-f actor or five-factor model of obsessive–compulsive disorder (OCD) symptoms, including a ‘contamination’ dimension (contamination or cleanliness obsessions and cleaning compulsions), a ‘harmful thoughts’ dimension (thoughts of harm to self and others and checking compulsions), a ‘forbidden thoughts’ dimension (aggressive, sexual, religious obsessions with mental rituals or praying), a ‘symmetry’ factor (symmetry obsessions, and repeating, ordering and counting compulsions), and a ‘hoarding’ factor (hoarding or saving obsessions and related compulsions)[2,3]. Hoarding disorder is considered as a separate entity in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, although hoarding symptoms can also be found in patients with OCD in some cases.

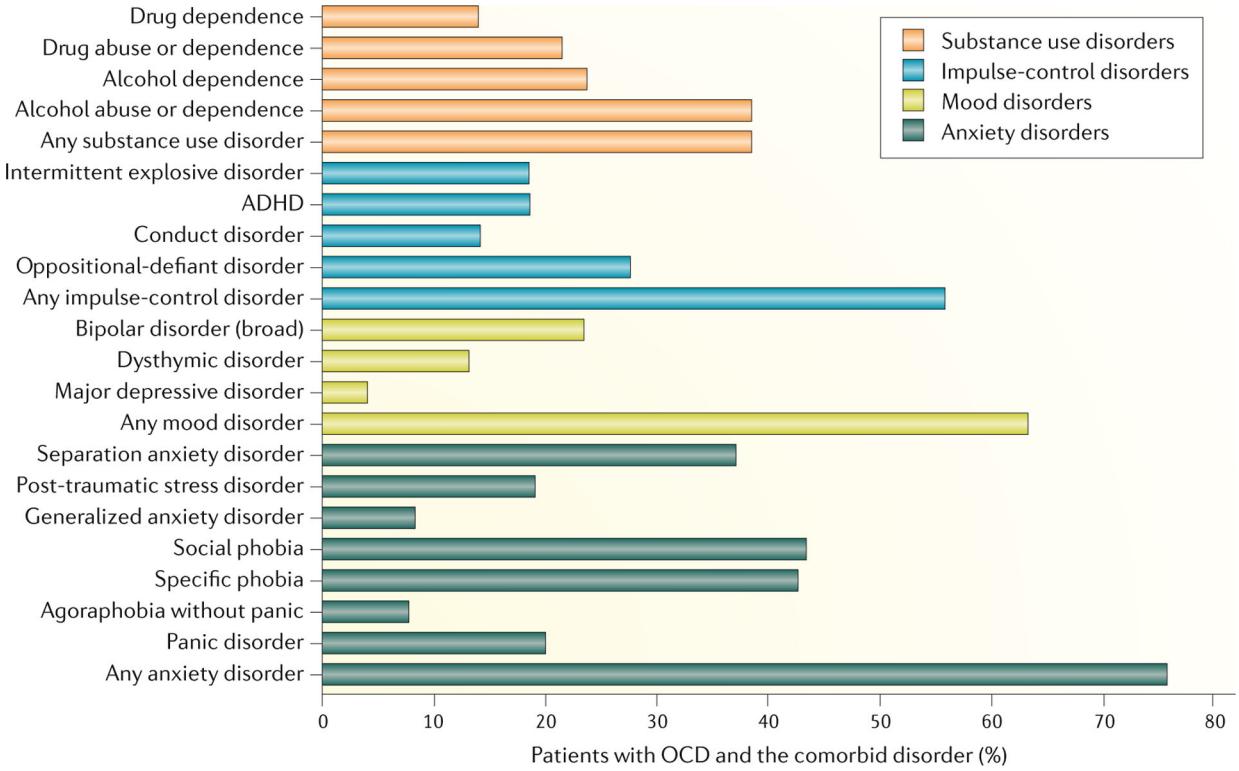

Fig. 3 |. Comorbidities of OCD.

The prevalence of comorbid mental disorders in patients with obsessive–compulsive disorder (OCD) in the National Comorbidity Survey-Replication (NCS-R). ADHD, attention-deficit/hyperactivity disorder.Data from REF.[14].

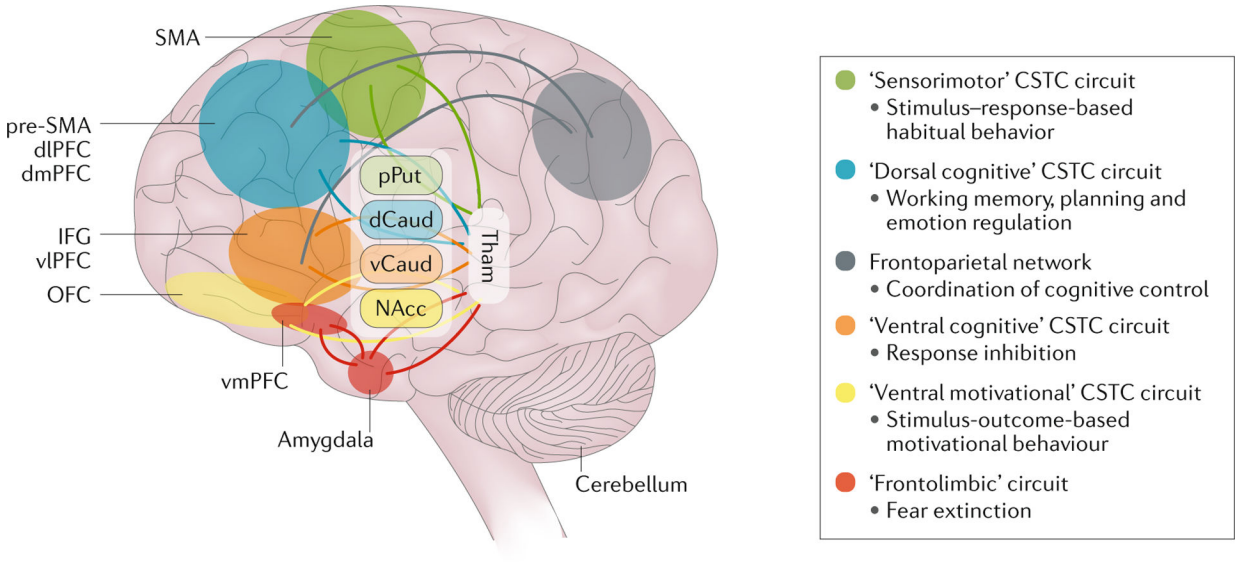

Fig. 4 |. Circuits involved in OCD.

Obsessive–compulsive disorder (OCD) is mediated by parallel, partly segregated, cortico–striato–thalamo–cortical (CSTC) circuits that are involved in sensorimotor, cognitive, affective and motivational processes. dCaud, dorsal part of caudate nucleus; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; pPut, posterior part of putamen; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Tham, Thalamus; vCaud, ventral part of caudate nucleus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Adapted with permission from REF.[48], Elsevier.

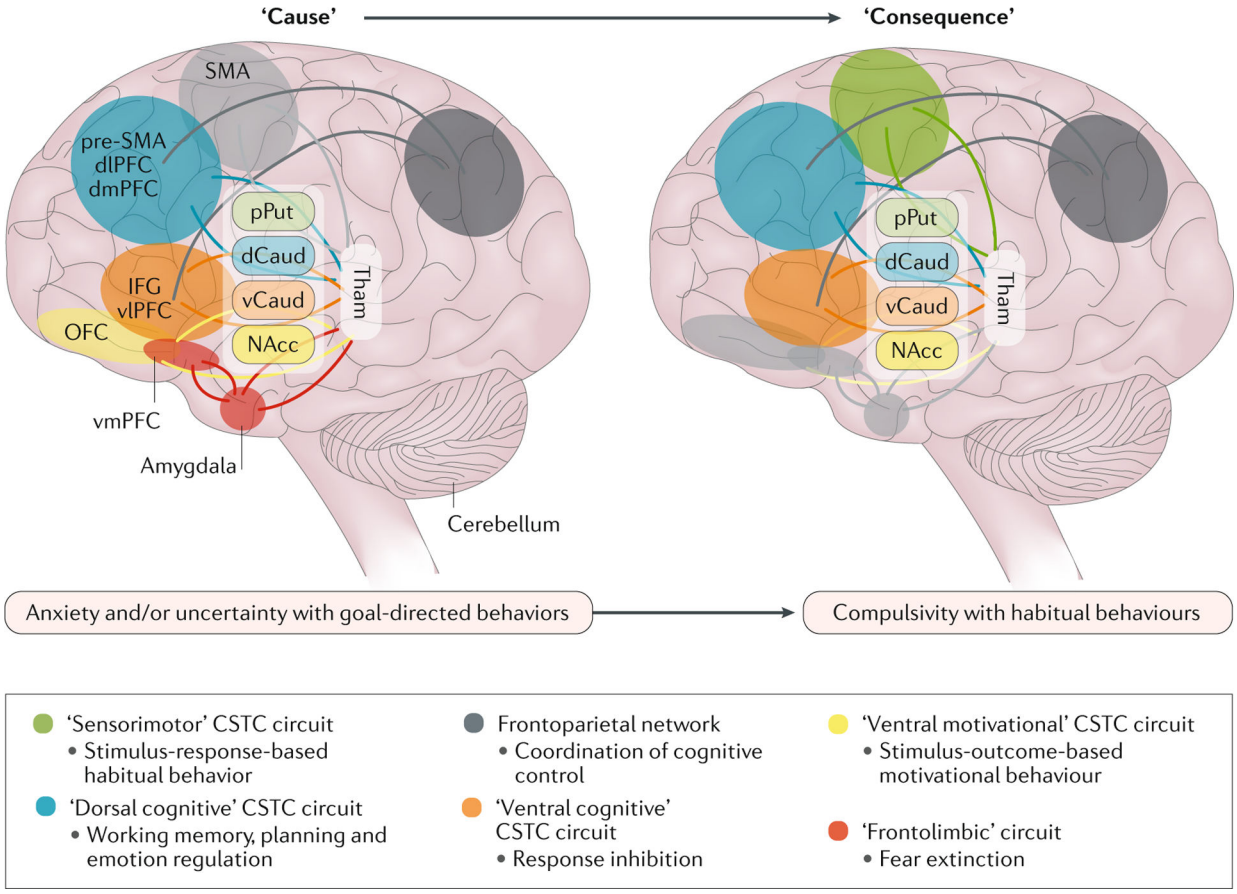

Fig. 5 |. Lifespan changes related to disease stage — brain changes as a cause and consequence of OCD.

The involvement of the circuits is hypothesized to depend on the symptom profile and the disease stage. In early phases of obsessive–compulsive disorder (OCD), alterations within the dorsal cognitive, ventral cognitive and ventral reward cortico–striato–thalamo–cortical (CSTC) circuits and the frontolimbic circuit are hypothesized to be related to symptoms involving anxiety, uncertainty, and goal-directed behaviours. In later phases of OCD, alterations within the sensorimotor, dorsal cognitive and ventral cognitive CSTC circuits are hypothesized to be related to symptoms involving habitual behaviours. dCaud, dorsal part of caudate nucleus; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; pPut, posterior part of putamen; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Tham, Thalamus; vCaud, ventral part of caudate nucleus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Adapted with permission from REF.[48], Elsevier.

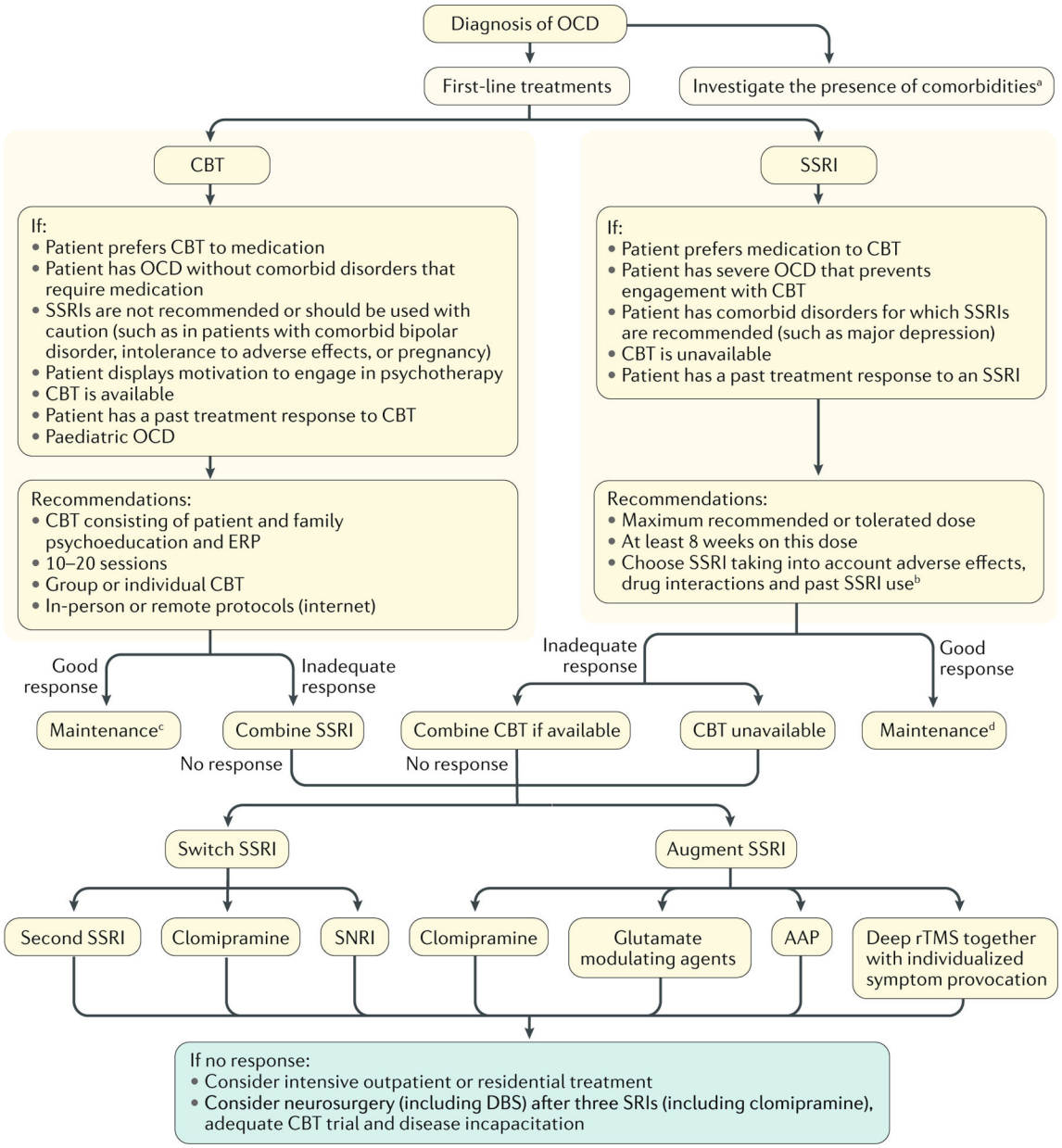

Fig. 6 |. OCD treatment algorithm.

Cognitive–behavioural therapy (CBT) or selective serotonin reuptake inhibitors (SSRIs) are the first-line treatments for obsessive–compulsive disorder (OCD). Unresponsive patients can receive augmentation with other treatment modalities. Neurosurgery is only considered in highly refractory and severe cases. AAP, atypical antipsychotics; DBS, deep brain stimulation; rTMS, repetitive transcranial magnetic stimulation; SNRI, serotonin-noradrenaline reuptake inhibitor ; SRI, serotonin reuptake inhibitor. [a]The presence of specific comorbidities may change the algorithm (for example, focus on mood stabilizers plus CBT in the presence of bipolar disorder, and the addition of antipsychotics in those with psychotic symptoms or tics). [b]Effect sizes are similar for different SSRIs. [c]Monthly booster sessions for 3 to 6 months. [d]12–24 months.

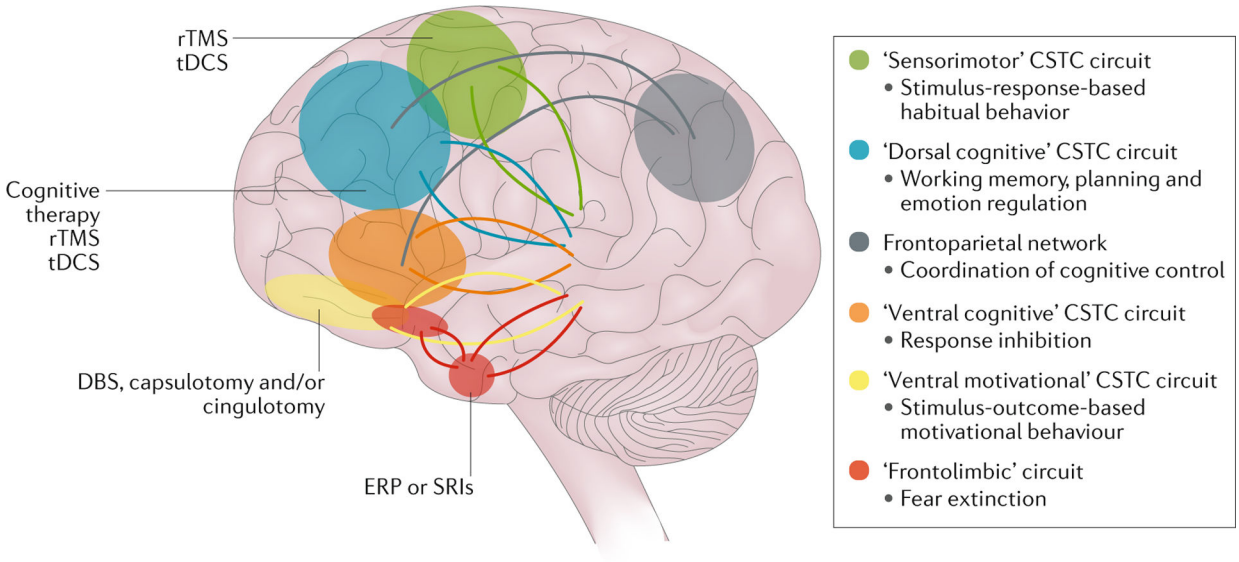

Fig. 7 |. Targets for treatment.

Different treatment modalities, including neuromodulation, neurosurgery and pharmacological therapy, might target different neurocircuits that have been implicated in obsessive–compulsive disorder. CSTC, cortico–striato–thalamo–cortical; DBS, deep brain stimulation; ERP, exposure and response prevention; rTMS, repetitive transcranial magnetic stimulation; SRI, serotonin reuptake inhibitor ; tDCS, transcranial direct current stimulation. Adapted with permission from REF.[48], Elsevier.

Table 1 |

Ongoing RCTs in OCD

Title	Design	Interventions	Population	NCT number
Psychotherapy				
An eHealth intervention for OCD in youths with autism spectrum disorder	Open-label	Internet CBT	Children and adolescents	NCT03473080
Treatment effects of family based CBT in children and adolescents with OCD	RCT	Family-based CBT versus family-based psychoeducation/ relaxation training	Children and adolescents	NCT03595098
Internet-delivered CBT for paediatricOCD	RCT	Internet-delivered CBT versus CBT	Children and adolescents	NCT03263546
Overlapping neural circuits in paediatric OCD	Open-label	ERP and when indicated medication treatment	Children and adolescents	NCT02421315
Clinical outcomes in paediatric OCD	RCT	Croup-based family CBT versus waitlist	Children and adolescents	NCT01635569
Neurocircuit mechanisms of OCD across the lifespan	RCT	CBT, stress management therapy, optional CBT for adolescents and adults; fMRI only for healthy control adolescents and adults	Adolescents and adults	NCT02437773
Quality assessment in exposure therapy	Open-label	Exposure therapy	Children, adolescents and adults	NCT03182101
BIP in Jamtland Harjedalen: increased access to CBT within regular healthcare in northern Sweden	Open-label	Internet CBT	Children and adolescents	NCT02926365
Building an outcomes assessment infrastructure to assess anxiety treatment	Open-label	CBT	Children and adolescents	NCT02305537
Metacognitive therapy for OCD	RCT	Metacognitive therapy versus ERP	Adults	NCT02867449
Internet-based versus face-to-face CBT for OCD	RCT	CBT (face-to-face) versus internet-based CBT versus internet-based CBT without therapist support	Adults	NCT02541968
Fear extinction and mechanisms of change in OCD	RCT	Exposure therapy versus waitlist	Adults	NCT02467374
Cognitive training in OCD	Open-label	n-Back (cognitive training)	Adults	NCT02818088
Inference-based cognitive therapy versus ERPforOCD	RCT	Inference-based cognitive therapy versus ERP	Adults	NCT03677947
Decision-making impairments in OCD: an integrated behavioural economics model	Open-label	Decision-making tasks	Adults	NCT03420495
Mindfulness meditation utilizing an EEG biofeedback device for the treatment for OCD	RCT	Mindfulness meditation versus waitlist	Adults	NCT03273699
Feasibility, acceptability, and preliminary efficacy of a mobile app (nOCD) for OCD	Open-label	Therapist-assisted mobile intervention	Adults	NCT03476902
Cognitive checking intervention for maladaptive beliefs about memory	RCT	CBT for maladaptive beliefs about memory versus treatment as usual	Adults	NCT03241056
Mindfulness-based cognitive therapy: efficacy and fMRI-based response predictors in a group of OCD patients	RCT	Mindfulness-based intervention versus treatment as usual	Adults	NCT03128749
Computerized training for individuals diagnosed with obsessive-compulsive and related disorders	Open-label	Computerized training	Adults	NCT03182075
The role of cognitive control in the transdiagnostic conceptualization of “Intrusive thoughts”	Open-label	Cognitive control tasks and script driven imagery	Adults	NCT03414619

Pharmacotherapy				
Efficacy of adding topiramate to current treatment in refractory OCD	RCT	Topiramate versus placebo	Adults	NCT00182520
Fear conditioned response in healthy subjects and in OCD patients pretreatment and post-treatment with sertraline	Open-label	Sertraline	Adults	NCT03068429
Pharmaco(epi)genetic study of OCD	Open-label	SSRIs and clomipramine	Adults	NCT02431845
A pilot study examining the gut microbiota in patients with OCD versus healthy controls and following 12 weeks of open-label SSRI treatment	Open-label	SSRIs	Adults	NCT02285699
BHV-4157 in adult subjects with OCD	RCT	BHV-4157 versus placebo	Adults	NCT03299166
A study of pregabalin (Lyrica) augmentation in serotonin reuptake inhibitor-refractory OCD	RCT	Pregabalin versus placebo	Adults	NCT00994786
TolcaponeinOCD	Randomized and crossover trial	Tolcapone versus placebo	Adults	NCT03348930
Efficacy of psilocybin in OCD: a double-blind, placebo-controlled study	RCT	Psilocybin versus niacin	Adults	NCT03356483
Understanding how ketamine brings about rapid improvement in OCD	RCT	Ketamine versus midazolam	Adults	NCT02624596
Probiotic treatment in adult OCD	RCT	Probiotic formula *(LactobaciUus helveticus* R0052 and *Bifidobacterium longum* R0175) versus placebo	Adults	NCT02334644
Effects of marijuana on symptoms of OCD	RCT	High-THC/low-CBD marijuana versus low-THC/high-CBD marijuana versus placebo	Adults	NCT03274440
Effect of vitamin C on SSRI-treated OCD patients	RCT	SSRI plus vitamin C versus SSRI	Adults	NCT03754647
Effects of ondansetron in obsessive-compulsive and tic disorders	RCT	Ondansetron versus placebo	Adults	NCT03239210
Psilocybin for treatment of OCD	RCT	High-dose psilocybin versus low-dose psilocybin versus lorazepam	Adults	NCT03300947
Bioequivalence study of paroxetine tablets and Paxil under fasting and fed conditions in Chinese healthy volunteers	RCT	Paroxetine hydrochloride tablet 20 mg versus Paxil 20 mg	Adults	NCT03504475
Psychotherapy and pharmacotherapy				
Efficacy of ERP and SSRIs in Chinese OCD patients	Randomized and crossover trial	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and ERP	Adolescents and adults	NCT02022709
Influence of pregnenolone on exposure therapy in OCD	RCT	Exposure therapy with pharmacological facilitation versus exposure therapy	Adults	NCT01949753
The study of mindfulness-based cognitive therapy and OCD	RCT	Mindfulness-based cognitive therapy versus psychoeducation versus SSRI	Adults	NCT03179839
Cannabinoid medication for adults with OCD	RCT	Nabilone versus nabilone plus ERP	Adults	NCT02911324
Open/aftercare treatment for participants diagnosed with OCD	Open-label	Pharmacotherapy versus psychotherapy	Adults	NCT03511534
The study of the pathogenesis and cognitive behavioural group therapy in OCD	RCT	CBT versus SSRI versus CBT plus SSRI	Adults	NCT02739061
***Psychotherapy and transcranial magnetic* stimulation**				
Neuromodulation enhanced cognitive restructuring: a proof-of-concept study	RCT	Cognitive restructuring plus rTMS (left) versus cognitive restructuring plus rTMS (right)	Adults	NCT02573246

		versus cognitive restructuring plus sham rTMS		
Neuromodulation				
tDCS for treatment-resistant OCD	RCT	Active tDCS versus sham	Adults	NCT03304600
tDCS as an add-on treatment in SSRI-resistant OCD	RCT	Active tDCS versus sham	Adults	NCT02407288
Neurocircuitryof OCD: modulation by tDCS	Open-label	tDCS	Adults	NCT02704117
TMS in OCD: mechanisms and biomarkers	RCT	Active TMS versus sham	Adults	NCT02355002
rTMS over the supplementary motor area for treatment-resistant OCD	RCT	Active rTMS versus sham	Adults	NCT03211221
rTMS in OCD	RCT	Active rTMS versus placebo rTMS	Adults	NCT02884674
Tolerability, safety and efficacy of the H AC-coil deep TMS in medication-resistant OCD subjects	Randomized and crossover trial	Low-frequency TMS versus high-frequency TMS versus sham	Adults	NCT01343732
rTMS in treatment-refractory OCD	Randomized and crossover trial	Active rTMS versus sham	Adults	NCT02450695
Study of magnetic brain stimulation in treatment of OCD	RCT	Active TMS versus sham	Adults	NCT02018185
rTMS treatment for OCD	RCT	Active TMS versus sham	Adults	NCT03393078
Theta burst stimulation for compulsive behaviour noninvasive brain stimulation study	RCT	Continuous theta burst stimulation (cTBS) pattern TMS and habit override practice versus intermittent theta burst stimulation (iTBS) pattern TMS and habit override practice	Adults	NCT03265015
Magnetic seizure therapy for treatment-resistant depression, schizophrenia and OCD	Open-label	Magnetic seizure therapy	Adults	NCT01596608
NeurofeedbackforOCD	RCT	Neurofeedback versus control feedback	Adults	NCT02206945
Neurosurgery				
Reclaim DBS therapy for OCD	Open-label	Reclaim DBS therapy	Adults	NCT02773082
DBS for OCD: improving targeting precision	RCT	Microelectrode-assisted technique versus standard technique	Adults	NCT02377375
DBS of the bilateral habenula for treatment-refractory OCD	Open-label	Bilateral surgical implantation of DBS system to habenula	Adults	NCT03463590
Novel DBS in ventral capsule and stratum for refractory OCD	Randomized and crossover trial	Active stimulation: stimulator on followed by off versus sham stimulation: stimulator off followed by on	Adults	NCT02590445
Combined cortical/subcortical recording and stimulation as a circuit-oriented treatment for OCD	Open-label	Medtronic primary celland sensing DBS	Adults	NCT03184454
Development of adaptive DBS for OCD	Case series	DBS discontinuation follow-up	Adults	NCT03457675
DBS and OCD	RCT	DBS of subthalamic nucleus versus DBS of ventral striatum	Adults	NCT01329133
European study of quality of life in resistant OCD patients treated by STN DBS	RCT	DBS versus psychotherapy and pharmacological treatment	Adults	NCT02844049
Efficacy and adverse events of bilateral single-shot ventral capsular or ventral striatal gamma capsulotomy for OCD: a pilot study	Open-label	Gamma ventral capsulotomy	Adults	NCT02433886
Evaluation of capsulotomy by linear accelerator radiosurgery in severe and refractory OCD	Open-label	Bilateral gamma-knife capsulotomy	Adults	NCT02500888

Trial of MR-guided focused ultrasonography (MRgFUS) bilateral capsulotomy for the treatment of refractory OCD	Open-label	Focused ultrasonography	Adults	NCTO3156335

CBD, cannabidiol; CBT, cognitive behavioural therapy ; DBS, deep brain stimulation; EEG, electroencephalography ; ERP, exposure and response prevention; fMRI, functional MRI; MR, magnetic resonance; OCD, obsessive–compulsive disorder ; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SSRI, selective serotonin reuptake inhibitor ; STN, subthalamic nucleus; tDCS, transcranial direct current stimulation; THC, tetrahydrocannabinol; TMS, transcranial magnetic stimulation.

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

The two main treatments for Obsessive-Compulsive Disorder are psychotherapy and medication.

Psychotherapy:
Cognitive-behavioral therapy (CBT) is the most common form of psychotherapy for OCD. CBT comprises two components: cognitive reappraisal and behavioral intervention. Behavioral intervention (ERP), is the psychological treatment of choice for OCD and involves gradual and prolonged exposure to fear-provoking stimuli combined with instructions to abstain from the compulsive behavior. For example, gradually exposing the patient to a feared object or obsession, such as dirt, and having the patient learn ways to resist the urge to perform compulsive rituals. ERP takes effort and practice.

Medications:
The only medications approved by the Food & Drug Administration for the treatment of OCD are serotonin reuptake inhibitors (SRIs, e.g., clomipramine and the selective SRIs (SSRIs)), which often only provide limited relief of symptoms and are ineffective for some patients.[3] As a rule, higher doses of SSRIs are used for OCD than for other anxiety disorders or major depression; higher doses of SSRIs are associated with greater treatment efficacy, but also with higher rates of dropout owing to adverse effects (such as initial gastrointestinal symptoms and sexual dysfunction). Thus, a careful assessment of SSRI adverse effects is crucial when establishing the best dose for each patient. The effect sizes of SSRIs were similar in systematic reviews; however, their adverse effects differ and should be taken into account in the choice of a specific SSRI.[4]

Antipsychotics may be effective added to SRIs for some patients, but there are significant side-effects associated including weight gain, metabolic syndrome, Parkinsonism, tardive dyskinesia, and neuroleptic malignant syndrome.[5]

Neurosurgery:
Neurosurgery is another treatment option for OCD and is only considered in highly refractory and severe cases. Currently, four lesioning neurosurgical procedures are utilized for treatment refractory OCD and major depressive disorder (MDD): cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. Deep brain stimulation (DBS) is a novel neurosurgical approach that has some distinct advantages over lesioning procedures. With DBS, the desired clinical effect can be achieved by reversible, high frequency stimulation in a nucleus or at a node in the circuit without the need to produce an irreversible lesion.[6] No topic in psychiatry is as controversial as treating psychiatric disorders with neurosurgery.

[3] Cannabis and Cannabinoid Research, Volume 4, Number 2, 2019 "The Endocannabinoid System" A New Treatment Target for Obsessive Compulsive Disorder?", Kayser et. al (Attachment #3)

[4] Nature Reviews Disease Primers July 20, 2020 "Obsessive-Compulsive Disorder" Dan J. Stein, et al (Attachment #2)

[5] Cannabis and Cannabinoid Research, Volume 4, Number 2, 2019 "The Endocannabinoid System" A New Treatment Target for Obsessive Compulsive Disorder?", Kayser et. Al (Attachment #3)

[6] Psychiatry 2008 "Functional Neurosurgery in the Treatment of Severe Obsessive-Compulsive Disorder and Major Depression" Dhwani Shah, MD, et. al (Attachment #4)

Success Rates of OCD Treatments:

Few studies have examined the long-term outcome (greater than 5 years) of obsessive-compulsive disorder in adults following the development of validated OCD rating scales. A 2013 study investigated 10 – 20 year outcomes of 83 of 165 eligible subjects previously enrolled in placebo-controlled trials of SRI medications for OCD. Only 20% (17 of 83) had experienced remission of OCD symptoms. Forty-nine percent (41 of 83) were still experiencing significant OCD symptoms. Initial response to SRI pharmacotherapy was strongly associated with long-term outcome. Most adult OCD patients do not achieve remission.[7]

The Need for New Treatments:

OCD is associated with significant functional disability and impairment and many patients do not achieve remission despite evidence-based treatments. There is an urgent need for new targets for treatment development, especially for the large portion of the population that does not experience adequate symptom relief from SRIs.[8] One target is the endocannabinoid system.[9]

[7] Depress Anxiety Feb 2014, "Long Term Outcome in Adults with Obsessive-Compulsive Disorder," Michael Bloch (Attachment #5)

[8] Depress Anxiety Feb 2014, "Long Term Outcome in Adults with Obsessive-Compulsive Disorder," Michael Bloch (Attachment #5)

[9] Cannabis and Cannabinoid Research, Volume 4, Number 2, 2019 "The Endocannabinoid System" A New Treatment Target for Obsessive Compulsive Disorder?", Kayser et. al (Attachment #3)

Cannabis and Cannabinoid Research
Volume 4, Number 2, 2019

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ATTACHMENT #3)

REVIEW

The Endocannabinoid System: A New Treatment Target for Obsessive Compulsive Disorder?

Reilly R. Kayser,[1,*] Ivar Snorrason,[1] Margaret Haney,[1] Francis S. Lee,[2] and H. Blair Simpson[1]

Abstract

Introduction: Obsessive-compulsive disorder (OCD) is a disabling illness that is associated with significant functional impairment. Although evidence-based pharmacotherapies exist, currently available medications are ineffective in some patients and may cause intolerable side effects in others. There is an urgent need for new treatments.

Discussion: A growing body of basic and clinical research has showed that the endocannabinoid system (ECS) plays a role in anxiety, fear, and repetitive behaviors. At the same time, some patients with OCD who smoke cannabis anecdotally report that it relieves their symptoms and mitigates anxiety, and several case reports describe patients whose OCD symptoms improved after they were treated with cannabinoids. Taken together, these findings suggest that the ECS could be a potential target for novel medications for OCD. In this study, we review evidence from both animal and human studies that suggests that the ECS may play a role in OCD and related disorders. We also describe findings from studies in which cannabinoid drugs were shown to impact symptoms of these conditions.

Conclusions: An emerging body of evidence suggests that the ECS plays a role in OCD symptoms and may be a target for the development of novel medications. Further exploration of this topic through well-designed human trials is warranted.

Keywords: anxiety, cannabinoid, endocannabinoid system, OCD, repetitive behavior

Introduction

Obsessive-compulsive disorder (OCD) is a disabling illness with an approximate lifetime prevalence of 2–3% worldwide.[1] The disorder is marked by intrusive repetitive thoughts and behaviors, which must be significantly time consuming, distressing, or functionally impairing to meet DSM 5 criteria.[2] There is a bimodal distribution of age at onset, with peaks in childhood and early adulthood, and roughly equal distribution in adults between males and females. The illness typically follows a chronic course, with symptoms waxing and waning over time. OCD is associated with significant functional disability and impairment,[3] and many patients do not achieve remission despite evidence-based treatments. Evidence suggests that abnormalities in cortico-striatal-thalamic-cortical circuitry and specific gene variants contribute to the pathogenesis of the disorder.[4]

The only medications approved by, for example, the Food and Drug Administration (FDA) for the treatment of OCD are serotonin reuptake inhibitors (SRIs, e.g., clomipramine and the selective SRIs).[5] However, these drugs often provide only limited relief of symptoms, and are ineffective in some patients. Furthermore, SRIs typically require at least 6 weeks of sustained treatment before clinically meaningful improvement can be seen.[5,6] Antipsychotics may be effective when added to SRIs for a subset of patients, but are ineffective in others. Although novel (e.g., second-generation) antipsychotic drugs there is not strong evidence suggesting that these are more effective in OCD. Moreover, antipsychotics as a class are associated with an increased

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risk for side effects, including weight gain, metabolic syndrome, Parkinsonism, tardive dyskinesia, and even neuroleptic malignant syndrome.[7–9] Thus, there is an urgent need for new targets for treatment development.

One potential target is the endocannabinoid system (ECS). Recent studies in both humans and animals have shown a critical role for the ECS in anxiety, stress, fear, and repetitive/habitual behaviors.[10] Moreover, many patients with OCD who use cannabis anecdotally report that it improves their symptoms and reduces anxiety. However, to date, few studies have systematically investigated this connection.

Methods

In this review, we discuss evidence linking the ECS to the neurobiology underlying OCD, and consider the potential role of this system as a target for pharmacological intervention. Given the heterogeneity in the OCD phenotype as well as evidence of both symptom overlap and shared neurobiological underpinnings in OCD and anxiety, tic, and impulse control disorders,[11,12] the scope of our aims was broad. Thus, we elected to complete a narrative review, including a discussion of relevant data from studies on OC spectrum illnesses.

We searched the PubMed database from inception to 2018 using the search terms [cannabis], [cannabinoid], and [endocannabinoid] paired with broad terms (Table 1) to identify relevant articles. We reviewed titles and abstracts, examining full text for articles that provided data on original studies or reviews discussing the ECS and/or cannabinoids in relation to anxiety and OC spectrum illnesses. To identify other relevant articles, we reviewed references of articles identified in the initial search. As this was a narrative review, we did not record the total number of articles screened, identified, or reviewed, although over 150 articles were referenced in an initial draft. This list was then paired to limit redundancy and maximize the overall quality of evidence cited.

Neural Correlates of OCD: Current Models

Aberrant activity in cortico-striato-thalamo-cortical circuits has been linked to OCD symptoms.[13–16] Dysfunction in these circuits, which comprise a system of multiple loops through which information is passed in a coordinated fashion (Fig. 1), could bias an individual toward excessive selection of particular actions or inhibit screening out of inappropriate behaviors.

Table 1. Search Strategy

PubMed search terms	
General terms	**Paired terms**
Cannabis, cannabinoid, endocannabinoid	"obsessive compulsive disorder", OCD, obsession, compulsion, obsessive, compulsive anxiety, fear, stress, trauma, "post-traumatic" tic, "Tourette Syndrome", trichotillomania, excoriation repetitive, habit, habitual

One area of focus has been the orbitofrontal cortex (OFC). For example, imaging studies in OCD patients have shown a shift in the balance of activity between the lateral and medial OFC, such that the lateral region (associated with responsiveness to threat and ritualized behaviors) becomes hyperactive, while the medial (associated with emotional regulation and reward processing) is hypoactive.[17]

The OFC also facilitates the flexible use of goal-directed and habitual behaviors. Data suggest that OCD patients may have deficient control over the balance between these competing action strategies, resulting in a bias toward habit formation.[17–19] Rodent models have demonstrated that OFC regulates this balance through its projections to the dorsal medial striatum (DMS), which promotes goal-directed activity, and the dorsal lateral striatum (DLS), which supports habitual behaviors. Thus, some hypothesize that OCD symptoms result in part from a decrease in OFC-mediated control over the striatum, leading to an excess of DLS relative to DMS activity.[18]

Other brain regions have also been implicated in OCD. These include the dorsal anterior cingulate cortex (dACC), which has been associated with deficient error processing, and the hippocampus and amygdala, which are thought to impact fear and anxiety responses in OCD patients.[17]

The ECS

Overview

The ECS is widely distributed throughout the central and peripheral nervous systems (CNS/PNS). Maintenance of homeostasis is thought to be one of the ECS' major functions, and it has also been implicated in caloric energy balance, immune function, neurogenesis, pain, arousal, sleep, stress reactivity, and reward processing. ECS activity within the CNS prevents the development of excessive neuronal activitation,[20] producing downstream effects which, broadly speaking, have been described as supporting the goal to "relax, sleep, forget, and protect".[19]

Although efforts to study the properties of tetrahydrocannabinol (THC, the primary psychoactive ingredient in the cannabis plant) began in the early 1940s, its endogenous receptor, the cannabinoid receptor type 1 (CB1R), was not identified until 1988.[20] Since then,

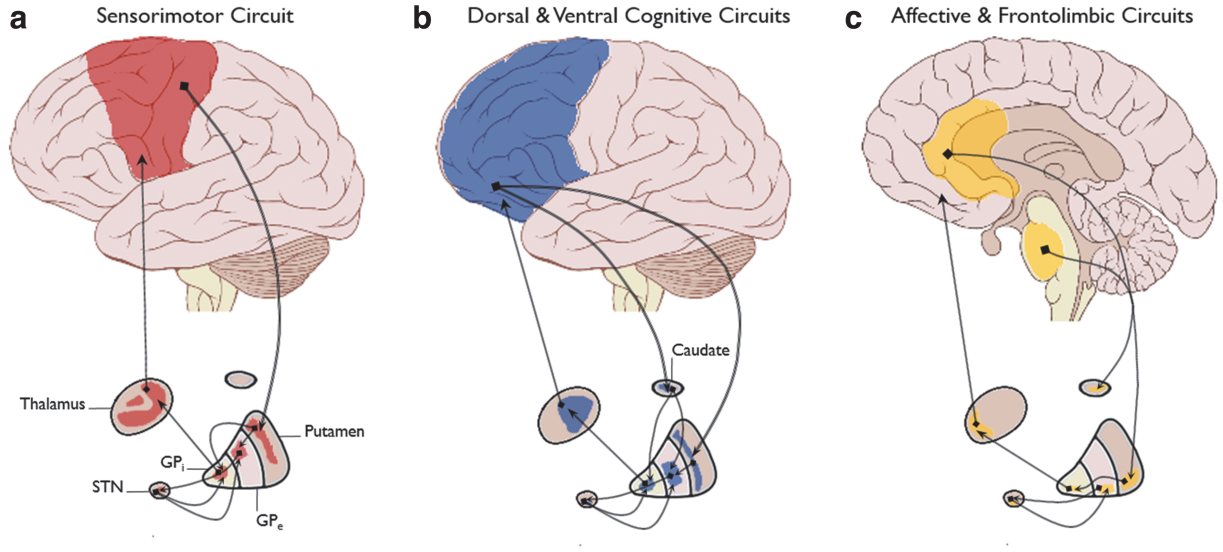

FIG. 1. Schematic of CSTC Loops. **(a)** Sensorimotor circuit, **(b)** dorsal and ventral cognitive circuits, **(c)** affective and frontolimbic circuits. (Image is a derivative of "Brain human lateral view" and "Brain human sagittal section," both by Patrick J. Lynch. The originals are licensed under the Creative Commons Attribution 2.5 Generic License and can be found at https://commons.wikimedia.org/wiki/File:Brain_human_lateral_view.svg and https://commons.wikimedia.org/wiki/File:Brain_human_sagittal_section.svg respectively). CSTC, cortico-striato-thalamo-cortical.

there have been increasing efforts to characterize the components of this system. This work resulted in the discovery of a second receptor type (CB2R), endogenous lipid-based ligands for these receptors (known as "endocannabinoids" [eCBs]), and enzymes which synthesize and degrade eCBs, such as fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase (MAGL).[10] Altogether, eCBs, their receptors, and the enzymes involved in their synthesis and degradation comprise what is now considered the ECS.

Cannabinoid receptors

CB1/2R are G protein-coupled receptors which, when bound by eCBs, initiate a cellular signaling cascade leading to changes in gene transcription, synaptic function, and cell migration during development. Although primarily targeting CB1/2R, eCBs activate a variety of noncannabinoid receptors, including the transient receptor potential vanilloid 1 (TRPV1) receptor, peroxisome proliferator-activated receptor (PPAR) γ, and the orphan G protein-coupled 55 receptor (GPCR55),[21,22] which may account for some of the ECS' diverse functions.

CB1R is the major receptor of the ECS in the CNS, and as such its presence is indicative of ECS activity in a given region. At the neuroanatomical level, high densities of CB1R have been identified in the basal ganglia, cerebellum, hippocampus, prefrontal cortex, and amygdala (Fig. 2). These regions have been implicated in OCD, suggesting that the ECS plays a role in OCD-relevant neural circuitry.[10]

CB1R is found in a variety of cell types, but is most highly expressed in the presynaptic axon terminals of inhibitory GABAergic interneurons. CB1R is expressed to a lesser degree in glutamatergic interneurons, where it localizes similarly to presynaptic axon terminals.[10] CB1R is also expressed in other cell types, including astrocytes, where it impacts control over working memory and other cognitive functions,[23,24] and mitochondria, where it participates in the regulation of adenosine triphosphate production and respiration.[10]

CB2R is rarely seen in the CNS in nonpathological states, but is ubiquitous throughout the PNS. CB2R is known to impact immune activity, inflammation, and response to injury.[25,26]

Endogenous cannabinoids

The first discovered and best-described eCBs are 2-arachidonoyl glycerol (2-AG) and *N*-arachidonoylethanolamine (AEA; also known as anandamide).[22] These

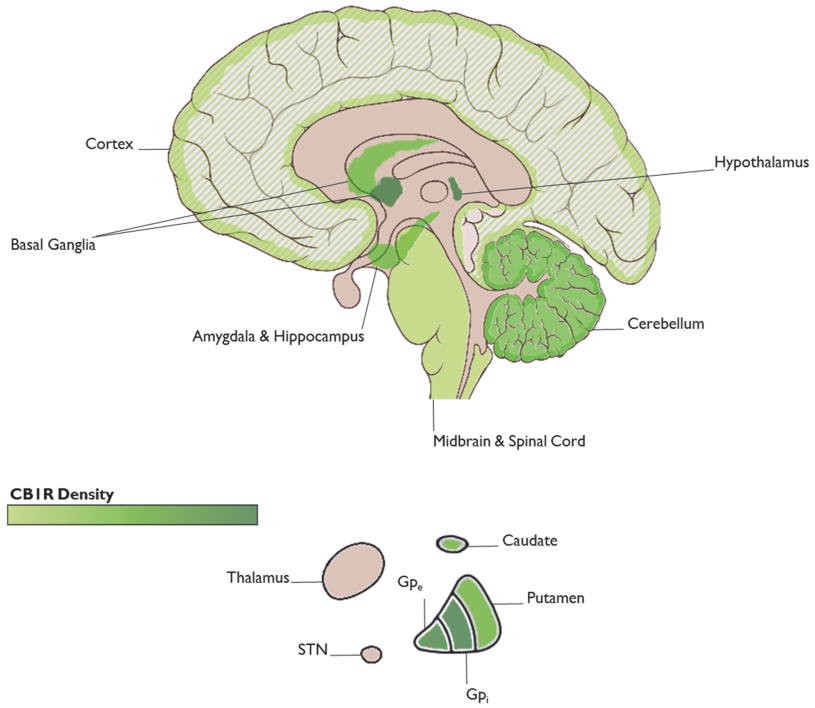

FIG. 2. CB1R distribution in the brain. (Image is a derivative of "Brain human sagittal section" by Patrick J. Lynch. The original is licensed under the Creative Commons Attribution 2.5 Generic License and can be found at https://commons.wikimedia.org/wiki/File:Brain_human_sagittal_section.svg). CB1R, cannabinoid receptor type 1.

are metabolized by the enzymes, MAGL and FAAH, respectively.[25] AEA can alternatively be degraded by N-acylethanolamine-hydrolizing acid amidase (NAAA) or by cyclooxygenase-2 (COX-2), with variant downstream effects on cell functioning depending on the metabolic pathway to which AEA is shunted.[27] 2-AG is a potent agonist of both CB1R and CB2R, whereas AEA is a relatively weak agonist of both receptors, and in the presence of an agent with stronger affinity may act as an antagonist.[25]

As described above, CB1R concentrates predominantly at presynaptic axon terminals of cortical GABAergic and glutamatergic neurons. However, it is also found throughout the cholinergic, serotonergic, and noradrenergic systems of the CNS. eCBs act as retrograde messengers, binding to presynaptic CB1R to cause suppression of neurotransmitter release, leading over time to both short- and long-term depression of synaptic transmission.[26,28] eCBs can also regulate neurotransmission at neighboring synapses by both diffusing into the extracellular space and activating CB1R in nearby astrocytes.[10]

eCBs are unusual neurotransmitters in that their synthesis occurs "on demand".[10,21,28] Rather than being stored in synaptic vesicles, eCBs are synthesized from cellular membrane lipids in response to stimulation of the postsynaptic neuron. They are then released into the extracellular space,[10,26] after which they are rapidly hydrolyzed and inactivated by FAAH, MAGL, and other metabolic enzymes.[10,29] This unique mechanism enables an activity-driven functionality (e.g., increased when neural activity is high). By activating transiently at a particular synapse when the cellular constituents of that system have been stimulated beyond a given threshold, the ECS may serve as a brake mechanism, fine-tuning activity within specific neural circuits.

Exogenous cannabinoids

Exogenous cannabinoids can be subdivided into two categories (Table 2). *Phytocannabinoids* consist of over 108 compounds which are found in the cannabis plant, including THC and cannabidiol (CBD).[10,30,31] Phytocannabinoids have been isolated in the laboratory, producing purified compounds or mixtures such

Table 2. Currently Available Exogenous Cannabinoids

Agent	Class	US legal status	Method of delivery	Approved use
THC	Phytocannabinoids	Same as cannabis (FDA Schedule I)	Smoked/vaporized, oromucosal spray, capsules	None
CBD	Phytocannabinoids	Same as cannabis (FDA Schedule I), capsule form recently approved	Smoked/vaporized, oromucosal spray (not approved for use); capsules	Pediatric epilepsy
Nabiximol (THC & CBD)	Phytocannabinoids	Approved in Canada and parts of Europe, not in the US	Oromucosal spray	Adjunct treatment for spasticity, pain, nausea/vomiting
Dronabinol (THC)	Phytocannabinoids	FDA Approved	Capsules, oral liquid	Cancer-associated nausea/vomiting
Nabilone (Synthetic THC)	Synthetic Cannabinoid	FDA approved	Capsules	HIV, cancer-associated nausea/vomiting

CBD, cannabidiol; THC, tetrahydrocannabinol; FDA, Food and Drug Administration.

as nabiximol (THC and CBD in a 1:1 ratio, administered in an oromucosal spray). Nabiximol is approved in Canada and several European countries.[10] *Synthetic cannabinoids* have also been created. Nabilone (synthetic THC) and dronabinol (an alternate form of plant-derived THC) are both FDA approved for cancer-related nausea and vomiting.

CBD has garnered increasing interest as a potential treatment for a variety of neuropsychiatric conditions, including anxiety. Although both THC and CBD are phytocannabinoids, CBD is distinct in that it exhibits little to no activity at CB1R.[30] Based on its ability to antagonize the receptor under certain conditions, CBD has been characterized as a negative allosteric modulator at CB1R.[30,32] However, CBD may indirectly stimulate CB1R by inhibiting FAAH, thereby increasing levels of AEA and other eCBs.[30] CBD may also inhibit adenosine reuptake, which is notable given that facilitation of adenosine signaling produces anxiolytic effects.[32] Finally, CBD appears to have activity at a number of different receptor targets, including the $5HT_{1A}$ receptor, TRPV1, and GPCR55.[21] An oral formulation of CBD called Epidiolex was recently approved by the FDA for the treatment of seizures associated with Dravet and Lennox–Gastaut syndromes, two rare forms of pediatric epilepsy.

The ECS and OCD symptoms: From animal studies to human trials

Several lines of evidence suggest an association between the ECS and OCD symptoms. First, as reviewed above, CB1R are found in high densities in regions thought to be implicated in OCD, including the prefrontal cortex, basal ganglia, hippocampus, and amygdala.[10] Second, preclinical studies (primarily in rodents) suggest that cannabinoid signaling may impact OCD-relevant neurocognitive functions, including fear extinction and the balance between goal-directed and habitual action strategies. Moreover, cannabinoids can improve symptoms in animal models of anxiety and compulsive behavior. Finally, preliminary studies of cannabinoids in patients with OCD and related disorders (e.g., anxiety, tic disorders) suggest the potential clinical utility of cannabinoid agents. This evidence is briefly reviewed below.

Animal studies

The ECS, anxiety, and fear

CB1R agonists have a biphasic effect on anxiety symptoms, with low doses producing anxiolysis, and high doses, anxiogenesis. This effect is reliably demonstrated in rodents and appears to be driven in part by activation of TRPV1 by high (but not low) doses of CB1R agonists.[10,21,28] In contrast, direct activation of TRPV1 increases anxiety, suggesting that the balance between activation of CB1R versus TRPV1 may regulate anxiety-like behaviors.[21,33]

CB1R activation also impacts anxiety by modulating activity in excitatory and inhibitory outputs from the cortex.[34] In mouse studies, CB1R agonists at low doses (which are anxiolytic) primarily activate CB1R in cortical glutamatergic neurons. In contrast, high doses of CB1R agonists are anxiogenic and are associated with a relative increase in activity in forebrain GABAergic neurons.[35,36] In addition to dose dependence knockout, mice have also demonstrated that CB1R's impact on anxiety is responsive to environmental cues. Specifically, deleting CB1R from the cortex reduces exploratory behavior in mice (thought to reflect anxiety) under mildly stressful conditions, but not in highly aversive settings; on the other hand, loss of CB1R from forebrain GABAergic neurons increases exploratory behavior under mildly aversive conditions but does not impact responsiveness to highly aversive settings.[36,37]

Studies have also demonstrated that the ECS plays a complex role in the neuroendocrine response to stress. These findings are summarized in detail in a 2018 review by Hill et al.[38] Generally speaking, release of glucocorticoids promotes the release of AEA and 2-AG. eCBs bind to amygdalar CB1R to dampen the stress response, promote adaptation to prolonged stress, and reduce catecholamine release from sympathetic terminals. In contrast, THC and exogenous cannabinoids decrease the stress response at low doses while increasing it at high doses.[38] Taken together, these findings suggest that CB1R acts as a buffer on activity within anxiety circuits, exerting opposing effects depending on the dose of agonist and aversiveness of the local environment.[10]

Cannabinoids can also modulate extinction to conditioned fear, which is notable given that impaired fear extinction has been reported in OCD.[17] Studies using knockout mice and pharmacological antagonists suggest that CB1R is required for extinction of fear memories to occur and that extinction occurs through ECS-mediated long-term depression of local GABAergic inhibitory networks within the basolateral amygdala.[39] During fear extinction, eCB levels increase in the basolateral amygdala (which has been associated with extinction of aversive memories).[40] Presynaptic CB1R activity can also regulate the behavioral responsiveness of mice to aversive memories by modulating cholinergic signaling in projections from the medial habenula to the interpeduncular nucleus.[41] Exogenous cannabinoids, including THC and CBD, have been shown to reduce rodent responsiveness to conditioned fear,[42,43] while selective CB1R antagonists appear to inhibit the extinction process.[39]

Animal studies also show that the metabolic enzymes of the ECS can impact anxiety symptoms. A human variant of the gene encoding FAAH has been identified, which results from a common single nucleotide polymorphism carried by 38% of individuals of European descent.[10,44,45] A 2015 study of humans and mice with an analogous FAAH variant found that in both groups, FAAH expression was reduced, resulting in increased AEA levels in the CNS. Both groups also demonstrated decreased anxiety behaviors and an increased rate of fear extinction relative to control subjects. Resting-state functional magnetic resonance imaging (fMRI, in humans) and tract-tracing methods (in mice) revealed increased connectivity between frontal areas and the amygdala among individuals with the FAAH variant of both species, with mice also displaying reduced amygdala responsiveness to threatening stimuli, compared with controls.[45] These parallel findings across species provide strong evidence that the ECS modulates anxiety and fear response in humans, and posit that this effect may result from increased fronto-amygdala connectivity. The presence of a common gene variant which impacts both anxiety symptoms and capacity to extinguish conditioned fear may also help to explain the differential response to exposure-based psychotherapy among patients with anxiety disorders and OCD.

Pharmacological studies of drugs that inhibit eCB metabolism have also been conducted. FAAH inhibitors in mice appear to enhance AEA signaling, which is associated with reduced anxiety-like behavior, decreased responsiveness to stress, and facilitation of fear extinction. Similarly, pharmacological blockade in mice of MAGL appears to have anxiolytic effects under a variety of conditions.[10,46]

The ECS and habitual/repetitive behaviors

Rodent studies have linked the ECS to habit learning and repetitive behavior. One mouse study found that intrastriatal administration of a CB1R antagonist impaired the ability to "unlearn" previously acquired procedural memories in response to changing reward contingencies, whereas intrahippocampal administration facilitated this process. These findings suggest that habit learning is affected by the interplay between hippocampal and striatal CB1R activity. For example, insufficient CB1R activity in projection neurons to striatum might lead to perseveration on previously learned behaviors and difficulty adapting to environmental changes.[47]

In a series of studies by Gremel et al.,[18] ECS activity in corticostriatal circuitry was shown to modulate the shift between goal-directed and habitual action strategies. Using optogenetic techniques, the authors demonstrated that activating CB1R within OFC-DMS projection neurons decreased excitatory transmission, as measured by whole-cell patch clamp electrophysiology. CB1R deletion, both from OFC neurons in general and specifically from OFC-DMS projections, prevented habitual pressing of an instrumental lever during an outcome devaluation paradigm, leaving mice reliant on goal-directed strategies. Conversely, chemogenetic inhibition of transmission by OFC-DS neurons prevented mice from using goal-directed strategies. Taken together, these findings suggest that ECS activity in OFC impacts the balance between goal-directed and habitual action control. Loss of ECS-mediated plasticity within these circuits could thus contribute to OCD symptoms, perhaps by causing a

relative shift toward activity in OFC-DLS relative to OFC-DMS circuitry resulting in excessive reliance on habit.

Other studies have focused on the impact of the ECS on repetitive behavior. For example, mouse studies found that either CB1R agonists or an inhibitor of AEA metabolism reduced the number of buried marbles on the marble-burying test, an animal model of compulsivity.[48] In another mouse study, AEA decreased marble-burying behavior (MBB) at low doses, and increased MBB at high doses, an effect which was mediated by increased TRPV1 activation with high doses of AEA.[49] Pretreatment with a TRPV1 agonist prevented the reduction in MBB at low doses, while capsazepine (a TRPV1 antagonist) mitigated the increase in MBB with high doses of AEA. Notably, the effect of capsazepine itself on MBB was comparable to fluoxetine, suggesting that TRPV1 may also be a viable target for novel anticompulsive agents.

Systemically delivered CBD has also been shown to reduce MBB in rodent models.[50–52] Although CBD appears to be able to activate 5HT receptors (among a number of targets),[32] these studies suggest that its effect on MBB is driven specifically by CB1R activation, as (1) $5HT_{1A}$ receptor antagonists failed to prevent the effects of CBD[52] and (2) CB1R antagonists reversed the effects of both fluoxetine and CBD on MBB. Neither fluoxetine nor CBD impacted motor or exploratory behavior in these studies, suggesting that their effects were specific to MBB rather than reflecting a nonspecific decrease in anxiety or locomotion. CBD also reversed the effects of meta-Chlorophenylpiperazine, a nonspecific serotonin receptor agonist, which increases repetitive grooming behaviors and MBB.[50] CBD's effect on MBB was also shown to persist over 7 days of daily CBD administration,[51] as compared with diazepam, which showed decreasing efficacy over time.[43]

Other work has explored the impact of cannabinoid agents on the serotonin system. A mouse study comparing a FAAH inhibitor, AEA, and an AEA reuptake inhibitor found that the cannabinoid agents impacted MBB in a biphasic fashion (decreased at low doses and increased at high doses), whereas fluoxetine reduced MBB in a linear fashion. Subeffective doses of fluoxetine also potentiated the effect of subeffective doses of all three cannabinoids on MBB, and a CB1R antagonist blocked the effects of both fluoxetine and the cannabinoids.[53] In a separate study, paracetamol (acetaminophen, an analgesic/antipyretic), produced dose-dependent decreases in MBB that were comparable to those produced by fluoxetine. This effect was driven by paracetamol's effect at both 5HT receptors and CB1R. Furthermore, coadministration of paracetamol and fluoxetine had a synergistic effect toward reducing MBB.[54] Taken together, these data suggest that compulsive-like behaviors can be modulated through interactions between the ECS and serotonin system.

Studies in Humans

Substantial evidence from the nonpsychiatric literature supports the safety and efficacy of cannabinoids for treating symptoms of medical conditions, including HIV, chronic pain, cancer, and multiple sclerosis.[31] However, to date, few clinical studies have examined the role of these agents in psychiatric conditions. Relevant findings from these studies are discussed below.

Anxiety and fear

The relationship between cannabinoids, and anxiety and fear has been of particular interest in clinical research.[17,42] In imaging studies of healthy controls, CBD and dronabinol attenuated amygdala response to fear-inducing stimuli. Dronabinol also facilitated fear extinction in laboratory studies of healthy adults,[42] and was associated with increased vmPFC activity in a follow-up study of the same subjects.[55] In laboratory settings, CBD has been shown to reduce experimentally induced anxiety and enhance the extinction of fear memories in healthy adults.[44]

Clinical trials in patients with posttraumatic stress disorder (PTSD) have shown that dronabinol and nabilone can reduce symptoms, including the response to fearful stimuli. Several studies have also demonstrated that nabilone may improve PTSD-associated nightmares and insomnia.[44,56–59]

CBD has also been studied as a potential anxiety treatment, although the results of clinical studies are mixed. As described above, CBD acts at a range of pharmacological targets, including CB2R, TRPV1, the serotonin $5HT_{1A}$ receptor, GPCR55, and PPAR.[27,60] Moreover, CBD may inhibit FAAH, thereby increasing AEA levels (and indirectly activating CB1R).[30] CBD lacks toxic effects, even at high doses. Furthermore, as opposed to THC, CBD is nonpsychotogenic, and has been shown to reverse some of THC's negative effects, including paranoia and memory impairment.[21,27,30,32,44,60] Although trials of CBD have shown little impact on baseline levels of anxiety, it may reduce experimentally induced anxiety and fear.[21,23,32] For example, one study in healthy subjects and those with social anxiety disorder found that CBD reduced task-related anxiety with

an effect comparable to a serotonin agonist or diazepam.[21] Neuroimaging studies suggest that CBD reduces amygdala activation in response to threat and alters functional connectivity between prefrontal regions and the amygdala,[32] which may explain its potential anxiolytic effects. However, a recent evaluation of the literature by the National Academy of Sciences highlighted problematic design aspects of the above studies (for example, providing just one dose of CBD[61]). Thus, further studies are needed.

Repetitive behaviors

Both case reports and survey data from patients with Tourette Syndrome (TS) indicate that smoked cannabis can reduce motor tics and urges to perform compulsive behaviors.[62] Dronabinol has also been studied as a treatment for TS in two small clinical trials. In the first trial, a pilot study using a single-dose crossover design, 12 patients with TS showed a decrease in tic severity on the Tourette Syndrome Symptom List (TSSL) and reduced obsessive-compulsive behavior, relative to placebo, on a nonvalidated self-report scale developed by the investigators. A second trial in 24 adult patients with TS used a parallel design with daily dosing over 6 weeks. Dronabinol led to significant improvements compared with placebo on the Tourette Syndrome Clinical Global Impressions scale (TS-CGI), Shapiro Tic Syndrome Scale (STSS), and TSSL. Although the results of these studies are intriguing given the phenotypic overlap between OCD and tic disorders, these trials were limited by small sample sizes and high drop-out rates, and a recent Cochrane review found that there was insufficient evidence to recommend the clinical use of cannabinoids for TS.[63,64]

In a 2011 trial, 14 female subjects with trichotillomania received open treatment with dronabinol over a 12-week period. Although the trial lacked a placebo control, of the 12 subjects who completed the trial, 9 qualified as "responders" as measured by a reduction on the MGH Hairpulling Scale (MGH-HPS) of ≥35%.[65]

Obsessive-compulsive disorder

To date, only three case reports describe the effects of cannabinoids on OCD symptoms. In the first, a 38-year-old woman with major depression and OCD received dronabinol after responding poorly to paroxetine, clomipramine, and CBT, but reported that smoking cannabis usually relieved her symptoms. Over the course of 10 days in which clomipramine was augmented with dronabinol (10 mg thrice daily), the patient's score on the Yale–Brown Obsessive Compulsive Scale (YBOCS) decreased from 20 to 10 (i.e., from "moderate" to "mild" severity).

In the second case, a 36-year-old man with schizophrenia and OCD who was hospitalized for worsening psychotic and obsessive symptoms was treated with dronabinol after his OCD symptoms failed to respond to SSRIs and antipsychotics (including a year-long trial of clozapine and paroxetine, a 10-week trial of clozapine and clomipramine, and ECT). Dronabinol was added to clozapine and clomipramine at 10 mg twice daily, and within 2 weeks a decrease in the patient's YBOCS score from 25 to 15 was observed. The authors note that neither patient reported any side effects in response to adding dronabinol, nor was any deterioration of psychotic or mood symptoms observed.[66] The latter case is notable given that 20–30% of patients with schizophrenia experience OCD symptoms, and a body of literature linking clozapine treatment to the development of OCD symptoms. No single theory has explained the overlap between OCD and psychosis, but this evidence supports additional study of the ECS' role in patients with symptoms of both conditions.

In a third case, a 24-year-old man developed persistent obsessions and compulsions following a left thalamic stroke, but did not respond to several high-dose medication and augmentation trials, including SRIs, antipsychotics, benzodiazepines, glutamate modulators, and mood stabilizers. The patient requested neurosurgical consultation for deep brain stimulator placement, but elected to receive dronabinol (20 mg daily) before surgery. Over the course of 2 weeks, the patient's YBOCS score decreased from 39 to 10. The authors note that this correlated with a significant improvement in the patient's quality of life and his ability to participate in CBT, which had previously been intolerable for him.[67]

Summary and Future Directions

The ECS is ubiquitous throughout the CNS and, through various mechanisms, acts to modulate neural activity across multiple circuits and neurotransmitter systems. As summarized in this study, convergent streams of data from neuroimaging studies, animal models, and preliminary clinical studies have revealed associations between the ECS, anxiety, and compulsive/repetitive behaviors.

Animal models indicate that cannabinoid agents have both anxiolytic and anticompulsive effects, which are mediated by their activity at multiple receptor sites, including CB1R, $5HT_{1A}$, and TRPV1. Broadly

speaking, the ECS appears to regulate anxiety and OCD symptoms through its effects on top-down control by frontal cortical over striatal and limbic regions. More specifically, the ECS can modulate response to fearful stimuli, possibly by influencing signaling between frontal regions and the amygdala. Additionally, CB1R-mediated changes in frontal-striatal circuitry may impact the balance between goal-directed and habitual action selection. Altogether, these findings suggest that abnormalities within the ECS could underlie, at least in part, anxiety and compulsions in OCD populations, and that interventions targeting this system may be fertile ground for the development of new treatments.

Although preliminary, the available clinical data indicate that cannabinoids influence OCD-relevant processes, impacting anxiety symptoms, enhancing fear extinction, and reducing certain repetitive behaviors. To date, only case reports detail how cannabinoids affect OCD symptoms specifically, although the effects reported are promising. Further testing is warranted.

When considering the design of future studies, several key questions arise. First, which agents should be tested? THC analogs (e.g., dronabinol) and other CB1R agonists have generated the most positive results, but require careful monitoring for side effects (e.g., intoxication, increased anxiety at certain doses). Moreover, given the ubiquity of cannabinoid receptors throughout the CNS, agents that activate CB1R globally may have multiple, at times unwanted or competing, effects.[28] Nonetheless, preliminary data from trials of CB1R agonists in PTSD are promising and support testing of these agents in patients with anxiety and OCD.[56–59]

CBD also has a potential role in treatment given its favorable side effect profile, lack of psychotogenic/anxiogenic properties, and ability to enhance fear extinction in humans and to reduce compulsive-like behavior in mice. The challenge with CBD, however, is knowing which of its many targets might be responsible for its clinical effects[32,68]

Given that the synthesis (and subsequent degradation) of eCBs increases on-demand in response to increased neural activity, drugs that effect metabolic enzymes may provide more targeted control over ECS activity than drugs that broadly activate cannabinoid receptors, thereby reducing the risk for side effects, anxiogenesis, and addiction/abuse.[44,69] Thus, studies of FAAH and/or MAGL inhibitors are also of interest. Indeed, early evidence from rodent studies indicates that FAAH and MAGL inhibitors can reduce repetitive behaviors and anxiety. However, these compounds are not readily available for human research.

Other potential candidate drugs include cannabinoid reuptake inhibitors[69] and agents that target TRPV1. Alternatively, compounds that interact indirectly with the ECS such as capsazepine,[53] paracetamol,[54] or COX2 inhibitors,[32] may be useful. In addition to utility as monotherapy, novel agents could also be used in augmentation, as suggested by rodent models demonstrating synergistic effects with cannabinoids and SRIs.[26,32,53,54,70] Finally, agents with dual activity like N-arachidonoyl-serotonin, which inhibits FAAH (thereby activating CB1R) and antagonizes TRPV1 (preventing its anxiogenic effect),[32] are worth further exploration once compounds that are safe for human use become available.

After choosing a cannabinoid to test, selecting an appropriate measurement of its effects will be key. Although clinically validated, standard measures such as the YBOCS may not be sufficiently sensitive to the effects of cannabinoids. Designed to assess for OCD symptoms and distress over the past week, the YBOCS is also unable to detect acute changes in symptoms following drug administration. While the YBOCS remains the gold standard for use in large-scale treatment trials, behavioral paradigms that focus on underlying neurocognitive mechanisms could be an alternative means of assessing cannabinoid effects. For example, the two-step task, which uses computational modeling to differentiate goal-directed vs. habit-based learning, has been used to reveal a bias toward habit acquisition in disorders of compulsive behavior (e.g., binge eating, substance use, and OCD).[71] Such a task might more directly tap the effects of cannabinoids on brain function.

Modern neuroimaging techniques may also clarify how cannabinoids impact neural circuitry, which will be critical given the ECS' complex array of functions within the CNS. PET ligands for CB1R are available[72] and have been used to quantify its role in other psychiatric disorders.[72–75] Task-based and resting-state fMRI have also been used to measure cannabinoid effects in healthy[76,77] and psychiatrically ill subjects.[32,78] Nonetheless, to facilitate large-scale clinical trials of cannabinoids, there remains a need to develop and validate noninvasive measures of target engagement.

Despite decades of research since the development of SSRIs, our pharmacological armamentarium for OCD remains largely unchanged. The emerging body of research summarized in this study indicates that the ECS may impact the neural circuitry underlying OCD

and could be a target for novel treatments. Moving forward, further exploration of the complex relationship between OCD symptoms and the ECS will be critical to determining the utility of cannabinoids in treating OCD. Well-designed placebo-controlled studies are also needed to demonstrate the efficacy and tolerability of cannabinoid drugs in OCD populations, and to measure their impact on relevant neural targets, including frontostriatal and frontolimbic circuits. ECS-targeted drugs have the potential to yield novel pharmacotherapies which are long overdue for those who suffer the debilitating effects of OCD. Only further exploration of this topic will determine whether cannabinoids pass the most important test: Helping more patients with OCD to achieve wellness.

Author Disclosure Statement

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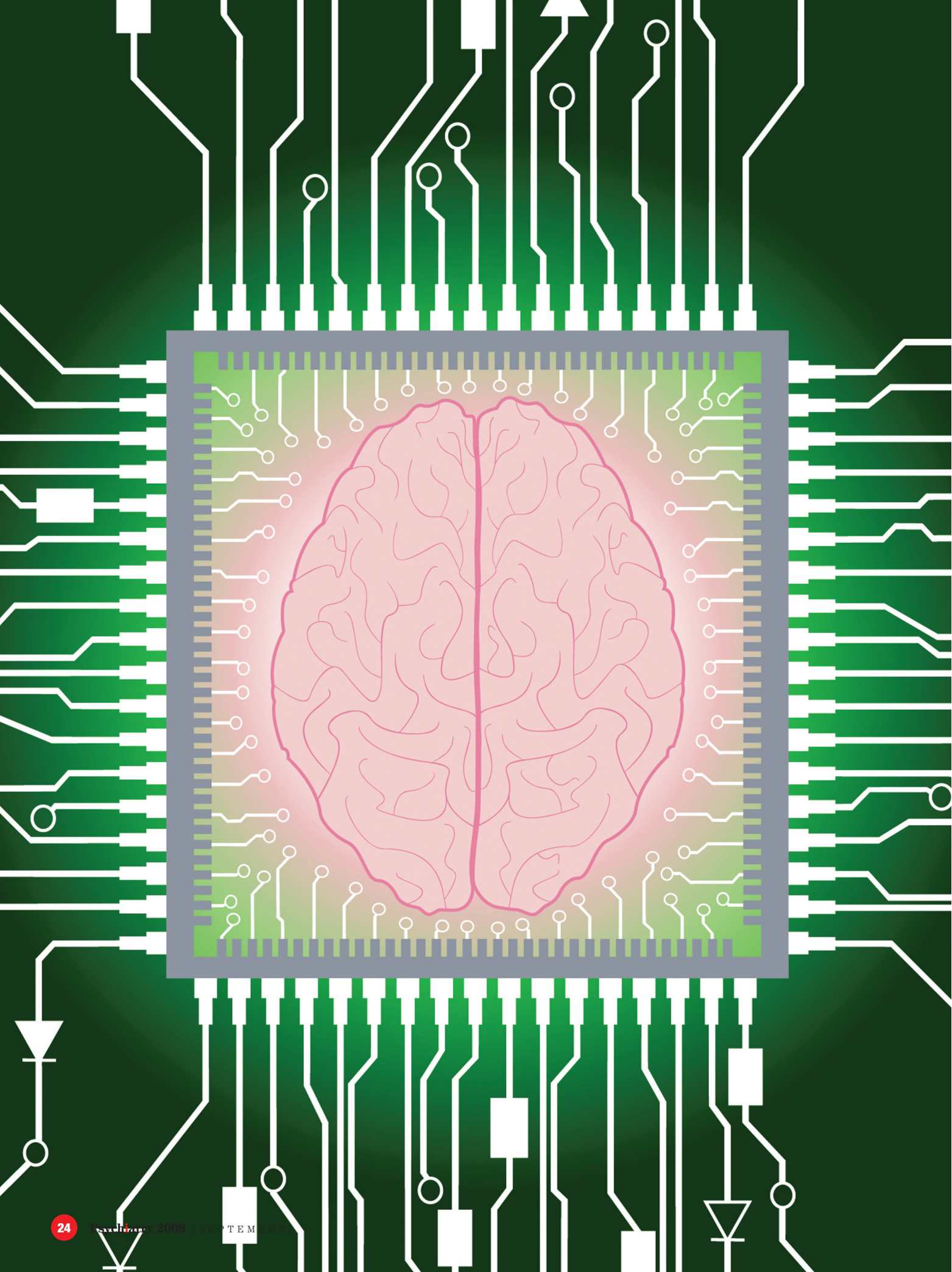
Abbreviations Used

2-AG = 2-arachidonoyl glycerol
AEA = *N*-arachidonoylethanolamine
CBD = cannabidiol
CNS = central nervous systems
COX-2 = cyclooxygenase-2
dACC = dorsal anterior cingulate cortex
DLS = dorsal lateral striatum
DMS = dorsal medial striatum
eCB = endocannabinoid
ECS = endocannabinoid system
FAAH = fatty acid amide hydroxylase
FDA = Food and Drug Administration
fMRI = functional magnetic resonance imaging
MAGL = monoacylglycerol lipase
MBB = marble-burying behavior
NAAA = N-acylethanolamine-hydrolizing acid amidase
OCD = obsessive-compulsive disorder
OFC = orbitofrontal cortex
PNS = peripheral nervous systems
PTSD = posttraumatic stress disorder
SRI = serotonin reuptake inhibitors
STSS = shapiro tic syndrome scale
THC = tetrahydrocannabinol
TS = tourette syndrome
TS-CGI = tourette syndrome clinical global impressions scale
TSSL = tourette syndrome symptom list
YBOCS = yale-brown obsessive compulsive scale



ATTACHMENT #4

FUNCTIONAL NEUROSURGERY IN THE TREATMENT OF SEVERE OBSESSIVE COMPULSIVE DISORDER AND MAJOR DEPRESSION:

Overview of Disease Circuits and Therapeutic Targeting for the Clinician

by DHWANI B. SHAH, MD; ANGELIKI PESIRIDOU, MD; GORDON H. BALTUCH, MD, PhD; DONALD A. MALONE, MD; and JOHN P. O'REARDON, MD

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Psychiatry (Edgemont) 2008;5(9):24–33

ABSTRACT

Over the past 20 years, there has been a concerted effort to expand our understanding of the neural circuitry involved in the pathogenesis of psychiatric disorders. Distinct neuronal circuits and networks have been implicated in obsessive compulsive disorder (OCD) and major depressive disorder (MDD) involving feedback loops between the cortex, striatum, and thalamus. When neurosurgery is used as a therapeutic tool in severe OCD and MDD, the goal is to modulate specific targets or nodes within these networks in an effort to produce symptom relief.

Currently, four lesioning neurosurgical procedures are utilized for treatment refractory OCD and MDD: cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. Deep brain stimulation (DBS) is a novel neurosurgical approach that has some distinct advantages over lesioning procedures. With DBS, the desired clinical effect can be achieved by reversible, high frequency stimulation in a nucleus or at a node in the circuit without the need to produce an irreversible lesion. Recent trials of deep brain stimulation in both OCD and MDD at several neuroanatomical targets have reported promising early results in highly refractory patients and with a good safety profile. Future definitive trials in MDD and OCD are envisaged.

INTRODUCTION

No topic in psychiatry is as controversial as treating psychiatric disorders with neurosurgery. Since the advent of scientific study of the human brain, biologically oriented

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KEY WORDS: obsessive compulsive disorder, major depression, neurosurgery, deep brain stimulation, neurocircuitry

psychiatrists have sought to unravel its mysteries by identifying underlying neuropathological mechanisms resulting in psychiatric disorders. It was hoped that such insights would lead to cures for the most debilitating forms of these disorders through targeting brain regions that were responsible for generating psychopathology. Unfortunately, the history of surgical interventions in psychiatry has been marred by misguided applications of erroneous or overly simplistic approaches to psychiatric disease, sometimes resulting in significant negative outcomes. The birth and subsequent demise of psychosurgery in the 20th century serves as an important caution in considering neurosurgical interventions today. However, despite the success of psychotherapeutic and psychopharmacological strategies to treat mental illness, there still remains a large proportion of patients who suffer with persistent and debilitating illness that fails to respond to standard treatments.

Until recently, many of our treatments in psychiatry were discovered serendipitously, including the initial discoveries of the effectiveness of antidepressants and electroconvulsive therapy.[1] Over the past several decades, there has been a concerted effort by means of neuroimaging to expand our understanding of the neural circuitry involved in the pathogenesis of psychiatric disorders. In this context, a novel neurosurgical treatment intervention, deep brain stimulation (DBS), has emerged that targets focused regions of the brain in an effort to alleviate psychiatric symptoms. A psychiatrist in general practice may well wonder what this new technology is and what it may offer therapeutically that is clinically distinct and relevant. We will review here the current literature pertaining to neurosurgical interventions in psychiatry, with a special emphasis on DBS and the underlying neurocircuitry involved in two major psychiatric disorders; obsessive compulsive disorder (OCD) and major depressive disorder (MDD).

HISTORY

Neurosurgical procedures to treat psychiatric disorders have been controversial, in part due to the significant morbidity associated with earlier approaches and, up to now, the irreversible nature of the procedure. In the past, there was also a lack of systematic follow-up to measure long-term functional outcomes following such interventions. Finally, the indiscriminate use of earlier crude neurosurgical procedures, such as prefrontal and transorbital lobotomy, resulted at times in irreversible personality change and cognitive decline. By the mid-1950s, over 30,000 frontal lobotomies were performed in the US alone.[2,3] Although some patients benefited from this procedure, many suffered permanent adverse consequences. Thus, *psychosurgery*, a term originally coined by Egas Moniz, who was awarded the Nobel prize for his efforts in pioneering prefrontal leucotomy, ultimately fell into disrepute.

...with the level of precision that is available with modern neurosurgical approaches, the emphasis has shifted away from ablative or lesioning procedures, however precisely placed they might be. Rather, the focus is one of stimulation or inhibition (modulation) of nodes or targets within neural circuits by means of precisely placed electrodes with the object of restoring normal activity and function within the identified circuit.

Given this troubled history, current approaches in neurosurgery to psychiatric disease are proceeding with due caution. In contemporary practice, patients must meet operationalized criteria for severity, chronicity, and disability and have a demonstrated inability to respond to standard available treatments, including psychopharmacology and psychotherapy. When surgical interventions are being considered, a multidisciplinary team consisting of psychiatrists, neurosurgeons, and other specialists involved in the care of the patient must review each case carefully to establish that conventional treatment has indeed failed and that a neurosurgical intervention is warranted. From an ethical standpoint, neurosurgery should be restricted to patients who have the requisite decision-making capacity, and the surgery must only be performed to restore function and relieve suffering. Needless to say, surgery should never be performed for political, law enforcement, or other nonmedical, sociological purposes.[4]

Finally, with the level of precision that is available with modern neurosurgical approaches, the emphasis has shifted away from ablative or lesioning procedures, however precisely placed they might be. Rather, the focus is one of stimulation or inhibition (modulation) of nodes or targets within neural circuits by means of precisely placed electrodes with the object of restoring normal activity and function within the identified circuit. A major virtue of this approach is the move away from irreversible or ablative lesions to one of reversible neuromodulation or what is termed *functional neurosurgery*.

BRAIN REGIONS OF INTEREST IN OCD AND DEPRESSION

Our understanding of the complex neurological underpinnings of mood and anxiety syndromes has improved over the past several decades, but much remains unknown. One reason

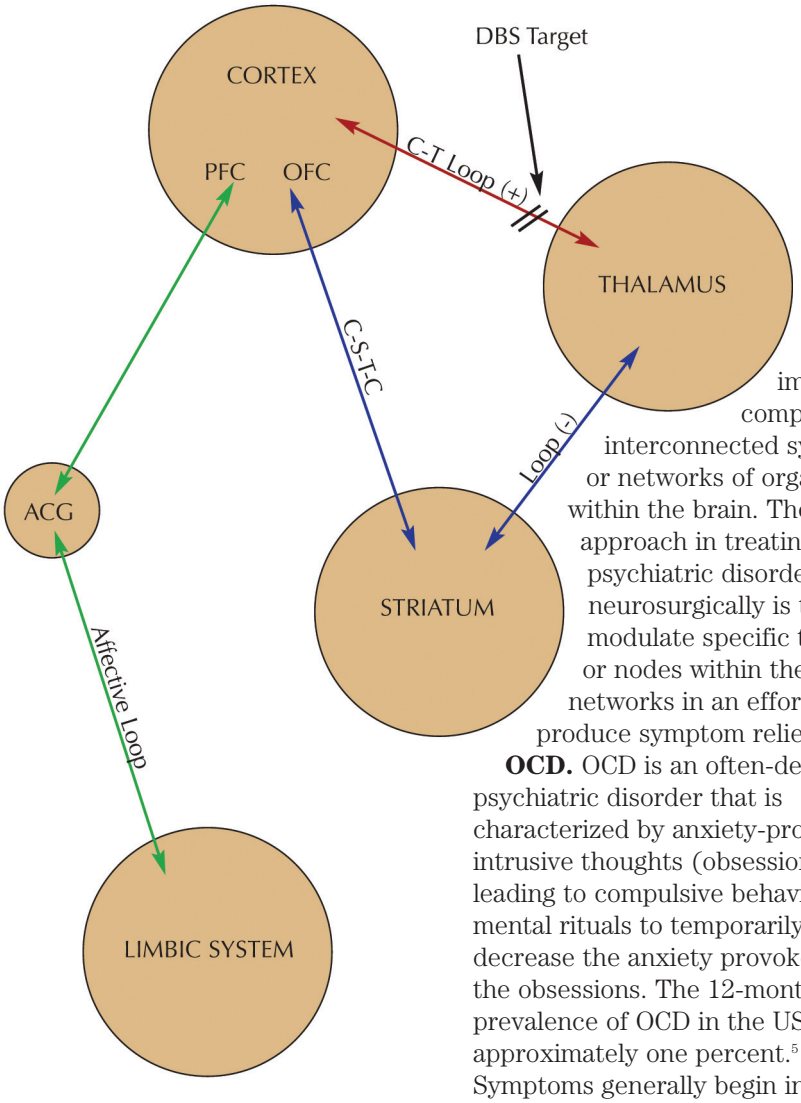

FIGURE 1. Neural circuitry of OCD and DBS target. Hyperactivity in the CT loop or hypoactivity of the C-S-T-C loop may produce OCD symptoms. DBS targets the C-T loop and normalizes activity in the circuit.

KEY: PFC: prefrontal cortex; OFC: orbitofrontal cortex; C-T: corticothalmic; C-S-T-C: cortico-striatal-thalamic-cortical; ACG: anterior cingulate gyrus; OCD: obsessive compulsive disorder; DBS: deep brain stimulation

for this is the lack of sophisticated animal models for these disorders, in part, because they are uniquely situated in our conscious subjectivity as humans. Analogous to neurological disorders, our understanding of the neurobiology of psychiatric disorders began with lesioning studies. Based on the seminal work of neurologists studying aphasias and movement disorders, researchers attempted to localize psychiatric syndromes to specific neuroanatomic regions. Once so defined, in theory the "abnormal" brain area could be surgically modulated for clinical benefit.

However, it has become clear that psychiatric syndromes cannot be localized in a single, so-called "abnormal" brain region. OCD and MDD are not located in a specific region of the brain. Rather, mood and anxiety disorders involve immensely complex interconnected systems or networks of organization within the brain. The current approach in treating psychiatric disorders neurosurgically is to modulate specific targets or nodes within these networks in an effort to produce symptom relief.[2]

OCD. OCD is an often-debilitating psychiatric disorder that is characterized by anxiety-provoking intrusive thoughts (obsessions) leading to compulsive behaviors or mental rituals to temporarily decrease the anxiety provoked by the obsessions. The 12-month prevalence of OCD in the US is approximately one percent.[5] Symptoms generally begin in childhood and adolescence and often result in severe impairments in social and occupational functioning. Currently, behavioral psychotherapy and high-dose serotonergic antidepressant medications are considered to be the standard of care (APA Practice Guidelines, 2007). Follow-up studies, however, suggest suboptimal outcomes with current treatments with complete sustained remission of symptoms occurring in only 12 to 20 percent of patients receiving standard care.[6] With more aggressive or optimized pharmacotherapy and behavioral therapies, an estimated 10 percent of OCD patients still manifest severe, intractable illness.[7]

Etiology. The etiology of OCD is currently hypothesized to relate to a combination of genetic and environmental factors. Epidemiological studies, including family and twin studies, strongly support a genetic component for OCD.[8] Recent evidence highlights an abrupt onset of OCD symptoms in some cases in the context of group A beta-hemolytic streptococcal (GABHS) infection, implying that environmental factors may also contribute to the etiology of this disorder.[9]

Many authors have commented on obsessions and compulsions as being similar to involuntary motor behaviors. Freud hypothesized this connection in his psychoanalytic case report of the "Rat Man" stating, "a thought-process is obsessive or compulsive when, in consequence of an inhibition (due to a conflict of opposing impulses) at the motor end of the psychical system, it is undertaken with an expenditure of energy which is normally reserved for actions alone."[10] Other observers have also commented on the relationship of OCD to movement disorders, including Sydenham's chorea, Tourette's syndrome, Huntington's disease, and involuntary tics.[11]

Recent studies have highlighted genetic links between Tourette's syndrome and OCD, suggesting a similar neurological substrate for these disorders, specifically in the basal ganglia.[8] Metabolic and volumetric neuroimaging studies of patients with OCD reveal abnormalities in several areas of the brain, including the caudate nucleus of the basal ganglia, as well as the orbitofrontal cortex.[7] The cingulate gyrus also has demonstrated hypermetabolism in patients with OCD.[12]

Circuitry. Based on these findings, distinct neuronal circuits

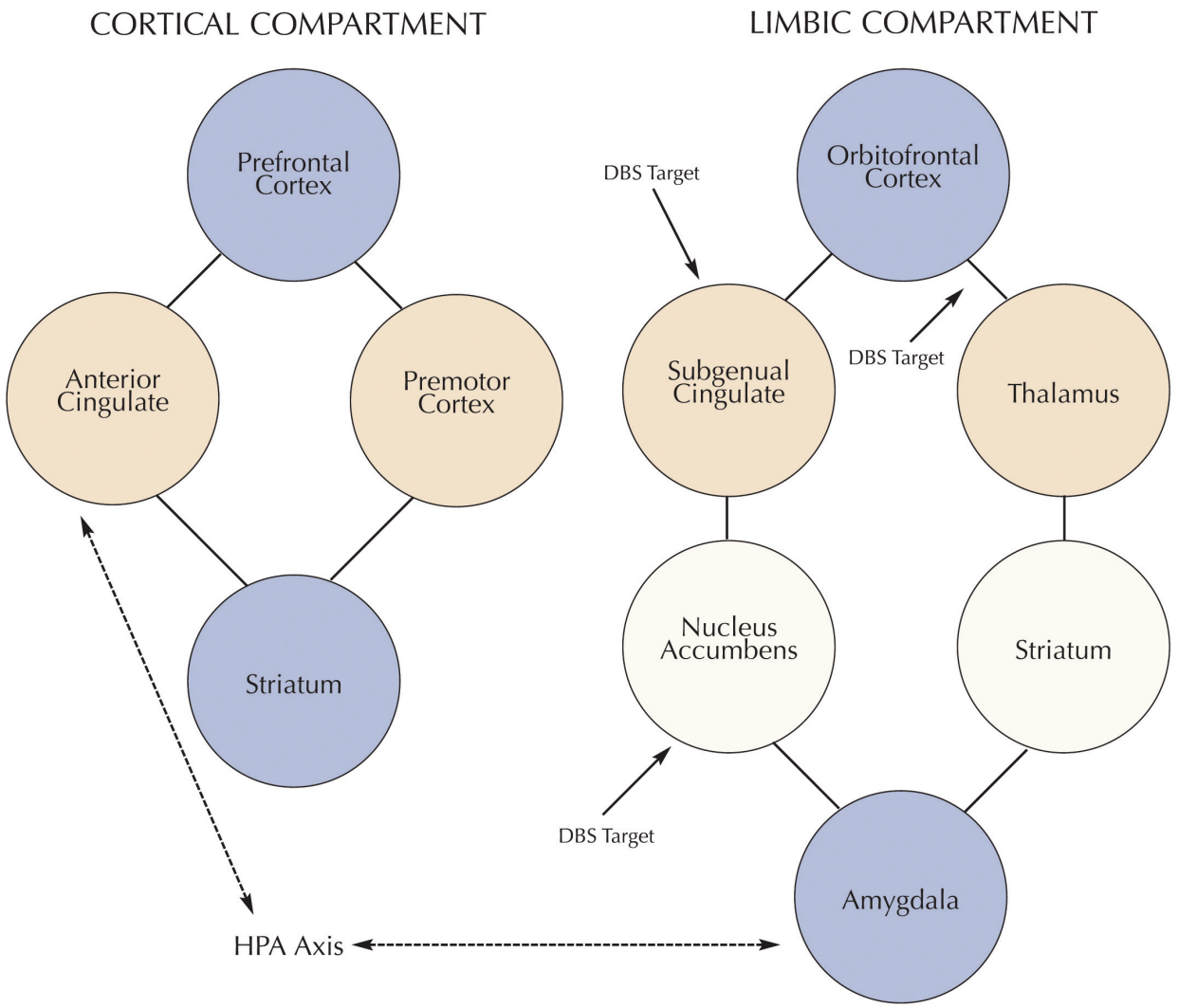

FIGURE 2. Neural circuitry of MDD and DBS targets. Circuitry is divided into cortical and limbic compartments with links between amygdala, ACG, and HPA axis forming a modulatory circuit between the cortical and limbic compartments. DBS interventions for MDD target nodes within the limbic compartment.

KEY: DBS: deep brain stimulation; MDD: major depressive disorder; HPA: hypothalamic-pituitary axis

have been implicated in symptoms of OCD involving feedback loops between the cortex, striatum, and thalamus. A multicircuit hypothesis of OCD states that the primary pathogenic mechanism is a dysregulation of the basal ganglia and limbic striatal circuitry working in concert with portions of the orbitofrontal and anterior cingulate cortex. Simplified, one can postulate the following three components to this model (Figure 1):[2]

1. A positive feedback loop from the orbital and prefrontal cortex to the thalamus via the anterior limb of the internal capsule. This cortico-thalamic pathway is excitatory and bidirectional.
2. A circuit linking the orbitofrontal cortex, caudate nucleus, globus pallidus, and the thalamus, known as the CSTC loop (cortex-striatum-thalamus-cortex). The overall output of this pathway is inhibitory and is thought to serve as a counterweight to the excitatory positive feedback loop as described in this article. This inhibitory pathway also receives serotonergic projections from the midbrain into the striatum.
3. A component linking portions of the limbic system, including the hippocampus, mammillary bodies and fornix, to the thalamus to the anterior cingulate cortex (ACC). These connections are hypothesized to contribute to the affective anxiety component of OCD symptoms.

Bringing together these three components of the circuit, OCD symptoms occur when there is an abnormal positive feedback in the orbito-fronto-thalamic circuit (# 1) that is, in turn, inadequately inhibited or modulated by the CSTC loop (# 2). One would then expect OCD symptoms to appear when the CSTC loop is abnormally decreased (too little inhibition), or when orbito-fronto-thalamic activity is abnormally increased (too much excitation).

From a therapeutic standpoint, increasing activity of the CSTC loop or decreasing activity of the orbito-fronto-thalamic loop would be expected decreased symptoms of OCD. Lastly, decreasing activity in the limbic component of the circuit (# 3) would decrease the distressing negative affects associated with obsessions.

MDD. MDD is a complex and heterogeneous disorder that is highly prevalent, recurrent, and disabling. It is a major cause of disability and functional impairment worldwide. A large proportion of sufferers, in the range of 20 to 40 percent, fail to benefit adequately from currently available treatments (e.g., antidepressants, psychotherapies, and electroconvulsive therapy), due to either a lack of efficacy or lack of tolerability of our current treatment options.[13]

The etiology of depression is complex and still only partially understood. Genetics, early environmental factors, and neurohormonal factors have all been implicated in the pathophysiology of depression. A neurological basis for depression has been posited based on certain disorders having a higher association with depression, as seen with left hemisphere strokes, certain types of epilepsy, Huntington's disease, and numerous other neurodegenerative disorders and injuries to discrete brain regions. Recent evidence suggests that specific neuronal pathways are implicated in depression. It is hypothesized that depressive symptoms occur when these neural systems do not exhibit appropriate, adaptive plasticity in response to external stimuli such as stressors. The dysfunction of specific pathways that help promote neuronal plasticity might also contribute to the depressive symptomatology.[14]

Systems model of depression. Depression is not the result of dysfunction in a single brain region or of a single neurotransmitter system. It can instead be conceptualized as a systems-level disorder affecting discrete but functionally integrated pathways. The symptoms of depression are not simply the result of one or more of these pathways not functioning appropriately, but also a failure of the other components of the system to maintain homeostasis in times of increased stress to the organism.[15]

Circuitry. Neurobiological correlates of depressive illness can be grouped into the following three main components: cortical, subcortical, and limbic (Figure 2):

1. Cortical component. This component appears to give rise to the psychomotor and cognitive aspects of depressive symptoms and consists of the prefrontal cortex, the dorsal portion of the anterior cingulate gyrus, and areas of the premotor cortex. This cortical component has access to the striatum and then creates a feedback loop via the thalamus.
2. Subcortical component. This component involves the affective experiencing of depressive symptoms, including anhedonia and sadness. This aspect of the neural circuit includes, among others, the subgenual anterior cingulate (Brodman's area 25), the orbitofrontal cortex, and limbic structures in the brain involved with negative emotions, including the nucleus accumbens and amygdala. This component also interacts with the striatum and subsequently the thalamus to create a loop. Brain imaging research and functional blood flow studies (positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) support depressive illness involving decreases in cortical regions with relative increases in limbic areas.[11]
3. Modulatory component. It is postulated that a modulatory component regulates the corticol and subcortical circuits and includes the critical neuroendocrine aspects of depressive symptoms. This "modulating pathway" involves the amygdala, pregenual anterior cingulate cortex, and the hypothalamic-pituitary-adrenal axis. It is hypothesized that it mediates the cortical and limbic circuits via inhibitory projections to these circuits.[2]

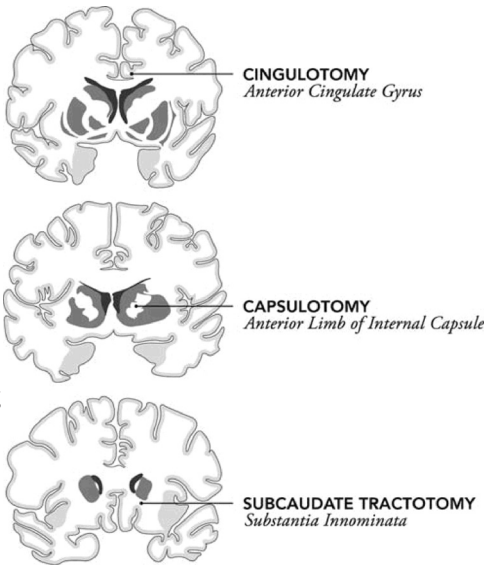

FIGURE 3. Sites of lesioning neurosurgical procedures for OCD and MDD. Limbic leucotomy combines the cingulotomy and subcaudate tractotomy procedures. [Adapted from Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* 2007;61(1):1-11]

NEUROSURGICAL INTERVENTIONS IN OCD AND MDD

Frontal leucotomy, the first applied neurosurgical procedure for psychiatric symptoms, was a gross method of interrupting the white matter tracts associated with the frontal cortex. Unfortunately, such procedures were performed indiscriminately without careful patient selection and were associated with serious neuropsychiatric morbidity. Recent approaches to treating treatment-refractory patients with neurosurgery differ substantially from these early interventions. Surgery is reserved for only the most severe of cases, when psychopharmacological and

or depression. On the basis of standard outcome measures, 36 to 50 percent of patients were considered to be treatment responders.[26] A recent study by Cho, et al., of 16 patients with intractable major affective disorders who underwent a limbic leucotomy, followed patients for seven years post-surgery. In the seven-year follow-up, mean scores on the Hamilton Depression Rating Scale and the Beck Depression Inventory declined significantly from 42±5.76 to 20±11.98 ($p<0.01$) and from 32±9.13 to 19±14.29 ($p<0.05$), respectively. There was no surgical mortality, and only three patients experienced temporary minor complications.[27]

Neuromodulation. Deep brain stimulation has several advantages over the lesioning procedures as just described. Surgeons using DBS can potentially achieve a clinical effect without producing an irreversible lesion. In DBS procedures, stimulation electrodes are implanted into specific brain regions and continuous electrical high frequency stimulation is delivered from an implanted, externally programmable pulse generator, similar to a cardiac pacemaker. DBS is reversible in that the stimulator can be turned on or off, and the output of the device and stimulation can be controlled at the discretion of the clinician. This also allows researchers to create sham conditions that allow for blinded placebo controlled trials, a method that is unavailable for practical and ethical reasons in lesioning operations. However, DBS still requires neurosurgery and has the potential for serious medical and neurological side effects. Symptomatic hemorrhage, infection, and seizure may occur in 1 to 4 percent of cases, but death is exceedingly rare.[28]

Contemporary use of clinical brain stimulation began in 1987 with Benabid, et al., reporting on the first successful use of thalamic DBS as a treatment for Parkinson tremor.[28] The subthalamic nucleus (STN) subsequently became a prime target in Parkinson's disease, with the finding that STN lesions reversed motor signs of Parkinsonism in experimental animals. Currently, DBS is FDA approved to treat Parkinson's disease and essential tremor. The mechanism of action of DBS is still unknown. Because clinical effects of DBS are similar to lesioning neurosurgery, it is hypothesized that DBS disrupts pathological neural activity, although there are several competing hypotheses regarding how this occurs.[29]

DBS in OCD. Recent trials of deep brain stimulation in OCD at several targets have indicated distinct benefit. One target is the anterior limb of the internal capsule, the site used in capsulotomy. Targeting of the anterior capsule is believed to disrupt activity in the loop fibers that connect the cortex with the thalamus, thus, in theory, disrupting that pathological circuit.

Greenberg, et al., reported on results from data collected by four groups, which worked in collaboration over eight years, for a total of 26 patients.[30] The percentage of patients meeting the full response criterion (≥35% YBOCS decrease) increased from 28 percent at one month to 61.5 percent at last follow-up. Conversely, the percentage with less than a 25-percent YBOCS decrease (no response) declined from 68 percent at one month to 27 percent at last follow-up. Overall, a total of 73 percent of patients had at least a 25-percent YOBCS improvement at last follow-up; a large majority of those improvements were a 35-percent or greater YBOCS reduction. Depression and anxiety also improved, as did self care, independent living, and work, school and social functioning. Surgical adverse effects included two asymptomatic, intracerebral hemorrhages, a single seizure, and a superficial wound infection. Device-related adverse events included a break in a stimulating lead and extension wire requiring a replacement in one patient each. Psychiatric adverse effects included transient hypomanic symptoms and worsened depression and OCD when DBS was interrupted by stimulator battery depletion.

Abelson, et al., examined the effects of DBS for treatment-refractory OCD in four patients with leads placed bilaterally in the anterior limbs of the internal capsule in a blinded, on-off design, with one patient experiencing substantial benefit in mood, anxiety, and OCD symptoms both during the blinded study and open, long-term follow-up. One patient committed suicide despite her OCD symptoms improving as per self report. One patient showed moderate benefit during open follow-up.[31] Other small case series and a case report have reported benefit.[32,33] Other brain regions have also received attention, including the nucleus accumbens with one case series reporting observed, but not quantified, clinical improvement in three out of four patients.[34]

DBS in depression. Based on neuroimaging findings that implicate hyperactivity of the subgenual cingulate region (BA 25) in treatment-resistant depression and association of decreases in cg25 activity with clinical improvement, Mayberg and colleagues targeted this area in a study of six patients implanted with bilateral leads in this area.[35] At one month postoperatively, 2 of the 6 patients met the criteria for clinical response, which was defined as a decrease in the Hamilton Depression Rating Scale (HRDS-17, also known as HAM-D-17) of 50 percent or more from the pretreatment baseline. At the six-month study endpoint, antidepressant response was maintained in four subjects (66%). Three of these responders attained remission or near remission of illness. From a safety standpoint, two of the patients developed persistent wound infections and required explantation of the device.

Another site utilized in DBS for depression is the nucleus accumbens, a site implicated primarily in the reward systems of the brain. Schlaepfer, et al., have reported on three patients suffering

psychotherapeutic alternatives have been utilized with no benefit, and a detailed informed consent process, which involves both patient and family, are central.

Stereotaxis. Advances in neurosurgery now allow precise lesioning techniques via stereotaxis. Stereotaxis is the method by which neurosurgeons visualize the brain as volume in a three-dimensional space. The brain is then referenced to a specific coordinate system that allows for precision in reaching subcortical brain structures with minimal disruption of the surrounding tissue. Neurosurgeons currently use stereotactic techniques with computer-based functional neuroimaging and physiologic recordings to allow for submillimeter accuracy.[2] Currently, there are four ablative neurosurgical procedures utilized for treatment-refractory OCD and MDD: cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. Each of these procedures seeks to modulate the activity of the neurocircuitry described previously, including the interactions between various components of the frontal cortex and cingulate cortex and their interactions with the basal ganglia and the thalamus.

Lesioning procedures.

Cingulotomy. Neurosurgery of the cingulate gyrus has been reported since the 1940s, with Freeman and Watts reporting that severing fibers from the cingulate gyrus led to an improvement of anxiety symptoms and Whitty reporting a bilateral resection of the cingulate gyrus in 1952.[2] Currently stereotactic, bilateral lesioning of the cingulate gyrus is the most common neurosurgical procedure for treatment refractory psychiatric syndromes, specifically OCD. The cingulate gyrus is critical in cortico-striatal-thalamic pathways in mediating the transfer of information from the anterior cingulate cortex to the orbitofrontal cortex and to the limbic system.[16] In a cingulotomy, the anterior portion of the cingulate gyrus is lesioned, interrupting tracts between the cingulate gyrus and the frontal lobes, eliminating the efferent projections of the anterior cingulate cortex.[11] See Figure 3.

Results. One retrospective study demonstrated a mean 30-percent improvement in patients (n=33) who underwent cingulotomy for OCD.[17] Eighteen of these patients were included in a follow-up study with a 30-percent success rate.[18] Jung, et al., followed 17 patients with treatment refractory OCD who had received bilateral stereotactic cingulotomy for a period of 24 months and reported response in eight patients (47%) with a mean reduction of 48 percent in their baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) scores.[19]

In a recent prospective study, Dougherty, et al.,[18] reported on 44 patients undergoing cingulotomy for OCD, with 32 percent meeting criteria for response and 14 percent meeting criteria for partial response at 32 weeks post-surgery. Cosgrove, et al., recently reported on the safety of over 800 cingulotomies performed over a 40-year period at Massachusetts General Hospital, with no deaths and only two infections being reported.[20] For intractable major depression, response rates have been high, with a 68-percent response rate (n=198) reported by Ballantine[21] and a 60-percent response rate (n=34) by Greenberg, et al.[22] A recent study by Steele, et al., reported on eight patients with treatment refractory MDD undergoing anteriorly placed cingulate cortex lesions with beneficial results.[21]

Capsulotomy. Developed by Lars Leksell and Jean Talairach in the 1940s, the anterior capsulotomy has been in use for treatment refractory OCD and depression for over five decades.[2] This surgery targets the anterior limb of the internal capsule, which serves as a relay route between cortical structures and the thalamus. A prospective study of 15 patients who underwent bilateral anterior capsulotomy for OCD reported that 53 percent of the patients showed a 33-percent reduction in symptoms, 29 percent of the cases experienced a 50-percent reduction, and 17 percent were improved by as much as 66 percent. Complications were observed in three cases: one with transitory hallucinations, one with a single epileptic seizure, and one case who developed a progressive behavior disorder that became permanent.[23] A more recent study by Liu, et al., reported on 35 patients with treatment refractory OCD who underwent stereotactic bilateral capsulotomy with a three-year follow-up. Results were robust: Twenty patients became OCD symptom-free (57%), 10 experienced significant improvement (29%), and five experienced no meaningful improvement (14%).[24]

Subcaudate tractotomy. Another neurosurgical procedure that is hypothesized to exert its effects by interrupting the relay between the cortex and thalamus via the striatum is subcaudate tractotomy. This procedure was developed by in London by Knight in 1965 and has primarily been used for treatment refractory depression. The target site is a region of white matter localized beneath the head of the caudate known as the substantia innominata.[2] Poynton, et al., prospectively studied 23 patients undergoing a stereotactic subcaudate tractotomy for treatment refractory depression. There was no significant correlation except for the six-month assessment when lower Hamilton scores were found to be associated with better global outcome.[25] Greenberg, et al., reviewed outcomes with subcaudate tractotomy that included 1,300 patients and reported 40 to 60 percent of patients benefiting.[22]

Limbic leucotomy. This procedure was developed by Kelly and Richardson in the 1970s. The surgery is essentially a combination of subcaudate tractotomy and cingulotomy. Montoya, et al., conducted preoperative evaluations and postoperative follow-up assessments of efficacy and complications for 21 patients who underwent limbic leucotomy for OCD

from treatment-resistant depression who had not responded to trials of pharmacotherapy, psychotherapy, and electroconvulsive therapy, and were implanted with bilateral DBS electrodes in the nucleus accumbens.[36] Stimulation parameters were modified in a double-blind manner, and clinical ratings were assessed at each modification. Clinical ratings improved in all three patients when the stimulator was on, and worsened in all three patients when the stimulator was turned off. Effects were observable immediately, and no side effects occurred in any of the patients.

Lastly, in a third target area, in the largest study of DBS in MDD reported to date, 15 chronically depressed patients underwent bilateral DBS implantation in the ventral internal capsule/ventral striatum (VC/VS). Responses were seen in 7/15 (47%) at six months, 5/11 (45.5%) at 12 months, and 8/15 (53.3%) at last follow-up. This was accompanied by long-term improvements in depression severity, functioning, quality of life, and short-term memory. Safety outcomes were good with no hemorrhages, infections, or neurological deficits reported.[37]

CONCLUSIONS

From this overview of surgical procedures and DBS techniques for OCD and treatment-resistant depression, it is clear that although much remains unknown about the underlying neurobiology of these disorders, progress in helping the most severely afflicted is being made. Currently, large scale, multicenter, sham-controlled trials for DBS in major depression are being planned in the US. Thus, it is likely that further progress by means of functional neurosurgery approaches will be made before too long in this field. If this occurs, it will be of great benefit to the many patients suffering with OCD and MDD who have not responded to traditional treatments and remain extremely disabled by their illnesses.

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ATTACHMENT #5

LONG-TERM OUTCOME IN ADULTS WITH OBSESSIVE-COMPULSIVE DISORDER

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Abstract

Background—Obsessive-compulsive disorder (OCD) is a chronic condition that often produces lifelong morbidity, but few studies have examined long-term outcome (greater than 5 years) in adult patients. Available studies suggest that 32–74% of adult OCD patients will experience clinical improvement over the long term. However, these studies were conducted before validated OCD rating scales were established and the development of evidence-based treatments for OCD.

Methods—We investigated the 10–20 year outcome of 83 of 165 eligible subjects previously enrolled after participation in placebo-controlled trials of serotonin reuptake inhibitor (SRI) medications for OCD. We examined the association between clinical characteristics at initial assessment and OCD symptom severity at follow-up. We hypothesized that primary OCD symptom dimension and initial response to pharmacotherapy with serotonin reuptake inhibitors would be associated with later symptom severity.

Results—Only 20% (17 of 83) of subjects had experienced a remission of their OCD symptoms at follow-up (Y-BOCS ≤ 8). Forty-nine percent (41 of 83) of subjects were still experiencing clinically significant OCD symptoms. Response to initial SRI pharmacotherapy was significantly associated with long-term outcome: 31% (13 of 42) of subjects who responded (CGI < 3) to initial SRI pharmacotherapy were remitted at follow-up, compared to 12% (3 of 25) of partial responders and none of the 16 subjects who had no response to initial SRI pharmacotherapy. We did not find a significant association between long-term clinical outcome and any of the OCD symptom dimensions.

Conclusion—Despite the introduction and dissemination of several evidence-based treatments for OCD, most adult OCD patients do not achieve remission. Initial response to pharmacotherapy was strongly associated with long-term outcome.

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Keywords

OCD/obsessive compulsive disorder; pharmacotherapy; anxiety/anxiety disorders; treatment; treatment resistance

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric disorder characterized by obsessions (recurrent or persistent unwanted thoughts, images, or impulses) and/or compulsions (repetitive behaviors or mental acts), which are often performed to relieve anxiety associated with underlying obsessions. Once believed to be rare, OCD is now considered one of the most common psychiatric illness, affecting 1.8–2.5% of the general population.[1–5] Patients with OCD experience an overall lower quality of life as evidenced by significantly poorer academic functioning, increased occupational problems, and interpersonal issues.[6]

OCD is often characterized by a fluctuating course but generally is unremitting with low remission rates. In a follow-up study of 144 patients treated for OCD in Sweden, only 20% experienced remission after 40 years.[7] Although a substantial proportion (83%) experienced a decline in symptom severity from the point of their initial hospitalization, over half (52%) still had clinically significant OCD symptoms 40 years later. Other retrospective studies from the same time period followed-up with patients at time intervals of 5 years or longer and found that 32–74% of OCD patients demonstrated some improvement in symptoms.[8–13]

While these studies added substantially to our understanding of the natural history of OCD, they had several methodological limitations: (1) the studies did not use standardized rating scales of OCD severity such as the Yale-Brown obsessive compulsive scale (Y-BOCS), which was introduced in 1989. Such scales allow for more objective measure of symptom improvement.[14, 15] (2) There has been substantial diagnostic refinement since these initial studies were conducted. Most specifically, diagnostic clarification has resulted in the disentangling of OCD from obsessive-compulsive personality disorder. (3) Many of these studies relied exclusively on retrospective data collection. (4) When prospective studies were conducted, follow-up ratings were not conducted by individuals blinded to symptom severity at the time of initial evaluation, and thus any conclusions drawn concerning predictors of outcome are highly prone to bias.

Perhaps more importantly, improvements have been made in our understanding and treatment of OCD since these original studies were performed. The discovery and use of serotonin reuptake inhibitors (SRIs), especially the selective serotonin reuptake inhibitors (SSRIs), has dramatically improved patient outcome. Between 40–60% of OCD patients given an adequate trial of a SSRIs experience a response to treatment.[16] Effective behavioral treatment involving cognitive-behavior therapy (CBT) with exposure and response prevention has become well established over the past two decades and further has improved outcomes, at least in the short term. Few studies have assessed long-term outcomes since the widespread adoption of evidence-based treatments.[17] Therefore, most of the studies of the long-term natural history of OCD described above are outdated. The few studies specifically examining predictors of long-term treatment outcome in adults with OCD have failed to reach any consensus regarding predictors of poor outcome.[7, 18]

We investigated predictors of clinical outcomes in a sample of OCD patients enrolled in pharmacotherapy trials at our site from 1986–1995 who received a follow-up interview to assess long-term outcome from July 2006–July 2007. We sought to determine whether the

following variables are related to long-term outcome: age of onset, symptom dimensions, presence of comorbid conditions, early response to SRI treatment, and duration of illness. We hypothesized that a nonresponse to initial SRI trial would be associated with reduced rates of long-term remission (Y-BOCS ≤ 8). Previous meta-analysis has demonstrated an association between poor medication treatment response and long-term outcome in pediatric OCD.[19] We also hypothesized that those with predominant symptoms in the aggressive symptom dimension would show higher rates of remission. Previous research had demonstrated an association between predominant OCD symptoms in the aggressive dimension and improved short-term pharmacological response in this same study population.[20]

METHODS

SUBJECTS

One hundred and sixty-five subjects who were diagnosed with OCD and participated in a SRI clinical trial between 1986 and 1995 at the Yale OCD Research Clinic were eligible for this study. Each subject received a trial of at least one of three SRI medications (fluoxetine, fluvoxamine, clomipramine) for at least 8 weeks at the maximum tolerated dose as part of at least one of three randomized clinical trials (RCTs).[21–23] Eligible subjects were recontacted 10–20 years after their trial participation (and 10–15 years after their last contact in our clinic) and asked to participate in a follow-up clinical interview to assess their current level of OCD symptom severity and of related conditions. Eighty-three (51%) of 165 subjects contacted agreed to participate in follow-up interviews. Table 1 depicts the characteristics of participants and nonparticipants in the follow-up study.

ASSESSMENT

Baseline Assessment—At baseline, as part of their participation in an RCT of SRI pharmacotherapy for OCD, each subject had a clinical interview and was diagnosed with OCD by an expert clinician. Each subject was additionally asked to describe their major and minor OC symptoms based on the 15 categories of the Y–BOCS symptom checklist. Based on these answers, subjects were rated in the four previously described OC symptom dimensions[24] as having either no symptoms present in a particular dimension (coded as a 0), any symptoms present in a particular dimension (coded as 1) or predominant symptoms in a particular dimension (the most impairing of the four dimensions, coded as 2). Medication response for all subjects was assessed using the clinical global improvement scale (CGI).[25] Subjects were rated on response to the first SRI treatment they received at our research clinic. Subjects were asked about other clinical aspects of their OCD history such as age of onset, duration of illness and past treatment history. Comorbid conditions were determined based on the judgment of an MD-level clinician performing a clinical evaluation.

Follow-Up Assessment—Subjects who agreed to participate were brought back to the Yale OCD clinic or assessed by phone from July 2006–July 2007. Participants were interviewed by an experienced clinician about their current symptoms and previous treatments. Raters were blind to the specific answers and ratings conducted at baseline assessment and study hypotheses. The interviews took roughly 3 hr, and included both self-reports and evaluations done by the clinician. The interview asked questions about the current severity of the subject's OCD symptoms, measured by the Y-BOCS,[14, 15] as well as other related anxiety conditions, measured by the HAM-A (Hamilton anxiety rating scale).[26] The subject's depression ratings were taken using the HAM-D (Hamilton depression rating scale).[27] Previous and current medications were recorded as well.

Data Analysis—All data analysis was performed in SPSS 19.0 for Windows. For a priori hypothesis testing, we used linear regression analysis. In linear regression models, OCD symptom severity at follow-up (Y-BOCS) was the dependent variable and gender, baseline age, and duration of follow-up were included as covariates. Variables of interest were added separately as independent variables to the model. Variables of interest included: Primary OCD symptom dimensions (forbidden thoughts [aggressive and sexual/religious separately], cleaning, symmetry, and hoarding), comorbid conditions (major depression, other anxiety disorders, substance abuse, eating disorders, and tic disorders), response to first SRI trial (responder (CGI ≤ 2), partial responder (CGI = 3), or nonresponder (CGI ≥ 4)), age of onset and duration of illness at baseline assessment. We had two a priori hypotheses that (1) nonresponse to initial SRI trial would be associated with reduced rates of long-term remission and that those with (2) predominant symptoms in the aggressive dimension would show higher rates of remission. We set the significance threshold for a priori hypothesis testing at $P < .025$ to account for our two hypotheses using a Bonferroni correction. By contrast, we set our threshold for statistical significance at $P < .05$ for all exploratory analyses. The variables examined in exploratory analysis were OCD symptom dimensions (other than aggressive dimension symptoms which was a primary hypothesis), comorbid conditions, age of OCD onset, and duration of illness at baseline assessment. Given our nine additional exploratory models, there was a significant likelihood of false-positive error in exploratory hypothesis testing, and thus all significant exploratory findings should be regarded as exploratory. Given our nine exploratory hypothesis tests, there was a 37% chance of finding at least one significant result at the $P < .05$ level. In order to express significant results in the most clinically salient terms, we also reported the likelihood of remission for subjects and proportion of individuals with clinically significant OCD symptoms. The threshold for OCD remission at follow-up was a Y-BOCS ≤ 8 and the threshold for clinically significant symptoms at follow-up was a Y-BOCS ≥ 16.

RESULTS

SUBJECTS

Eighty-three (51%) of 165 eligible subjects agreed to participate in follow-up interviews. There were no significant differences at baseline assessment between participants and nonparticipants (Table 1).

LONG-TERM OUTCOME

Seventeen (20%) of 83 subjects achieved OCD remission (Y-BOCS ≤ 8) 11.7 ± 1.2 years after initial assessment. Forty-one (49%) of 83 subjects were still experiencing clinically significant OCD symptoms (Y-BOCS ≥ 16) at follow-up. These individuals had severe enough OCD symptoms at follow-up that they could have qualified for another clinical trial for OCD.

TREATMENT STATUS

Of the 83 participants completing the follow-up assessment, 59 (71%) were taking an SSRI or SNRI at follow-up (11 [65%] of the remitted cases; and 28 [68%] of the subjects with clinically significant symptoms at follow-up). Twenty-eight subjects (34%) reported receiving antipsychotic augmentation treatment for OCD and only 10 subjects (12%) were currently taking antipsychotic medications (1 [6%] of the remitted cases; and 6 [15%] of the subjects with clinically significant symptoms at follow-up). Forty-two participants (51%) reported previously receiving cognitive behavioral therapy for OCD involving exposure and response prevention. Only 7 subjects (8%) reported currently being enrolled in CBT for OCD (0 of the remitted cases; and 5 [12%] of the subjects with clinically significant symptoms at follow-up).

OCD SYMPTOM DIMENSION

There were no significant associations between primary OCD symptom dimension at baseline and severity of OCD at follow-up assessment as measured by YBOCS. Symptoms in the aggression dimension were associated with improved OCD symptoms at trend levels ($\beta = -0.35$, $t = -2.0$, $P = .055$) but not at the threshold for statistical significance in our study. Primary symptoms in the following symptom categories were not associated with OCD severity at follow-up assessment: cleaning ($\beta = -0.12$, $t = -0.7$, $P = .50$), sexual/religious ($\beta = -0.11$, $t = -0.6$, $P = .53$), symmetry ($\beta = 0.27$, $t = 1.5$, $P = .14$), and hoarding ($\beta = 0.16$, $t = 0.9$, $P = .38$). There was also no significant association with OCD severity at follow-up when sexual/religious and aggressive symptoms were combined into a single forbidden thoughts dimension ($\beta = -0.16$, $t = -1.4$, $P = .16$).

INITIAL RESPONSE TO PHARMACOTHERAPY WITH SEROTONIN REUPTAKE INHIBITORS

We found a significant association between improved initial response to SRI pharmacotherapy and severity of OCD at follow-up assessment. None of the 16 individuals who were rated as nonresponders to their initial SRI trial had OCD symptoms that remitted by follow-up assessment (Y-BOCS ≤ 8). By contrast, 31% (13 of 42) of individuals who showed a full response to their first SRI trial were remitted at follow-up assessment. Twelve percent (3 of 25) of partial responders were remitted at follow-up. Figure 1 depicts the long-term outcome of subjects stratified by their initial response to SRI pharmacotherapy.

Similarly, the likelihood that an individual would still have OCD symptoms severe enough to qualify for another OCD treatment study at follow-up (Y-BOCS ≥ 16) was significantly associated with initial SRI response. Seventy-five percent (12 of 16) of individuals who did not respond to their initial SRI had severe enough OCD symptoms to qualify for another OCD treatment study at follow-up. By contrast, 38% (16 of 42) of full responders and 52% (13 of 25) of partial responders to initial SRI pharmacotherapy had clinically significant OCD symptoms at follow-up.

COMORBID PSYCHIATRIC CONDITIONS

We found no association between comorbid conditions at baseline and follow-up OCD severity. No association was demonstrated for depression ($\beta = 1.78$, $t = 0.94$, $P = .35$), eating disorder ($\beta = -5.11$, $t = -1.16$, $P = 0.25$), substance abuse ($\beta = 0.26$, $t = 0.12$, $P = 0.90$), tic disorder ($\beta = -1.63$, $t = -0.41$, $P = .69$), or anxiety disorders ($\beta = -1.88$, $t = -0.65$, $P = .52$).

AGE OF ONSET AND DURATION OF ILLNESS

We demonstrated no significant association between age of OCD onset (($\beta = -0.20$ $t = 1.55$, $P = .12$) or duration of illness ($\beta = 0.92$, $t = 0.92$, $P = .36$) at baseline and follow-up OCD severity.

DISCUSSION

This study examined long-term clinical outcomes in OCD patients since the introduction of modern pharmacological and psychotherapeutic interventions with demonstrated efficacy. Unfortunately, our results confirm that, despite the availability of such treatments, a very small proportion of adults with OCD achieve clinical remission over the long term. We found that initial response to SRI pharmacotherapy was strongly predictive of long-term outcome. Thirty-one percent of responders to their initial SRI trial achieved remission at follow-up (defined as Y-BOCS ≤ 8), compared to 0% of nonresponders. These results are similar to the findings of a recent 2-year prospective longitudinal outcome study in adults with OCD.[28] That study also reported a strong association between initial treatment

response and 2-year outcome.[28] Our results expand upon finding and suggest that short-term treatment response is associated with more favorable long-term clinical outcomes a decade or longer after treatment. Although much of this association is likely do to efficacy of pharmacotherapy over the long term, it remains quite possible that other factors besides direct medication effects may account for this association. For instance, patients who experience a robust initial response to medication may also be more likely to engage in future treatment trials or ongoing clinical treatment for OCD than patients who do not respond to initial treatment. Ongoing clinical treatment and multiple therapies may be associated with improved likelihood of remission in OCD.

OCD symptoms in the aggression dimension were associated with decreased severity of OCD symptoms at follow-up at trend levels. However, this finding was likely the result of confounding because these symptoms were highly correlated with initial treatment response previously in this same sample.[20] We found no correlation with other clinical factors such as OCD symptom dimensions, baseline levels of comorbid psychiatric illnesses, the age of onset, or the duration of illness.

Remission of symptoms leads to a better quality of life, improved social functioning and better patient satisfaction with treatment and life. Remission, not response, should be the goal for any psychiatric condition. This study highlights the need for more effective treatments in adults with OCD by suggesting that clinical remission is experienced by only a minority of patients seeking treatment for OCD.[28] In this regard, a number of promising avenues are under investigation. Glutamate-modulating agents represent a promising new area for pharmacotherapy in refractory cases, although large, multi-center, double-blind, placebo-controlled studies are lacking.[29–42] Neurosurgical techniques such as deep-brain stimulation or anterior capsulotomy remain a treatment option for the most severely impaired OCD patients.[43]

Given the potential clinical relevance of our findings, it is important to highlight several study limitations. First, OCD severity and medication improvement at baseline was assessed using the CGI and the not current gold-standard measurement of OCD severity—the Y-BOCS. Y-BOCS ratings were not available on a large proportion of our sample at baseline (most specifically subjects who participated in the earlier trials) as they were not entered into electronic clinical databases and physical research charts had been destroyed. Therefore, the assessment of the subjects' severity of OCD at the follow-up assessment was measured differently than at the baseline assessment. Second, there was not a full participation rate in the follow-up study, leaving a smaller and potentially biased sample for the follow-up assessment. We did not find any significant differences between participants and nonparticipants in their baseline assessment; but this does not entirely exclude the possibility that the groups may have differed during the follow-up period. The modest sample size for this follow-up sample also limited our statistical power, especially with regards to the analysis of symptom dimension used to predict long-term outcome. These power issues were particularly apparent when examining hoarding symptoms as a predictor of long-term outcome as few subjects had primary hoarding symptoms.

Additionally, we could not control for treatments that subjects received during the follow-up interval. We did not have detailed prospective information on symptom severity before and after receiving individual treatments over this time period. If we had this detailed prospective information, we could have adjusted for treatment as a time-dependent covariate. However, we only had reliable information on current and past treatments received at baseline and follow-up, which is not appropriate for use as a covariate because the decision made by subjects to start or continue treatments (such as CBT or SRI pharmacotherapy) is not made at random and is influenced by both initial treatment efficacy

and residual OCD symptom severity. In our sample, subjects receiving SRI pharmacotherapy and/or CBT at follow-up had higher Y-BOCS scores than those not receiving treatment suggesting that subjects with greater residual OCD severity were self-selected to be more likely to engage in ongoing treatment. Specifically, the average Y-BOCS of 19.9 ± 6.2 in subjects receiving CBT at follow-up compared to Y-BOCS = 15.3 ± 8.5 in subjects not receiving CBT. The average Y-BOCS was 15.9 ± 8.3 in subjects taking an SRI at follow-up compared to15.3 ± 8.8 in subjects who were not. The inability to adjust for treatments received during the follow-up interval remains a significant limitation of our study that cannot be reconciled through statistical analysis of the available data.

Additionally, we could not control for treatments that subjects received during the follow-up interval. We were unable to control for treatments being received at follow-up because we did not have detailed prospective information on symptom severity before and after receiving treatments. If we had this detailed prospective information, we could have adjusted for treatment as a time-dependent covariate. However, we only had reliable information on current and past treatments received at baseline and follow-up. The decision made by subjects to start or continue treatments (such as CBT or SRI pharmacotherapy) is not made at random and is influenced by both initial treatment efficacy and residual OCD symptom severity. Thus there is likely a self-selection bias toward more severely affected subjects receiving treatment at follow-up. This self-selection bias in treatment selection at follow-up is evidenced in our study by the worse OCD symptom severity experienced by subjects receiving SRI pharmacotherapy and/or CBT at follow-up than those subjects who were not. (Average Y-BOCS of 19.9 ± 6.2 in subjects receiving CBT at follow-up compared to Y-BOCS = 15.3 ± 8.5 in subjects not receiving CBT. The average Y-BOCS was 15.9 ± 8.3 in subjects taking an SRI at follow-up compared to 15.3 ± 8.8 in subjects who were not.) Adjusting for treatment at follow-up would have produced spurious analyses whereby known effective treatments for OCD (such as SRI pharmacotherapy or CBT) were being adjusted for as negative risk factors regarding outcome. The inability to adjust for treatments received during the follow-up interval remains a significant limitation of our study that cannot be reconciled through statistical analysis of the available data.

Our finding that OCD patients who do not respond to their first trial of SRI medications rarely achieve remission of symptoms over the longer term has important implications for both treatment and research. It would be of interest to investigate whether response to an initial round of CBT similarly predicts long-term outcome. Future investigations should focus on replication of our results using more nuanced baseline assessments involving the Y-BOCS but extended over longer durations than well-conducted previous longitudinal studies. It is also critical that we develop new treatments that help the large proportion of patients who do not experience adequate symptom relief from SRIs.

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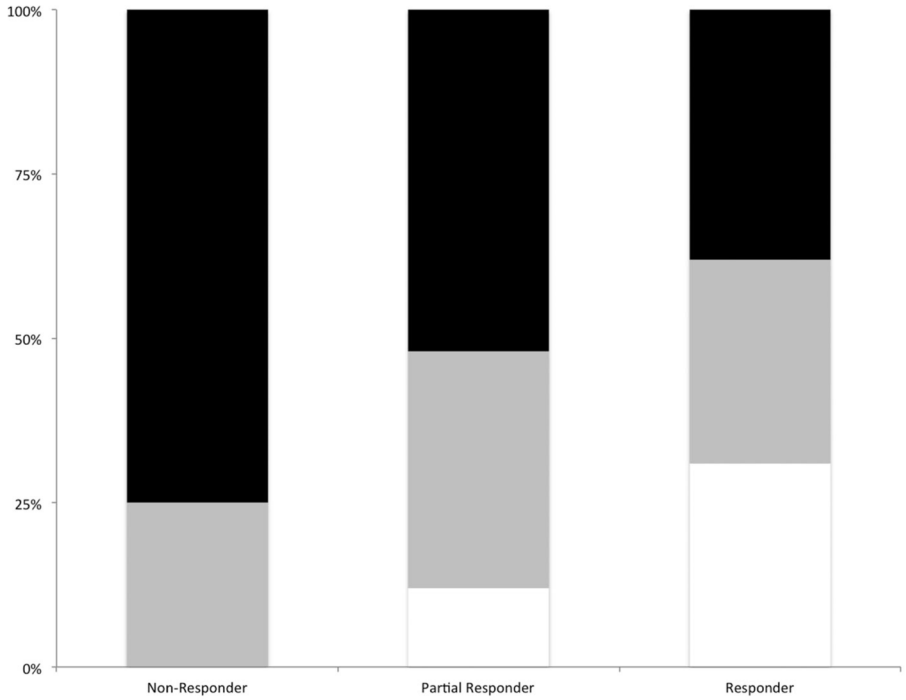

Figure 1.

Long-term outcome in adults with OCD stratified by initial response to SRI pharmacotherapy. Initial response to SRI pharmacotherapy was significantly associated with long-term outcome. Proportion of OCD patients remitted at follow-up is shaded in white, subjects with subclinical OCD symptoms are shaded in gray and those with clinically significant OCD symptoms at follow-up are shaded in black.

TABLE 1

Comparison of baseline characteristics between participants and nonparticipants in follow-up assessment

	Participants (*N* = 83)	**Nonparticipants (*N* = 82)**
Baseline age	42.0 ± 9.9 years	39.7 ± 12.1 years
Age of OCD onset	23.4 ± 7.9 years	24.8 ± 9.7 years
Duration of illness	15.9 ± 11.9 years	12.4 ± 11.2 years
GAF	55.6 ± 11.7	55.0 ± 12.5
Lifetime comorbid disorders		
MDD	45% (*n* = 37)	37% (*n* = 30)
Anxiety disorder	12% (*n* = 10)	20% (*n* = 16)
Tic disorder	6% (*n* = 5)	4% (*n* = 3)
Eating disorder	8% (*n* = 7)	7% (*n* = 6)
Substance abuse	31% (*n* = 26)	34% (*n* = 28)
Initial SRI response		
Full response	51% (*n* = 42)	49% (*n* = 40)
Partial response	30% (*n* = 25)	29% (*n* = 24)
Nonresponse	19% (*n* = 16)	22% (*n* = 18)

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

The "Research" Challenge for Medical Marijuana:

Often, medical marijuana is held to the standards applied to traditional pharmaceutical drugs – a standard that is impossible for medical marijuana to achieve. The challenges are well highlighted in the article "Acute Effects of Cannabis on Symptoms of OCD" published by researchers at Washington State University (excerpt below).

> *"Trends toward the legalization of cannabis in North America make it particularly important to examine the potential short- and long-term effects of cannabis on mental health. However, while changes in laws have increased public access to a wide variety of cannabis-based products, the U.S. Drug Enforcement Administration (DEA) continues to classify cannabis as a Schedule 1 illicit drug. As a result of the strict regulation of cannabis by the U.S. federal government, all researchers at federally funded institutions must undergo lengthy legal and ethical approval processes before they can administer cannabis to humans. Additionally, per federal regulations, researchers administering cannabis must use cannabis supplied by the National Institute of Drug Abuse However, this research-grade cannabis is far less potent (rarely exceeding 10% THC) than the high potency products available to consumers through statewide legal cannabis markets. Indeed, cannabis flower exceeding 20% THC and cannabis concentrates containing over 60% THC are presently dominating the recreational cannabis markets. These federal restrictions have dramatically stalled the progress of research and have left us with an impoverished understanding of the potentially therapeutic effects of cannabis on OCD."*

The OMCIA asks the State Medical Board to take into consideration the inherent challenges associated with researching medical marijuana under the current federal prohibition when reviewing this petition and to strongly consider the actions of medical experts in other states with medical marijuana programs.

Article: The Endocannabinoid System: A New Treatment Target for Obsessive Compulsive Disorder? [10]

The article evaluates multiple animal and human studies that suggest the endocannabinoid system (ECS) may play a role in OCD and related disorders and may be a target for the development of novel medications. Dronabinol (tetrahydrocannabinol) has been demonstrated to beneficially impact patients with Tourette Syndrome* and reduce obsessive-compulsive behavior. The article also considers a 24-year old man who developed persistent obsessions and compulsions following a stroke, but did not respond to several high-dose medications including SRIs, antipsychotics, benzodiazepines, glutamate modulators, and mood stabilizers. The patient requested neurosurgical consultation for deep brain stimulator placement, but elected to receive dronabinol (20 mg daily) before surgery. Over the course of 2 weeks, the patient's Yale-Brown Obsessive Compulsive Scale score decreased from 39 to 10. The authors note

[10] Cannabis and Cannabinoid Research, November 2, 2019 "The Endocannabinoid System: A New Treatment Target for Obsessive Compulsive Disorder" Kayser et. al (Attachment #3)

that this correlated with a significant improvement in the patient's quality of life and his ability to participate in Cognitive Behavioral Therapy, which had previously been intolerable for him.

The article concludes that the endocannabinoid system appears to regulate anxiety and OCD symptoms, more specifically through modulation of the response to fearful stimuli.

*It should be noted that a significant overlap exists between tic disorders and OCD. Tourette syndrome is an approved condition in Ohio's medical marijuana program.

Article: Minnesota Department of Health Issue Brief – Obsessive-Compulsive Disorder

Following extensive review of the scientific literature, the Minnesota Department of Health added Obsessive-Compulsive Disorder as an approved condition to its medical marijuana program in November 2022. A copy of Minnesota's Issue Brief[11] developed by the Department of Health is attached.

Minnesota's list of nineteen approved conditions for its medical marijuana program closely mirrors Ohio, with the following fourteen conditions appearing in both states:

Alzheimer's disease
Amyotrophic lateral sclerosis (ALS)
Cancer
chronic pain
glaucoma
HIV/AIDS
inflammatory bowel disease, including Crohn's disease
PTSD
Seizures, including those characteristic of epilepsy
severe and persistent muscle spasms, including those characteristic of multiple sclerosis
sickle cell disease
terminal illness, with a probable life expectancy of less than one year, and
Tourette syndrome

It should be noted that Minnesota groups conditions differently than Ohio – with IBD and Crohn's counting as one condition in Minnesota and two conditions in Ohio (the same for HIV/AIDS and muscle spasms/MS). This brings the total like conditions to seventeen.

Five additional conditions have been approved by the Minnesota Department of Health that are not currently approved in Ohio including;

Autism spectrum disorder
chronic motor or vocal tic disorder
irritable bowel syndrome (new in 2022)
obsessive-compulsive disorder (new in 2022)
obstructive sleep apnea

[11] Minnesota Department of Health October 2022 Obsessive-Compulsive Disorder Issue Brief (Attachment #6)

The OMCIA strongly encourages the State Medical Board to ask colleagues at the Minnesota Department of Health to as their "expert reviewer" when further considering this petition to understand both the recent addition of Obsessive-Compulsive disorder and Irritable Bowel Syndrome (submitted separately to Ohio) to their medical marijuana program. These experts have considered the scientific literature in the context of approving the condition for real world use by medical patients and opted to add both conditions to Minnesota's program.

Article: Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder[12]

The goal of the study was to examine short-term effects and potential longer-term consequences of cannabis on the intrusions, compulsions, and anxiety symptoms characteristic of OCD, using an innovative methodology that allowed researchers at Washington State University to bypass federal restrictions imposed on researchers studying acute effects of the drug.

To skirt federal challenges, the researchers on this study utilized an app called Strainprint, which allows cannabis users in Canada to report their starting symptoms, the specific cannabis products and dose used, and the resulting impact those products had on their symptoms, to investigate the connection between cannabis and OCD in human subjects. The researchers tracked the responses of 87 individuals who self-identified as having OCD for over two years - looking specifically at inhaled cannabis use like vaping and smoking. Patients evaluated their starting symptoms prior to cannabis use, and the symptoms after cannabis use by responding to questions like "How intrusive are your thoughts?" or "How bad is your compulsive behavior" on a 0-10 scale.

Researchers then analyzed the data to see whether cannabis seemed to help or hurt when it came to managing OCD symptoms. The analysis revealed that cannabis use was tied to a reduction in OCD symptoms. In fact, most cannabis sessions recorded resulted in a reduction of symptoms. 95.4% of all sessions resulted in reduction of compulsions, 89.6% resulted in reduction of intrusive thoughts, and 93.8% of sessions resulted in reduction of anxiety.

On the other hand, only 1.9-3% of sessions resulted in a worsening of these symptoms (depending on the symptom). Ultimately, these patients reported an average 60% reduction in compulsions, 49% reduction in intrusive thoughts and 52% reduction in anxiety.

Article: Patterns of Cannabis Use Among Individuals with Obsessive Compulsive Disorder: Results from an Internet Survey[13]

As trends towards greater access to marijuana and legalization continue, there is a growing public health need to understand why individuals with OCD use cannabis. On average, nearly 30% of adults seeking intensive OCD treatment endorsed current or past cannabis use. The internet survey included 601 participants, of which 203 (33.8%) reported having a physician's recommendation to use cannabis; indications included OCD, anxiety, PTSD, depression, insomnia and pain. However, only 66 (11.0%)

[12] Journal of Affective Disorders Vol. 279 January 2021 Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder, Mauzay, LaFrance, Cuttler, Washington State University (Attachment #7)
[13] Journal of Obsessive Compulsive Related Disorders July 2021, Patterns of Cannabis Use Among Individuals with OCD, Kayser (Attachment #8)

reported using cannabis exclusively medicinally: 447 (74.3%) reported both medicinal and recreational use, and 88 (14.6%) reported only recreational use. Of the 601 participants, 175 (29.1%) reported they used cannabis specifically to manage OCD symptoms. Most participants reported that cannabis typically improved their obsessions (68.3%) and their compulsions (36.6%). A small subset reported worsened obsessions (17.3%) or compulsions (13.8%).

The article hypothesizes that cannabis use many decrease patients' likelihood of seeking treatment for OCD. The success of self-medicating with cannabis may deter patients from seeking professional support, specifically when cannabis is an exclusion criteria for enrolling in treatment programs. "Given the risks associated with untreated OCD and cannabis-related problems, our findings suggest that providers of OCD treatment may need to reevaluate their "zero-tolerance" policies around cannabis use."

CONCLUSION:

Data in these articles indicates that a significant percentage of Ohio's OCD population are likely self-medicating with marijuana sourced from the illicit market or a neighboring recreational state. Those patients may not be disclosing their marijuana use to their treating physician. Ninety percent of the patients participating in the internet survey reported using marijuana for medicinal purposes, and 29% for OCD specifically[14]. These statistics should encourage the State Medical Board to add OCD as a condition to the MMCP, not only because actual cannabis use statistics strongly indicate a positive impact on OCD symptoms but also to encourage these patients to incorporate their physician into their self-treatment protocol.

[14] Journal of Obsessive Compulsive Related Disorders July 2021, Patterns of Cannabis Use Among Individuals with OCD, Kayser (Attachment #8)

DEPARTMENT OF HEALTH

ATTACHMENT #6

Obsessive-Compulsive Disorder Issue Brief

OCTOBER 2022

Introduction

This briefing was prepared in response to a petition to consider adding obsessive-compulsive disorder as a new condition 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 are 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 can be 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 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 to identify any ongoing or completed clinical trials.

Definition

Obsessive-Compulsive Disorder (OCD) is a disorder characterized by recurring, intrusive thoughts (obsessions) that often cause significant emotional distress and anxiety. This can lead to behaviors (compulsions) that the affected individual feels compelled to perform to manage/reduce that distress. Contrary to popular belief, compulsions do not need to be observable behaviors. Compulsions can be mental. Some common OCD themes may involve the following:

1. Contamination (fear of germs, dirt, etc.)
2. Harm/violence (fear of hurting others or oneself)
3. Sexual themes (thoughts/mental images related to sex)
4. Religious/Moral scrupulosity (concerns about offending God or violating moral code)
5. Perfectionism themes ("just right" feelings, fear of making mistakes)
6. Identity-related themes (concerns about sexual orientation, gender identity, etc.)

Strict criteria for the diagnosis of OCD is defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR; American Psychiatric Association [APA], 2022) and is presented verbatim below.

Diagnostic Criteria

A. Presence of obsessions, compulsions, or both:

   Obsessions are defined by (1) and (2):

   1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
   2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

   Compulsions are defined by (1) and (2):

   1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
   2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

      Note: Young children may not be able to articulate the aims of these behaviors or mental acts.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder [repetitive or ritualistic movement, posture, or utterance]; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders;

guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:

With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:

Tic-related: The individual has a current or past history of a tic disorder.

The most commonly used and validated tool for measuring OCD severity is with the Yale-Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989). It is administered by a clinician and is used to assess for changes in severity during treatment. Scores can range from 0-40, with higher scores reflecting greater OCD severity.

Prevalence

OCD is estimated to affect 2-3% of the population (Stein et al., 2019). Within the U.S., 12-month prevalence is estimated to be at 1.2% (APA, 2022). Some speculate these estimates are low because individuals that present with mild symptoms may not seek treatment, and health care practitioners may not necessarily be knowledgeable about the various ways in which OCD can manifest, thus leading to inaccurate or delayed diagnosis (Fenske & Petersen, 2015; Hirschtritt et al., 2017). In addition, people who suffer from OCD often feel extreme shame about their obsessions, which makes them reluctant to come forward and receive treatment. It has been estimated that it can take roughly 8 years from the onset of symptoms before receiving any type of medication for treatment for the first time (Hirschtritt et al., 2017).

An oft-cited statistic from 1995 by DuPont et al. estimates the total economic cost of OCD to be $8.4 billion dollars—5.7% of the total $147.8 billion cost for all mental illness. This data are close to 30 years old, but even recent literature continues to cite it. It would be reasonable to expect these costs are significantly outdated and most likely low when factoring in inflation over time and decreased stigmatization over seeking mental health services.

Current Therapies

Both pharmacologic and non-pharmacologic treatments are used to manage OCD symptoms, and gold standards exist in both treatment domains. First-line medications for treating OCD are selective serotonin reuptake inhibitors (SSRIs), which are a class of drugs often used for treating major depressive disorder and anxiety disorders. Clomipramine, a tricyclic antidepressant (a historically older group of antidepressants than SSRIs) is another commonly prescribed

medication for OCD. A study using data from a Cochrane[1] database of randomized controlled trials found that the efficacy of SSRIs and clomipramine in treating OCD were relatively similar and considered moderately effective (Skapinakis et al., 2016). However, SSRIs are generally better tolerated than clomipramine, making SSRIs the more desirable choice in OCD patients.

Within cognitive-behavioral therapy (CBT), exposure and response prevention (ERP) is considered the gold standard for managing OCD. Individuals with OCD struggle to tolerate distress and uncertainty coming from obsessions, and the act of performing compulsions helps regulate that distress. In ERP training, the client goes through work to sit with and tolerate the distress or uncertainty coming from the obsessions and not perform compulsions. The idea is that clients should naturally allow their obsessions to occur as they do, but not to give in to compulsions to manage the distress coming from those obsessions. At first, this can be very challenging and highly uncomfortable for OCD sufferers because they are being told to *respond* differently to obsessions; they are to sit with the distress signals coming from their minds and, over time, they are retraining their nervous systems to process their obsessions as not a true threat. ERP can reduce OCD symptoms by 77% (Franklin et al., 2000), making it a fairly successful treatment. However, it has been estimated that 15% of patients will discontinue ERP treatment due to difficulty or intolerability of the treatment (Ong et al., 2016).

In summary, treatment with an SSRI alone or with CBT alone are moderately effective, with evidence suggesting superiority of CBT over SSRIs as monotherapy[2]. Given their independent successes, both SSRIs and CBT are sometimes combined for OCD treatment. At the same time, it is also important to acknowledge that roughly 25% of patients will not respond to either medication or psychotherapy, which means that a proportion of OCD sufferers remain treatment-resistant (Hirschtritt et al., 2017).

Preclinical Research

There has been some interest in finding new medications to treat OCD. One such area of interest includes exploring cannabis and cannabinoids in treating OCD symptoms. Firstly, cannabinoid receptor 1 (CB1-receptor)[3] is abundantly found in brain regions implicated in OCD, including in the prefrontal cortex (decision-making, goal-directed behaviors), amygdala (emotion regulation), hippocampus (memory, fear extinction), and the basil ganglia (repetitive behaviors). (Kayser et al., 2019). Secondly, cannabidiol (CBD; a cannabinoid found in the cannabis plant) has shown some promise in the preclinical literature for relieving fear and anxiety (Blessing et al., 2015). While OCD is not categorized under anxiety disorders in the DSM-

[1] Cochrane: a well-regarded not-for-profit organization that partners with the scientific and medical communities to provide up-to-date, high quality information about managing a range of healthcare conditions.
[2] Monotherapy: being on one type of treatment at one time, regardless of whether that's a medication or something else (e.g., psychotherapy).
[3] Receptor (neuronal receptor): refers to a site within bodily cells (neurons) that cannabinoids can bind to – like a key fitting into a specific lock (key = cannabinoid, lock = cannabinoid receptor). Cannabinoids are either produced within the body (*endo*cannabinoids or endogenous cannabinoids) or can be introduced into the body (cannabinoids like THC or CBD from the cannabis plant that a person may smoke, or man-made cannabinoids introduced into the body; exogenous cannabinoids).

5-TR, anxiety is often present in OCD even if it is not a primary manifestation of OCD. This suggests that there may be some potential for CBD to help with some of the anxiety-provoking aspects of OCD.

The endocannabinoid system may also be involved in the manifestation of compulsive-like behaviors. For example, it has been documented that the administration of CBD decreases compulsive-like behaviors, as measured in the marble-burying test in rats and mice (Dixit et al., 2020). In this paradigm, the bottom of a cage is covered in a layer of sawdust (typically no more than 5 centimeters deep), and several marbles are lain across the top of this pile evenly spaced apart. A rodent is subsequently placed in the cage, and the number of marbles that are buried are observed over a set amount of time. Burying is a common stereotyped behavior that is observed in rodents, and it has been considered to potentially map to stereotyped human behaviors like compulsions. Previous data has shown that administering CBD can decrease marble-burying in mice, suggesting CBD's anticompulsive-like effects (Dixit et al., 2020).

Overall, the preclinical literature indicates that the endocannabinoid system may have a role in anxiety and compulsive/repetitive behaviors, both of which are present in OCD. However, the science is still emerging, and it's important to keep in mind that, while animal studies play an important role in understanding the neurobiology underlying psychiatric disorders, the construct validity[4] of these models can come under scrutiny.

Clinical Trials

Five studies investigating the effects of cannabis/cannabinoids on OCD were identified, three of which were case studies/reports and the remaining two being clinical trials. Chronologically, the case study/report data are older than the two clinical trials reported here, and the perceived effectiveness of cannabis/cannabinoids in those case studies/reports may have provided some impetus to pursue the clinical trials that followed. While clinical trial data are extremely limited, one of the clinical trial results indicate that cannabinoids may not independently improve OCD symptoms but work to help in the exposure and response prevention (ERP) treatment in alleviating OCD symptoms. However, those particular findings are significantly limited by the lack of a placebo-controlled comparison. In fact, the other clinical trial which was a randomized controlled trial, showed that even if OCD symptoms were improved with cannabis, this was true for all conditions including the placebo arm. This supports prior evidence to suggest that expectancy effects[5] may noticeably influence perceived effectiveness of cannabis in treating obsessive-compulsive (OC) symptoms.

Overall, more clinical research is needed to better ascertain the effects of cannabis/cannabinoids on OCD symptomatology. Clinical trials should be designed with a greater number of participants than the current trials have included, and they should be placebo-controlled due to possible expectancy effects that have been documented previously.

[4] Construct validity: the strength with which one can say one's test or measure is actually capturing the thing one wants (e.g., "is marble-burying behavior in rodents actually a good measure of compulsions?").
[5] Expectancy effects: a phenomenon whereby one's expectations for a particular outcome unconsciously influences the actual outcome of the study.

Trials that investigate the individual contributions of specific cannabinoids (e.g., delta-9-tetrahydrocannabinol (THC) vs. CBD) to OCD symptomology are important, as well as trials using cannabis flower. The latter may be important from an external validity standpoint since cannabis flower (which contains phytochemicals beyond just THC/CBD that may contribute to overall perceived effects) is far more commonly used among both medicinal and recreational users than cannabis extract products (Sexton et al., 2016).

Kayser, R.R., Haney, M., Raskin, M., Arout, C., & Simpson, H.B. (2020). Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. *Depression & Anxiety, 37*(8), 801-811. https://doi.org/10.1002/da.23032

Kayser et al. (2020) was the first double-blind, placebo controlled randomized trial to examine acute effects of cannabis on OCD. In a crossover design[6], patients with severe OCD (n = 12) were exposed to three different smokeable cannabis pre-roll preparations with different THC:CBD ratios in randomized order: high THC to low CBD, low THC to high CBD, and placebo. Using a cued-smoking procedure to maximize dosing consistency among patients, patients were asked to smoke 50% of their preparation within a certain timed schedule, after which time patients' obsessions, compulsions, and anxiety levels were self-reported at 20, 40 60, 90, 120, and 180 minutes after smoking. Results indicated that, while OCD symptoms and anxiety levels were reduced over time, those reductions were similarly observed across all conditions including placebo. Therefore, the authors were unable to conclude that THC or CBD could alleviate acute OCD symptoms and anxiety. This study could benefit from replication with a larger sample size and longer study duration (study only investigated short-term, acute changes in OCD symptoms).

Kayser, R. R., Raskin, M., Snorrason, I., Hezel, D. M., Haney, M., & Simpson, H. B. (2020). Cannabinoid augmentation of exposure-based psychotherapy for obsessive compulsive disorder. *Journal of Clinical Psychopharmacology, 40*(2), 207–210. https://doi.org/10.1097/JCP.0000000000001179

This study investigated the efficacy of nabilone (a synthetic THC) on OCD, either in conjunction with ERP treatment or administering nabilone alone. Adult patients who scored at least moderately on the Yale-Brown Obsessive Compulsive Scale (YBOCS score >= 16) were included in the study (n = 11) and were randomized into one of the two treatment groups: nabilone alone vs. nabilone + ERP. Both treatment groups were in the study for 4 weeks, and third-party evaluators rated OCD symptoms in the patients using the YBOCS at baseline, 2-weeks, and 4-weeks (evaluators were blind to participants' treatment group). Results showed that those in the nabilone + ERP group showed significantly greater change in their YBOCS scores from baseline to 4-weeks, compared to those given nabilone alone. In fact, the nabilone alone condition did not result in significantly improved OCD symptoms within 4 weeks. Authors conclude that nabilone may enhance ERP efficacy to help treat OCD symptoms. However, the

[6] Crossover design: a study design where participants are assigned to all treatment conditions over different periods of time.

omission of a placebo control in this study along with its small sample size limit the interpretive power of this study.

Szejko, N., Fremer, C., & Müller-Vahl, K. R. (2020). Cannabis improves obsessive-compulsive disorder—case report and review of the literature. *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.00681

Szejko et al. (2020) published a case report on a young adult male with severe OCD since childhood. The motivation for this case report was spurred by this patient's prior experience with street cannabis and having reported that it had helped with OCD symptoms. Another reason for motivating this study was that he did not want to take SSRIs or seek out psychotherapy. Bedrocan (22% THC to <1% CBD; predominately available in Europe) was provided to this patient, and clinical assessments were administered at baseline and compared to results at 3-months, 6-months, and 20-months after treatment start. Due to a sample size of 1, no statistical tests were conducted, but the researchers noted that the patient reported a decrease in OCD symptoms over time, with a 90-95% reduction in obsessions and compulsions by the end of the study.

Schindler F., Anghelescu I., Regen F., & Jockers-Scherubl, M. (2008). Improvement in refractory obsessive compulsive disorder with dronabinol. *American Journal of Psychiatry, 165*(4), 536-537. https://doi.org/10.1176/appi.ajp.2007.07061016

This was a case study following two adult patients with treatment-resistant OCD; both had previously used paroxetine (an SSRI) for OCD symptoms with limited success. These individuals also suffered comorbid diagnoses, one with major depressive disorder and the other with schizophrenia. For the study, these patients augmented their existing medication regimen with dronabinol (a synthetic THC). At study outset, both were exhibiting moderate OCD symptoms according to YBOCS scores (scores of 20 and 23), and they had decreased to mild symptoms (scores of 10 and 15) within two weeks. Even with the apparent success in reducing OCD symptoms in the individual with comorbid schizophrenia, the authors caution treatment with cannabinoids in individuals with a history of, or predisposition to, psychoses.

Cooper J.J., & Grant J. (2017). Refractory OCD due to thalamic infarct with response to dronabinol. *Journal of Neuropsychiatry and Clinical Neurosciences, 29*(1), 77-78. https://doi.org/10.1176/appi.neuropsych.16030053

Cooper and Grant (2017) reported on a single patient (case report) who suffered from extreme OCD (YBOSC score: 39) after experiencing a stroke within a region of the thalamus that has been associated with the pathophysiology of OCD. He also had insulin-dependent diabetes and bipolar I disorder (both existed prior to the stroke) and was receiving medical treatment for both. A variety of treatments to curb OCD symptoms were unsuccessful, and dronabinol was started, with dosing titrated up to 20 mg a day. By the second week, the patient reported decreases in OCD symptoms, scoring as low as a 10 on the YBOSC at one point in time. In addition, this patient was able to tolerate starting cognitive-behavioral therapy which had been difficult previously.

Ongoing Clinical Trials

A search for ongoing clinical trials on ClinicalTrials.gov (https://ClinicalTrials.gov) was conducted using cannabis keywords ("cannabis", "cannabinoids", "marijuana", "thc", "cbd") and OCD keywords ("obsessive-compulsive disorder", "obsessions", "compulsions", "ocd"). The search led to the identification of two ongoing studies, both listed as being in the recruitment phase as of August 2022.

Multimodal Assessment of Cannabinoid Target Engagement in Adults With Obsessive-Compulsive Disorder (https://clinicaltrials.gov/ct2/show/NCT04880278)

This study is investigating the effects of nabilone (a synthetic THC) on neurocognitive processes associated with OCD. Adult patients with a prior diagnosis of OCD are being recruited for the study (target sample size: n = 60). Primary measures include brain imaging and neurophysiological measures performed during neurocognitive testing, while secondary measures include various anxiety-related measures, physiological measures (heart rate, blood pressure), and drug effects measures. Patients will be randomly assigned to either nabilone or placebo (parallel assignment), and between-subjects comparisons will be made. This study is estimated to be completed July 2026 and is being conducted by Kayser and colleagues, who are the authors of the two published clinical trials mentioned previously in this brief.

Epidiolex in Obsessive Compulsive Disorder and Related Disorders (https://clinicaltrials.gov/ct2/show/NCT04978428)

This study is examining the effects and safety profile of Epidiolex (CBD) on adult OCD patients and related disorders such as skin picking, trichotillomania (hair pulling), tic disorder, and hoarding. The description of the study does not indicate whether the patients are being sampled from the clinical populations of interest, or if it is relying on participant self-report for having one of those diagnoses. Nonetheless, authors are primarily interested in measuring for the severity of OCD, skin picking, hoarding, and tics at baseline and at Week 2 of the study. Patients (target sample size: n = 15) will start with a twice daily, 2.5 mg/kg dose of Epidiolex for Week 1. Week 2 will be at an increased dosage of 5 mg/kg of Epidiolex twice per day. This is not a placebo-controlled study. Estimated study completion date is listed as September 2023, and it is being conducted by Grant and colleagues (Grant is a co-author in the case report mentioned previously in this brief).

Observational Studies

A handful of observational studies have been published investigating the relationship between cannabis use and OCD symptomatology. Taking the literature altogether, while some evidence suggests that individuals who use cannabis/cannabinoids perceive benefits to obsessive-compulsive symptoms, this finding is accompanied by literature indicating that these users may also be at greater risk for developing cannabis problems or cannabis use disorder (CUD). Therefore, the perceived benefits of cannabis in this population are tempered by potential harmful public health effects. This section presents some representative observational studies on the current state of knowledge.

A review of the literature also shows some limitations. For example, many observational studies use a cross-sectional design which makes the directionality of any observable associations unclear. Furthermore, a number of studies have targeted non-clinical populations for their sample (e.g., college students, general population) to answer questions about OCD symptomatology. This limits the generalizability of findings to actual clinical populations. Even if the authors administered validated tools to identify participants exhibiting obsessive-compulsive symptomatology, this is not verified by a professional evaluation, and some studies include patients who self-report having OCD. There may also be selection bias depending on recruitment methods.

Spradlin, A., Mauzay D., & Cuttler, C. (2017). Symptoms of obsessive-compulsive disorder predict cannabis misuse. *Addictive Behaviors, 72*, 159-164. https://doi.org/10.1016/j.addbeh.2017.03.023

Spradlin et al. (2017) conducted an anonymous, online survey recruiting college students who had prior experience with using cannabis. These participants (n = 430), who were sampled from a non-clinical population (university), were administered the Obsessive-Compulsive Inventory-Revised (OCI-R; Foa et al., 2002) and asked to report on their cannabis usage (frequency of use, quantity consumed), cannabis misuse (measures to address cannabis problems and cannabis use disorder symptoms), and their levels of anxiety, stress, and depression. Results indicated that higher obsessive-compulsive (OC) scores were correlated with increased cannabis problems (detrimental personal, social, and occupational issues due to cannabis use), cannabis use disorder (CUD) symptoms, and coping motives (the use of cannabis to cope with distress). However, OC scores were not associated with cannabis use (how frequently they used cannabis or the quantity consumed). When researchers controlled for the participants' reported anxiety, stress, and depression, the positive association between OC scores and cannabis problems, CUD symptoms, and coping motives remained. Furthermore, their analysis indicated that coping motives may mediate the association between OC symptomatology and cannabis misuse/problems. It may be that, in an effort to cope with stress and anxiety induced by obsessions and compulsions, they may seek out cannabis and thereby increase their risk for cannabis-related problems.

In summary, while the frequency and quantity consumed is not associated with OC symptomatology, those who display OC symptoms may be more prone to cannabis misuse/problems. Those effects remain even when controlling for participants' reported anxiety, stress, and depressive symptoms. Despite these findings, it should be noted that the cross-sectional nature of this study makes claims on the directionality of these associations challenging. In addition, their study could benefit from sampling methods that target a clinical population rather than a non-clinical population. They do, however, point out that 13% of their sample reached clinical cut-off scores indicative of OCD according to the OCI-R.

Bakhshaie, J., Storch, E.A., Tran, N., & Zvolensky, M.J. (2020). Obsessive-compulsive symptoms and cannabis misuse: The explanatory role of cannabis use motives. *Journal of Dual Diagnosis, 16*(4), 409-419. https://doi.org/10.1080/15504263.2020.1786616

Bakhshaie et al.'s (2020) cross-sectional study was somewhat similar to Spradlin et al.'s (2017) study in its objective: to examine for associations between OC symptomatology and cannabis

misuse, along with any mediating effects of coping to explain cannabis misuse. Unlike Spradlin et al., however, they included a few additional measures. Most notably, they also measured other substance usage, specifically whether they were recent tobacco users as well as a measure to assess for alcohol use problems. Their study sample consisted of college students (non-clinical sample) which is similar to Spradlin et al. (2017), but their sample was roughly 40% smaller (n = 177) and more racially diverse. Results from their online survey showed a significant positive association between OC symptomatology and risky cannabis use; greater OC symptomatology was correlated with increased risky cannabis use (self-reported difficulty in controlling, decreasing, or ceasing cannabis use). Unlike Spradlin et al. (2017), however, OC symptomatology was not correlated with cannabis problems (self-reported detrimental effects to personal, social, occupational, and physical circumstances due to cannabis use). In other words, while greater OC symptoms were associated with self-reported difficulties in controlling their cannabis usage, it was not associated with any detrimental effects to their personal, occupational, or social lives. When controlling for problematic alcohol use and tobacco smoking status, coping motives (usage of cannabis to cope with distress) were not found to mediate the association between OC symptomatology and cannabis misuse. This diverges from Spradlin et al. (2017); however, Spradlin et al. did not collect data on problematic alcohol use or tobacco smoking status to control for in their study.

Nicolini, H., Martínez-Magaña, J.J., Genis-Mendoza, A.D., Villatoro Velásquez, J.A., Camarena B., Fleiz Bautista, C., Bustos-Gamiño, M., Aguilar Garcia, A., Lanzagorta, N., & Medina-Mora, M.E. (2021). Cannabis use in people with obsessive-compulsive symptomatology: Results from a Mexican epidemiological sample. *Frontiers in Psychiatry, 12*, 664228. https://doi.org/10.3389/fpsyt.2021.664228

This cross-sectional study investigated the association between OC symptomatology and cannabis dependence via a large nationally-representative survey conducted in Mexico (non-clinical population). As a part of a household survey and among the subset of individuals who agreed to provide a DNA sample, questions on drug, alcohol, and tobacco use were collected along with questions on psychiatric history – namely prior history of obsessive-compulsive, anxiety, depression, hypomania (milder form of mania), and psychosis symptomatology. Cannabis dependence was identified in participants exhibiting three or more of the following: "tolerance, abstinence, a longer time or greater amount of use, persistent or uncontrollable cravings, excessive time spent in getting drugs or recuperating from their effects, reduction in social, work, or recreational activities, or continued use in spite of awareness of harmful effects". Of the total sample (n = 13,130), 2.4% (n = 288) exhibited OC symptomatology. In addition, the prevalence of ever having used cannabis in those exhibiting OC symptomatology was greater than in those found in the population as a whole (24.4% vs. 9.7%). Another interesting finding was that those who had ever exhibited OC symptomatology reported higher rates of ever having used cannabis than those who had ever exhibited symptoms for anxiety, depression, and hypomania. Those having ever experienced psychosis symptomology were the only group to have higher rates of ever having used cannabis, compared to those ever experiencing OC symptomology. The authors found this finding interesting given prior evidence to indicate that cannabis use is higher in many psychiatric populations than in non-psychiatric populations, yet where OCD may specifically fall along this spectrum among other psychiatric

conditions has been relatively unknown. Lastly, DNA analysis revealed that those who have ever exhibited OC symptomatology were at greatest risk for becoming cannabis-dependent, as measured by polygenic risk scores. Those who displayed OC symptomatology but had never used cannabis had statistically lower risk of becoming cannabis-dependent, which the authors interpreted to mean the following: the mere act of using cannabis in OC-vulnerable individuals may elevate their risk for developing cannabis dependence.

Kayser, R.R., Senter, M.S., Tobet, R., Raskin, M., Patel, S., & Simpson, H.B. (2021). Patterns of cannabis use among individuals with obsessive-compulsive disorder: Results from an internet survey. *Journal of Obsessive-Compulsive and Related Disorders, 30*, 100664. https://doi.org/10.1016/j.jocrd.2021.100664

Unlike the previously mentioned observational studies in this brief, the authors of this study tried to recruit adults who 1) had a professional OCD diagnosis or had a score ≥ 21 on the Obsessive-Compulsive Inventory-Revised (OCI-R; previously established to be a potential clinical cut-off for OCD diagnosis), and 2) had used cannabis at least once in any preparation (flower, extracts, edibles). Recruitment for this online survey was through extensive public advertising through popular online websites (e.g., Reddit), various social media platforms (e.g., Facebook, Instagram), and OCD-related organizations (e.g., International OCD Foundation). Analysis was conducted on 601 patients (average age: 29 years old) who completed the entire survey and fit the above criteria. The survey included questions to measure cannabis use disorder (CUD), their patterns of cannabis usage (frequency, quantity, forms of cannabis used, methods of administration), and questions about current OCD symptomology. Forty-four percent (44%) of participants reported to come from states with both recreational and medical cannabis programs, 41% from states with only medical cannabis programs, and 15% from states where cannabis was completely illegal. Roughly 90% reported using cannabis at least once over the past month, with 57% reporting using cannabis at least daily. Mean age of OCD onset was 9.9 years of age, with first cannabis use reported on average to be at 17 years old; therefore, onset of OCD typically occurred prior to first cannabis use in this sample. Participants' primary formulation of choice for consuming cannabis was cannabis flower followed by cannabis extracts (65% and 25% of participants, respectively). When asked about THC and CBD concentrations (e.g., reporting on percentage of THC and CBD in products they consume), participants seemed generally more knowledgeable about THC concentrations in their preparations compared to CBD concentrations. THC concentrations were often reported to fall in the "high THC" range (>10% THC) for cannabis flower and cannabis extracts; whereas, it was more common for participants to report not knowing CBD concentrations or that CBD concentrations were low (<10% CBD) for those same formulations. For those who reported using edibles at least a quarter of the time, 75% reported not knowing the concentrations of THC and CBD in those products.

The majority of participants reported that cannabis helped their obsessions (68%) and compulsions (65%), and a smaller proportion either reported worsening of obsessions (17%) and compulsions (14%) or no change to obsessions (8%) and compulsions (21%). When assessing for CUD symptomatology, 42% met probable CUD diagnosis. Another 66% fell under the threshold for probable CUD but were high enough to be categorized as having problematic cannabis use. These results suggest that, while a decent proportion of participants experience

some OCD relief, this is also accompanied by problematic cannabis use. Lastly, the majority of participants (62%) were currently not in any evidence-based OCD treatment, with increases in cannabis usage frequency being associated with a decreased likelihood of seeking those treatments. While speculative, authors propose that the usage of cannabis may demotivate individuals from seeking those evidence-based treatments due to beliefs that cannabis could be an adequate replacement. Some limitations of this study include the cross-sectional nature of the study along with no independent verification of OCD diagnosis in participants. In addition, selection bias may have been present in the study and may not be representative of the wider OCD population. It is also possible for expectancy effects to have affected the results.

National Medical Organization Recommendations

No guidance documents or statements were found to recommend the therapeutic use of cannabis or cannabinoids in the management of OCD. However, Allina Health has submitted a letter to the Minnesota Department of Health expressing their opposition to adding OCD to the list of approved medical conditions. The National Academies of Sciences, Engineering, and Medicine produced a report on the health effects of cannabis in 2017, but the committee did not specifically speak to the health effects of cannabis on OCD.

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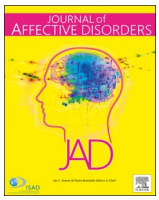

Research paper

Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder

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A B S T R A C T

Background: Little is known about the the acute effects of cannabis on symptoms of OCD in humans. Therefore, this study sought to: 1) examine whether symptoms of OCD are significantly reduced after inhaling cannabis, 2) examine predictors (gender, dose, cannabis constituents, time) of these symptom changes and 3) explore potential long-term consequences of repeatedly using cannabis to self-medicate for OCD symptoms, including changes in dose and baseline symptom severity over time.

Method: Data were analyzed from the app Strainprint® which provides medical cannabis patients a means of tracking changes in symptoms as a function of different doses and strains of cannabis across time. Specifically, data were analyzed from 87 individuals self-identifying with OCD who tracked the severity of their intrusions, compulsions, and/or anxiety immediately before and after 1,810 cannabis use sessions spanning a period of 31 months.

Results: Patients reported a 60% reduction in compulsions, a 49% reduction in intrusions, and a 52% reduction in anxiety from before to after inhaling cannabis. Higher concentrations of CBD and higher doses predicted larger reductions in compulsions. The number of cannabis use sessions across time predicted changes in intrusions, such that later cannabis use sessions were associated with smaller reductions in intrusions. Baseline symptom severity and dose remained fairly constant over time.

Limitations: The sample was self-selected, self-identified as having OCD, and there was no placebo control group.

Conclusions: Inhaled cannabis appears to have short-term beneficial effects on symptoms of OCD. However, tolerance to the effects on intrusions may develop over time.

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by obsessions – which are defined as recurrent, persistent, intrusive thoughts, urges, or images (e.g., the intrusive doubt that one has not locked their door, the intrusive thought that one has been contaminated by a virus) – and/or compulsions – which are defined as repetitive behaviors or mental acts (e.g., repeatedly checking a door, repeatedly washing hands) (American Psychiatric Association [APA], 2013). Individuals with OCD often also experience heightened anxiety and as such OCD was classified as an anxiety disorder in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV; APA, 2000). Nevertheless, it was recently reclassified as an obsessive-compulsive and related disorder in the 5th edition of the DSM (APA, 2013). Approximately 2.5% of the population has been diagnosed with OCD, with sub-clinical symptoms being common among the general population (APA, 2013).

Current first-line psychotherapeutic treatment for OCD is exposure and response prevention (ERP; Society of Clinical Psychology, 2015) and evidence suggests that this form of therapy can reduce symptoms by up to 77% (Franklin et al., 2000). However, approximately 15% of patients drop out of ERP treatment due to the difficulty and intensity of this approach (Ong et al., 2016). Serotonin reuptake inhibitors are also commonly prescribed to treat symptoms of OCD (Stahl, 2013) with approximately 70% of patients with OCD experiencing clinically significant reductions in symptoms (Pittenger & Bloch, 2015). However, effects tend to be modest (Hollander et al., 2003), many patients do not respond to these medications, and they are associated with several undesirable side effects (Stahl, 2013). Thus, it is imperative to explore novel treatment options and better understand factors that may improve treatment outcomes for OCD.

Neurobiologically OCD is similar to anxiety, with the cortico-striatal-thalamo-cortical loop being one of the primary circuits implicated in the obsessions, ruminations, and anxiety characteristic of OCD. Specifically, it is believed that individuals with OCD experience initial overactivation of the dorsolateral prefrontal cortex (DLPFC) which leads to activation of the thalamus and striatum, followed by further overactivation of the DLPFC (Stahl, 2013). The orbitofrontal cortex (OFC), which is involved in the flexible use of goal-directed and habitual behaviors, has also been implicated in OCD. Namely, projections from the lateral region of the OFC to the dorsal lateral striatum, which promotes habitual behaviors, may be hyperactive in individuals with OCD; whereas projections from the medial region of the OFC to the dorsal medial striatum, which facilitates goal-directed activities, may be hypoactive among individuals with OCD. It is believed that the shift in balance between these two competing systems may result in a bias

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towards habitual behaviors (Kayser et al, 2019; Stahl, 2013). Lastly, the hippocampus and amygdala are implicated in the fear and anxiety responses in OCD (Kayser et al., 2019).

The endocannabinoid system (ECS) has recently been identified as a potential therapeutic target for OCD because it plays important roles in anxiety, fear, and repetitive/habitual behaviors (Kayser et al., 2019). This system is heavily distributed throughout the brain with cannabinoid (CB1) receptors found in high densities throughout a number of the brain regions implicated in OCD, including the prefrontal cortex, amygdala, basal ganglia, and hippocampus (Kayser et al., 2019). Two primary constituents of the cannabis plant, namely tetrahydrocannabinol (THC; the primary psychoactive constituent of cannabis) and cannabidiol (CBD; the primary non-psychoactive constituent) activate the ECS. As such, cannabis may have the potential to reduce symptoms of OCD (Kayser et al., 2019).

While there is evidence that cannabis has acute anxiolytic effects (e.g., Bergamaschi et al., 2011; Cuttler et al., 2018; Zuardi et al., 1993), only a small number of studies have examined cannabis use in relation to other OCD symptoms. The results of this literature support the presence of significant associations between symptoms of OCD and cannabis misuse (Buckner et al., 2007; Douglass et al., 1995, Spradlin et al., 2017). Further, Albertella and Norberg (2012) found that both pre- and post-treatment OCD symptom severity were related to higher post-treatment frequency of cannabis use, suggesting people may be self-medicating with cannabis. Similarly, Daumann and colleagues (2004) found that baseline OCD symptoms were related to more frequent cannabis use. However, participants who continued to use cannabis during an 18-month follow-up period demonstrated an increase in OCD symptoms relative to baseline, whereas those who remained abstinent showed a decrease in symptoms, indicating cannabis use may aggravate OCD symptoms (Dauman et al., 2004). These studies establish links between OCD and cannabis use/misuse however the direction of these links remains unclear.

To our knowledge only one previous empirical study has examined the acute effects of cannabis on OCD symptoms in humans. Specifically, Kayser and colleagues (2020a) recently published a placebo-controlled investigation of the effects of smoked cannabis on symptoms of OCD and found reductions in symptoms from before to after use that were not significantly larger than those observed after placebo administration. However, their sample size was small (n = 12) and relatively low potency cannabis was used (THC = 7% and 0.4%), which may have diminished their power to detect effects significantly larger than those associated with the placebo. The remaining investigations of the effects of cannabinoids on OCD have relied on synthetic forms of THC that are orally administered (e.g., dronabinol and nabilone). Specifically, three case studies have revealed evidence that 14+ days of treatment with dronabinol, in combination with more traditional medications (e.g., clomipramine), decreased symptom severity in patients with treatment resistant OCD (Cooper & Grant, 2016; Sachdeva et al., 2015; Schindler et al., 2008). Moreover, Kayser and colleagues (2020b) recently published preliminary data from a small clinical trial (n = 11) designed to examine effects of augmenting ERP with a 4-week regimen of nabilone. They found that nabilone alone did little to decrease OCD symptoms; however, nabilone combined with ERP led to significant symptom reductions that were sustained for a one-month period after treatment termination. However, the sample sizes for all of these studies have been small and all relied on low potency cannabis or synthetic cannabinoids, while most medical cannabis users report inhaling high-potency whole-plant cannabis (Sexton et al., 2016; Smart et al., 2017).

Finally, additional evidence for the therapeutic potential of cannabinoids can be garnered from a small number of studies that have employed a marble burying paradigm to model compulsive-like behavior in rodents. Specifically, three studies have converged on the finding that CBD decreases compulsive marble-burying in rodents (Casarotto, et al., 2010; Deiana, et al., 2012, Nardo et al., 2014). Moreover, one study found that these effects persisted after 7-days of repeated administration, indicative of the absence of short-term tolerance to these effects (Casarotto et al., 2010). Collectively, this small literature on effects of cannabinoids on symptoms of OCD in humans and animals provides some encouraging evidence that cannabis may hold promise for reducing the severity of OCD symptoms.

Trends toward the legalization of cannabis in North America make it particularly important to examine the potential short- and long-term effects of cannabis on mental health. However, while changes in laws have increased public access to a wide variety of cannabis-based products, the U.S. Drug Enforcement Administration (DEA) continues to classify cannabis as a Schedule 1 illicit drug (Drug Enforcement Administration, 2018). As a result of the strict regulation of cannabis by the U.S. federal government, all researchers at federally funded institutions must undergo lengthy legal and ethical approval processes before they can administer cannabis to humans (The National Academies of Science, 2017). Additionally, per federal regulations, researchers administering cannabis must use cannabis supplied by the National Institute of Drug Abuse (National Institute on Drug Abuse [NIDA], 2016). However, this research-grade cannabis is far less potent (rarely exceeding 10% THC; NIDA, 2016) than the high potency products available to consumers through statewide legal cannabis markets. Indeed, cannabis flower exceeding 20% THC and cannabis concentrates containing over 60% THC are presently dominating the recreational cannabis markets (Smart et al., 2017). These federal restrictions have dramatically stalled the progress of research and have left us with an impoverished understanding of the potentially therapeutic effects of cannabis on OCD.

Thus, the goal of the present study was to examine short-term effects and potential longer-term consequences of cannabis on the intrusions, compulsions, and anxiety symptoms characteristic of OCD, using an innovative methodology that allows us to bypass federal restrictions imposed on researchers studying acute effects of the drug. Specifically, we analyzed real-time changes in these three symptoms from before to after cannabis use that were tracked by medical cannabis users using the Strainprint® application (app). Our first aim was to determine whether symptoms of OCD would be significantly reduced from before to after cannabis use. Our second aim was to examine predictors of cannabis-related reductions in OCD symptoms, including the influence of cannabis constituents, dose of cannabis used, cannabis use sessions over time, and gender. Our third aim was to explore potential long-term consequences of repeatedly using cannabis to self-medicate for OCD symptoms, including changes in dose of cannabis used and changes in baseline (pre-cannabis use) symptom severity over time. These analyses were performed to examine evidence for tolerance and to explore whether the repeated use of cannabis might exacerbate, maintain, or ameliorate the severity of these symptoms in the long-term. We hypothesized that cannabis intoxication would be associated with short-term reductions in reported OCD symptoms, CBD would predict acute cannabis-related reductions in compulsions, tolerance to the effects of cannabis on OCD symptoms would develop over time, and that symptoms of OCD would be maintained over time.

Method

Procedure

To bypass federal restrictions on the administration of cannabis to research participants, archival data were obtained from Strainprint® Technologies (Strainprint®). Strainprint® is a real-world technology platform with a medical cannabis journaling app which provides medical cannabis patients with a means to track changes in symptom severity as a function of different strains and doses of cannabis. When first using the app, Strainprint® users indicate the conditions and symptoms that they use cannabis to manage as well as the conditions to which each symptom is associated. Immediately prior to using cannabis, patients select the symptom(s) they are experiencing and rate

Table 1
Cannabis Use Characteristics.

	Dose (# of Puffs)		THC (%)		CBD (%)	
Symptom	*M* (*SD*)	Range	*M* (*SD*)	Range	*M* (*SD*)	Range
Intrusions	6.50 (4.35)	1 – 30	16.46 (5.11)	0 – 28	0.96 (3.37)	0 – 20
Compulsions	10.27 (6.21)	1 – 25	13.47 (6.87)	0.52 – 28	3.55 (5.77)	0 – 25
Anxiety	8.50 (6.09)	1 – 30	13.62 (7.23)	0 – 84.4	3.41 (5.75)	0 – 25

Note: The table shows the means (*M*), standard deviations (*SD*), and ranges for the number of puffs, THC concentrations, and CBD concentrations used by the sample to self-medicate for intrusions, compulsions, and anxiety.

their baseline severity using a scale ranging from 0 (none) to 10 (extreme). Specifically, patients in the present investigation rated the severity of their intrusive thoughts by responding to the prompt "How intrusive are your thoughts?," they rated the severity of their compulsions by responding to the prompt "How bad is your compulsive behavior?," and they rated the severity of their anxiety by responding to the prompt "How bad is your anxiety?" After indicating the symptoms and conditions they are using cannabis to treat, patients are prompted to enter the strain of cannabis they are about to use and the producer from whom they obtained that cannabis. The Strainprint® app pulls information from Canadian producers' websites on the percentage of THC and CBD in over 3,000 strains. If this information is not pre-populated by the app, individuals can enter the THC and CBD concentrations manually. Further, users indicate their method of administration (e.g., smoke, vape, dab bubbler, edible, etc.) and the quantity of cannabis used (e.g., number of puffs). Finally, after an onset period determined by their selected method of administration (e.g., 20 minutes after smoking), users are prompted to re-rate their symptom severity.

For the present study, data were obtained from individuals who self-reported OCD as a condition, used the app to track changes in intrusive thoughts, compulsive behavior, and/or anxiety, and who further indicated that these symptoms were associated with their condition of OCD. These specific symptoms were selected because they were the symptoms most closely related to OCD that were available within the Strainprint® app. The obtained data included anonymous ID codes, cannabis treatment session numbers, gender, age, condition, symptom, self-reported symptom severity before and after each tracked session, cannabinoid content (% THC, % CBD), method of administration, and dose used for each cannabis use session, as well as the method of obtaining the cannabinoid content data (i.e., producer vs. app user). The Washington State University Office of Research Assurances determined that this study was exempt from the need for review by the Institutional Review Board.

Inclusion/Exclusion Criteria

Given that different routes of administration can produce differential effects across varying periods of time, analyses were restricted to sessions involving inhaled cannabis (e.g., smoking, vaping), which is the most common route of administration (Sexton et al., 2016). Further, only sessions in which symptoms were re-rated within 4 hours of cannabis use were included, since the effects of inhaled cannabis dissipate after 3-4 hours (Grotenhermen, 2003; Menkes et al., 1991). Finally, given concerns about the validity and reliability of user generated data, only sessions for which THC and CBD concentrations were obtained directly from producers were analyzed.

Participants

The final dataset included a total of 1,810 cannabis use sessions spanning a 31-month period (March 2017 – October 2019) that were tracked by 87 individuals (33 men, 53 women, 1 undisclosed) self-identifying as having OCD. The sample ranged in age from 18 to 56 (M = 32.00, SD = 8.80). Breaking these down by symptom, 23 of these individuals (8 men, 15 women) collectively used the app 393 times to track changes in intrusive thoughts, 37 individuals (11 men, 26 women) used the app a total of 263 times to track changes in compulsive behavior, and 77 individuals (31 men, 45 women, 1 undisclosed) collectively used the app 1,154 times to track changes in anxiety from before to after cannabis use. Table 1 displays descriptive statistics pertaining to the cannabis used (i.e., dose, THC, CBD concentrations).

Data Analysis

The percent of cannabis use sessions involving reductions, exacerbations, and no changes in severity were computed for each symptom. To further examine changes in symptom severity from before to after cannabis use, two-time point latent change score (LCS) models were used. These models allowed us to assess changes in OCD symptoms within subjects over time, and as a function of specific predictors of interest (e.g., gender, dose, cannabinoid content). A detailed description of this approach is provided in Cuttler et al. (2020). All LCS models were fit using Mplus version 8.3 (Muthén & Muthén, 2017).

To examine changes in baseline OCD symptom severity ratings and dose of cannabis used over time/cannabis use sessions, longitudinal multilevel models (MLM) were used. The fixed and random linear effects of time/cannabis use session on baseline severity and dose were estimated using SAS Proc Mixed, with maximum likelihood estimation and incomplete data treated using missing at random assumptions. Alpha was set at .05 (two-tailed) for all analyses.

Results

Percentage of Sessions Involving Symptom Change

The majority of cannabis use sessions resulted in reductions in intrusions (89.6%), compulsions (95.4%), and anxiety (93.8%). In contrast, only a small number of sessions were associated with a worsening

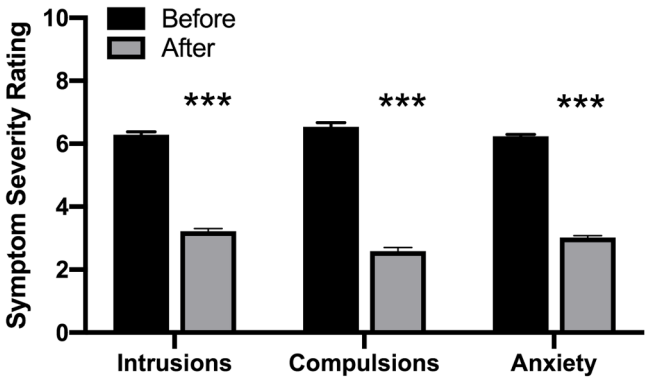

Fig. 1. Change in Symptom Severity Ratings Before and After Cannabis Use. Scores could range from 0 to 10, with higher scores indicative of worse symptom severity. *** $p < .001$

Table 2
LCS Models Predicting Change in Intrusive Thought Severity Ratings.

	Intrusions		Compulsions		Anxiety	
Predictor	β	*SE*	β	*SE*	β	SE
Time/Cannabis Use Session	0.18**	0.06	0.08	0.07	0.14	0.08
Gender (Women = 0)	-0.02	0.07	-0.01	0.10	-0.03	0.11
THC	0.04	0.04	-0.10	0.10	-0.11	0.10
CBD	0.01	0.07	-0.27*	0.13	-0.14	0.10
Dose	0.10	0.07	-0.17*	0.07	-0.13	0.09

Note: * $p < .05$, ** $p < .01$. The table present three separate LCS models, using time/cannabis use session, gender, THC, CBD, and dose to predict changes in the three symptoms of OCD (intrusions, compulsions, and anxiety). Models containing the interaction between THC x CBD were tested, but no significant interactions were detected, and the inclusion of the interaction term did not alter the pattern of results.

of intrusions (3%), compulsions (2.3%), or anxiety (1.9%). The remaining cannabis use sessions involved no changes in symptoms.

LCS Models Predicting Change in Symptom Severity Ratings

Fig. 1 depicts the average symptom severity ratings for each of the three symptoms both before and after cannabis use. There was a 49% reduction in intrusions, a 60% reduction in compulsions, and a 52% reduction in anxiety after cannabis use. The baseline LCS models confirmed that these decreases were statistically significant (Intrusions: μ_Δ = -3.07, SE = 0.14, $p < .001$; Compulsions: μ_Δ = -3.94, SE = 0.40, $p < .001$; Anxiety: μ_Δ = -3.22, SE = 0.28, $p < .001$). However, the variance of the change in severity ratings revealed that there were individual differences in the reduction of symptoms after cannabis use (Intrusions: estimate = 4.32, SE = 0.38, $p < .001$; Compulsions: estimate = 5.42, SE = 0.60, $p = .001$; Anxiety: estimate = 4.02, SE = 0.44, $p < .001$).

As shown in Table 2, the LCS models predicting change in symptom severity ratings revealed that cannabis use sessions across time predicted changes in intrusive thought severity ratings, while CBD concentrations and dose, predicted changes in compulsive behavior ratings. None of the predictors accounted for a significant portion of unique variance in change in anxiety ratings. The positive value of the regression coefficient for time/cannabis use session suggests that later cannabis use sessions provided less relief from intrusions than did earlier sessions. The negative coefficients for dose and CBD indicate that higher concentrations of CBD and higher doses were associated with greater reductions in compulsions.

MLMs Predicting Changes in Baseline Symptom Severity and Dose Over Time

The MLMs revealed no significant changes in baseline (pre-cannabis use) ratings of severity of intrusions (β = 0.002, SE = 0.001, p = .066), or compulsions (β = -0.001 SE = 0.04, p = .978) across time/cannabis use sessions. In contrast, the results of the MLM examining changes in baseline anxiety ratings suggested there were significant reductions in these ratings across time (β = -0.003, SE = 0.0008, $p < .001$). Finally, while there was no evidence that dose of cannabis used to manage compulsions (β = 0.07, SE = 0.08, p = .347) or anxiety (β = 0.01, SE = 0.03, p = .672) changed over time, significant reductions in dose of cannabis used to treat intrusions were detected over time (β = -0.01, SE = 0.003, p = .002).

Discussion

The goal of this study was to examine the acute effects of cannabis on symptoms of OCD using an innovative methodology that allowed us to bypass federal restrictions on studying the acute effects of cannabis on humans. Using a large dataset of medical cannabis users self-medicating for symptoms of OCD, we found that for the vast majority of cannabis use sessions individuals reported reductions in intrusions, compulsions, and anxiety. Moreover, results indicated that after inhaling cannabis, ratings of intrusions were reduced by 49%, compulsions by 60%, and anxiety by 52%%. Only one previous empirical study has examined the acute effects of cannabis on OCD symptoms in humans and while significant reductions in OCD symptoms were reported from before to after cannabis inhalation, these reductions were no larger than those associated with the placebo (Kayser et al., 2020a). As such, it is possible that the reductions observed in the present study represent expectancy effects that would be found with a placebo. Alternatively, it is possible that the previous study which relied on a small sample and low potency cannabis was underpowered to detect the effects we observed in the present study.

Compulsive behavior demonstrated the most dramatic reductions after cannabis use, and higher concentrations of CBD were associated with greater decreases in ratings of the severity of compulsions. This finding is consistent with previous studies demonstrating that CBD decreases compulsive marble burying in rodents (Casorotto et al., 2010, Deiana et al., 2012; Nardo et al., 2014). Collectively, these findings indicate that pure CBD or cannabis high in CBD may acutely reduce compulsions. These results are promising because CBD is not associated with the states of intoxication produced by THC, potentially making it a more desirable therapeutic agent. Nevertheless, Kayser et al. (2020a) found that smoked cannabis with 10.4% CBD and 0.4% THC reduced OCD symptoms but not significantly more than a placebo. As such, the present finding may once again be driven by users' expectations about the effects of CBD on OCD symptoms and larger scale clinical trials are needed to further examine the effects of CBD on OCD symptoms both acutely and over time.

Time cannabis use sessions was a significant predictor of changes in intrusions, with the positive value of this coefficient indicating that earlier cannabis use sessions were associated with larger decreases in intrusions than later sessions. This is indicative of the development of tolerance to the effects of cannabis on intrusions. However, examinations of changes in dose across time revealed that the dose of cannabis used to manage intrusions decreased across time, which conflicts with the notion that users are developing tolerance. Nevertheless, because dose was included as a predictor in the LCS model with time it was controlled for, meaning that the diminishing reductions in intrusions across time are independent of the decreases in dose. This suggests that users may indeed become tolerant to the effects of cannabis on intrusions over time. Alternatively, it may be that expectancy effects played a role in the observed symptom reductions and that declining expectations about the likelihood that cannabis would benefit their intrusions occurred over time.

In contrast, an MLM revealed that dose used to treat compulsions and anxiety remained static across time. Furthermore, dose was found to be a significant predictor of reductions in compulsions, with higher doses producing larger reductions. Therefore, despite experiencing more relief from larger doses, individuals are reporting using consistent doses across time for compulsions, and despite obtaining less relief from intrusions over time, individuals are reporting using smaller doses over time.

Baseline severity of anxiety was found to decrease over time. In contrast, neither baseline compulsions nor intrusions appeared to improve or worsen over the 31-month time period of the study. This suggests that as individuals continue to use cannabis to manage OCD their intrusions and compulsions are neither aggravated nor ameliorated across time. However, this contradicts recent evidence that synthetic cannabinoids combined with more conventional treatments decrease symptoms of OCD over time (Cooper & Grant, 2016; Kayser et al., 2020; Sacdeva et al., 2015; Schindler et al., 2008). Nevertheless, it is possible that individuals in the present study were

not involved in conventional treatments for OCD and it may be that cannabis only decreases these symptoms in the long-term when it is used in combination with such conventional treatments. Given the non-experimental nature of the present study it is also possible that the lack of changes in baseline intrusions and compulsions over time simply reflects a tendency for individuals to self-medicate with cannabis once these symptoms reach a specific threshold. Similarly, it is also possible that people's threshold for tolerating anxiety decreases over time and that they begin to self-medicate with cannabis at lower levels of anxiety. Future controlled longitudinal research is needed to determine the direction of these effects.

Limitations of the present study include possible sampling bias, lack of clinician-verified diagnoses of OCD, the measures of OCD symptoms, and the non-experimental nature of the study. Specifically, it seems likely that the sample predominantly comprises individuals who find cannabis effective in managing their symptoms. Individuals who find it ineffective and/or who do not tolerate its side effects would likely stop using cannabis and the app to track such use. This is further supported by evidence of individual differences in the efficacy of cannabis in reducing symptoms. Therefore, it is likely that a sub-set of individuals with OCD would not be interested in using cannabis and/or that they would not tolerate its effects and/or potential side effects. Further, it was not possible to verify self-reported OCD diagnoses. Nevertheless, OCD symptoms occur on a continuum (Olatunji et al., 2008) and sub-clinical symptoms serve as a useful proxy to understanding clinically severe OCD (Gibbs, 1996).

Because the app was created for industry use rather than scientific investigations, only a single item was used to rate each symptom. While single item indicators of constructs such as stress have been demonstrated to possess content, criterion, and construct validity (Elo et al., 2003), it is unclear whether this would generalize to the indicators of intrusions, compulsions, and anxiety used in the Strainprint® app. Given the terms intrusive thoughts and compulsive behavior were not defined within the app it is possible that some individuals were not able to properly distinguish between these symptoms, which would reduce the validity of these measures. Nevertheless evidence of differences in the size of the symptom reductions (49% for intrusions and 60% for compulsions) as well as findings of different predictors of these reductions suggests that the sample was differentiating between these two symptoms.

Finally, it was not possible to experimentally manipulate cannabis use or obtain a placebo control group. In the absence of these controls we cannot make causal conclusions nor rule out expectancy effects. Indeed, given recent evidence from Kayser et al. (2020a) that smoked cannabis reduced OCD symptoms but not more so than a placebo, it is likely that at least some of the observed symptom reductions can be attributed to users' beliefs about the acute effects of cannabis on these symptoms. Finally, the lack of experimental manipulation and the presence of individual differences in the number of tracked sessions also make it difficult to interpret changes in baseline symptoms across time.

These limitations are offset by several strengths. First, the data were obtained from individuals who were using a large variety of cannabis products in their natural environments. Indeed, the experience of using cannabis while being observed in a more sterile laboratory environment may be anxiety provoking for some individuals who might otherwise find the drug anxiolytic. As such, these results are highly ecologically valid and are likely generalizable to the broader population of medical cannabis patients using a variety of differing strains of cannabis in their own environments. Finally, the ability to track changes in symptoms across a large number of cannabis sessions (> 1,800) over a 31-month time period are additional strengths of the study.

In conclusion, results from the present study indicate that inhaled cannabis may acutely reduce symptoms of OCD. While the symptom severity ratings were reduced by approximately 50-60% from immediately before to after cannabis use, there was evidence that cannabis-associated reductions in intrusions may diminish over time. Collectively these results indicate that cannabis may have short- but not long-term beneficial effects on symptoms of OCD.

Contributors

Dakota Mauzay helped to conceive of the idea, performed the literature review, helped conduct the analyses, and wrote the first draft of the manuscript. Emily LaFrance helped to conceive of the research questions, conduct the analyses, and edit the manuscript. Carrie Cuttler conceived of the idea and research questions, obtained the data, assisted with analyses, created the figure, interpreted the results, and contributed to the preparation of all components of the manuscript.

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Declaration of Competing Interest

None of the authors have conflicts of interest to declare.

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ATTACHMENT #8

Patterns of Cannabis Use Among Individuals with Obsessive-Compulsive Disorder: Results from an Internet Survey

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Abstract

Background: Americans increasingly use cannabis, including those with psychiatric disorders. Yet little is known about cannabis use among individuals with obsessive-compulsive disorder (OCD). Thus, we conducted the first survey of cannabis users with OCD.

Methods: Adults with OCD (i.e., prior professional diagnosis and/or score above the cutoff on a validated scale) who reported using cannabis were recruited from internet sources to complete a survey querying demographic information, medical/psychiatric history, cannabis use patterns, and perceived cannabis effects.

Results: Of 1096 survey completers, 601 met inclusion criteria. Inhalation/cannabis flower were the most common method/formulation participants endorsed; most identified using high-potency cannabis products; 42% met criteria for cannabis use disorder. Nearly 90% self-reported using cannabis medicinally, 33.8% had a physician's recommendation, and 29% used specifically to manage OCD symptoms. Most participants reported cannabis improved obsessions/compulsions; those with increased obsession severity perceived less benefit. Finally, most participants were not receiving evidence-based OCD treatment, and the odds of receiving treatment decreased with increased cannabis use.

Conclusions: In this survey, participants with OCD reported both subjective benefits and harms from cannabis use. Future research should clarify the risks and benefits of cannabis use to those with OCD and develop treatment models to better support this population.

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Keywords

Obsessive Compulsive Disorder; Cannabis; Cannabinoids; Treatment; Cannabis Use Disorder

1. Introduction

Obsessive-compulsive disorder (OCD) is a disabling illness affecting approximately 2-3% of the population (Stein et al., 2019). Individuals with OCD experience intrusive thoughts (obsessions) and repetitive behaviors (compulsions), which lead to functional impairment. Emerging preclinical findings indicate that abnormal functioning in the brain's endocannabinoid system (ECS) may contribute to OCD symptoms (Kayser et al., 2019). The ECS is a regulatory neurotransmitter system that is involved in various homeostatic functions throughout the central nervous system and is targeted by cannabis and related substances (cannabinoids; Lu & MacKie, 2016). Both rodent models and human neuroimaging studies link ECS activity to changes in neurocognitive functions involved in OCD pathology; specifically, excessive threat response (Apergis-Schoute et al., 2017; Pietrzak et al., 2014), impaired fear learning (Jenniches et al., 2016; McLaughlin et al., 2015), and excessive deployment of habitual behavioral strategies (Gremel et al., 2016; Voon et al., 2015). In preclinical studies, ECS modulators attenuated threat responses (Mayo et al., 2019), facilitated fear extinction (Hammoud et al., 2019), and promoted goal-directed over habitual behavior action selection (Gianessi et al., 2021). Cannabis and other ECS modulators might therefore affect obsessions and/or compulsions.

However, the directionality of these potential effects is unclear: For example, agents that facilitate activity at the cannabinoid 1 receptor have been found to both promote and protect against habitual behavior development in different studies (Gianessi et al., 2021; Gremel et al., 2016), and thus might increase or decrease compulsions. Due to a lack of research in patients, it remains unclear whether cannabinoids are beneficial or harmful to individuals with OCD.

While research on cannabis and cannabinoids in OCD is emerging slowly, popular interest in their recreational and therapeutic uses is exploding. Between 2008 and 2018, the number of American adults reporting near-daily cannabis use grew by 4.8 million (Lipari & Park-Lee, 2019). Cannabis products are increasingly marketed as treatments for psychiatric conditions like OCD and anxiety (Richter & Levy, 2014; Subritzky et al., 2016), and as of May 2021, 37 states and the District of Columbia (DC) have legalized medicinal cannabis, while 17 states and DC permit recreational cannabis use. Physician-recommended cannabis is increasingly accessible to Americans, but medicinal cannabis use (i.e., using to treat one or more medical conditions) also occurs regardless of state policies or physician supervision (Azcarate et al., 2020). The exact prevalence of medicinal or recreational cannabis use among individuals with OCD is unknown. However, in 2019, a specialty clinical program reported that nearly 30% of adults seeking intensive OCD treatment endorsed current or past cannabis use (Storch & Kay, 2019).

As trends towards greater access and legalization continue, there is a growing public health need to understand why individuals with OCD use cannabis and the risks and benefits of

cannabinoids to this population. To explore this issue, the present study surveyed a large sample of adults with both OCD (based on scores on a validated diagnostic scale or self-reported professional diagnosis) and cannabis/cannabinoid use.

1.1 Prior studies involving cannabis use and OCD

1.1.1 Observational studies of OCD symptoms in cannabis users—

Small observational studies suggest that cannabis can have mixed effects on OCD symptoms. For instance, in 132 adolescents receiving residential treatment for cannabis use, greater pre- and post-treatment OCD symptom severity predicted more frequent post-treatment cannabis use, possibly reflecting participants' self-medication with cannabis (Albertella & Norberg, 2012). Similarly, another study including 44 users of both cannabis and ecstasy found that greater OCD symptom severity at baseline and 18-month follow-up was associated with more frequent cannabis use (Daumann et al., 2004). These studies are limited by the fact that participants were not primarily diagnosed with or treated for OCD.

Another study used a mobile app to track acute changes after smoking cannabis in 87 medicinal cannabis users who self-identified as having OCD symptoms (Mauzay et al., 2021). Participants reported short-term improvement in OCD symptoms and anxiety in more than 90% of the tracked cannabis use sessions, although pre-session symptom severity remained static over the course of repeated sessions. Study limitations included a modest sample size and lack of validated assessments of OCD symptoms and diagnosis.

1.1.2 Clinical studies of cannabinoids in patients with OCD—

Directly studying cannabis in human trials is challenging because of its Schedule I classification by the US Drug Enforcement Administration (DEA). Trials of single synthetic cannabinoids or isolated cannabis constituents have been more feasible to conduct given that many lack Schedule I restrictions: Agents tested include nabilone, a synthetic analogue of Δ-9-tetrahydrocannabinol (THC, the primary psychoactive component in cannabis) which is FDA-approved for treating chemotherapy-associated nausea and vomiting (Fraser, 2009; Kayser, Raskin, et al., 2020), and Epidiolex, an isolate of cannabidiol (CBD, another cannabis constituent with different mechanistic properties than THC), which is FDA-approved for two rare forms of pediatric epilepsy (Gaston, Bebin, Cutter, Liu, & Szaflarski, 2017; Hurd et al., 2019).

Three case reports document symptomatic improvement in patients with OCD who received dronabinol, an oral form of THC (J. J. Cooper & Grant, 2017; Schindler, Anghelescu, Regen, & Jockers-Scherubl, 2008). In another case report, a patient's symptoms resolved over 20 months of medicinal cannabis treatment (Szejko et al., 2020). There have been only two small cannabinoid trials in individuals with OCD. The first, a randomized, placebo-controlled, within-subjects human laboratory study in 12 adults, found that smoked cannabis containing primarily THC or CBD did not differ from placebo in its acute effects on OCD symptoms (Kayser, Haney, et al., 2020). In a second small pilot trial, 11 patients received nabilone over four weeks. Results suggested that nabilone had little effect on OCD symptoms on its own, but may have augmented the effects of exposure-based psychotherapy when both were delivered simultaneously (Kayser, Raskin, et al., 2020).

However, all of these studies were limited by small sample sizes, and the nabilone study lacked a placebo control. Moreover, these single synthetic and isolated cannabinoids are chemically and functionally distinct from cannabis flower, which contains >140 constituents with varied psychoactive properties (Russo & Marcu, 2017) and is by far the most common cannabinoid that recreational and medicinal cannabis users report using (Sexton et al., 2016a).

1.1.3 Surveys of OCD symptoms in cannabis users—

Given these challenges, direct patient surveys have become an important tool to better understand how cannabis interacts with psychiatric symptoms and disorders. Four prior anonymous surveys have explored the relationship between OCD symptoms and cannabis use. The first, a cross-sectional survey of an unselected birth cohort of 930 American 18-year-olds, found a higher rate of cannabis dependence in those who met OCD criteria (n=7 out of 37) than those who did not (n=45 out of 893; i.e., 19% versus 5%; Douglass, Moffitt, Dar, McGEE, & Silva, 1995). Three others (all in cannabis-using young adults, n=159, 430, and 177, respectively) found that self-reported OCD symptom severity (as measured by the Obsessive-Compulsive Inventory, Revised [OCI-R]) predicted cannabis misuse (Bakhshaie et al., 2020; Buckner et al., 2007; Spradlin et al., 2017). Two of these found that the relationship between OCD symptom severity and cannabis use was mediated by coping motivations (i.e., cannabis use to relieve stress and negative affect; Bakhshaie et al., 2020; Spradlin et al., 2017); one also identified an association between higher scores on the obsessing symptom subdomain and increased cannabis-related problems (e.g., failure to complete work/school obligations due to cannabis use; Spradlin et al., 2017). However, because few participants in these surveys met OCD criteria (n=37, 47, 57, and 50, respectively), the generalizability of their findings is unclear.

1.2 Rationale for the present study

To begin exploring patterns and effects of cannabis use in OCD, we conducted the first internet survey of adults with OCD (based on either self-report of diagnosis by a mental health professional or score on a validated symptom severity scale) and experience using cannabis products (≥1 reported lifetime use). Our goals were to characterize a population of cannabis users with OCD, examine their patterns of cannabis use (i.e., methods and formulations; medicinal vs. recreational use), and assess their self-reported perceptions of cannabis effects on OCD symptoms. Based on the extant literature, we made three hypotheses: First, prior research indicates that cannabis effects may vary based on demographics. Older age (Sexton, Cuttler, & Mischley, 2019), male gender (Z. D. Cooper & Craft, 2018b), and lower scores on the obsessing OCI-R subdomain (Spradlin et al., 2017) have all been associated with higher perceived benefit from cannabis. Thus, we expected that participants who were older, male, and reported less severe obsessions would have better subjective response to cannabis (i.e., higher YBOC-CS scores). Second, considering the two previous surveys linking OCD symptom severity to cannabis misuse (Bakhshaie et al., 2020; Spradlin et al., 2017), we also hypothesized that more severe OCD symptoms would be associated with more frequent cannabis use and higher risk for cannabis use disorder (CUD). Finally, because some patients may use cannabis as a replacement for psychiatric medication (Corroon et al., 2017) and cannabis use may also limit motivation to seek or access to

evidence-based OCD treatment (Storch & Kay, 2019), we hypothesized that more frequent cannabis use would reduce the likelihood that participants were currently receiving evidence-based treatment for OCD. For simplicity, throughout this report we use the term "cannabis" to refer to both cannabis plant material and cannabis-related substances (e.g., cannabis concentrates with varied THC/CBD concentrations); we defined these terms explicitly in all survey content.

2. Methods

2.1 Recruitment

The survey was developed by the authors and conducted under the auspices of the (Removed to preserve anonymity). With Institutional Review Board approval (Protocol #7745), it was posted online on SurveyMonkey.com between 1/7/2019 and 12/23/2019. Participants self-referred from advertisements on a variety of internet sites including forums on major portals (e.g., Reddit, Yahoo), social media pages (e.g., Facebook, Twitter, Instagram), consumer organizations (e.g., the International OCD Foundation, Anxiety and Depression Association of America, MQ: Transforming Mental Health), the nOCD mobile app, and (our website, details removed to preserve anonymity). Previous participants in research at our clinic who expressed interest in future studies and met eligibility criteria were also invited to participate.

We recruited adults (age≥18) who self-identified as having OCD symptoms and at least one lifetime use of cannabis, cannabis products (e.g., edibles), or cannabinoid isolates (e.g., THC capsules, CBD oil). Advertisements linked to a page informing participants that the survey would ask questions about their OCD symptoms and experiences using cannabinoids, that no identifying information would be collected, and that they would be offered entry into a raffle for a $100 gift card upon survey completion. Participants electronically provided informed consent before answering any survey questions.

2.2 Survey Content

2.2.1 Overview—Participants were queried about their background and demographics (e.g., age, gender, race, ethnicity, occupation). We also asked about their history of OCD symptoms (i.e., illness onset, receipt of professional diagnosis), prior OCD treatments (including selective serotonin reuptake inhibitors [SSRIs] or cognitive behavioral therapy [CBT] consisting of exposure and response prevention [EX/RP], the recommended first-line treatments for OCD; Koran et al., 2007) and history of other psychiatric and medical comorbidities and treatment. When querying about past psychotherapy treatment, we asked patients who had received CBT to specify whether this included exposure (i.e., EX/RP), as in prior surveys (Patel et al., 2017). Using the validated questionnaires listed below, we assessed OCD symptom severity and dimensions, patterns of cannabis use, CUD symptoms, and self-report of change in OCD symptoms following cannabis use.

In addition to these scales, the survey asked participants to describe qualitatively how cannabis affected their obsessions, compulsions, and anxiety symptoms, and to provide any

relevant information the questionnaires did not otherwise capture. On average, participants spent 16 minutes completing the survey.

2.2.2 Validated measures

a) Obsessive-Compulsive Inventory, Revised (OCI-R; Huppert et al., 2007): The OCI-R is an 18-item self-report questionnaire evaluating OCD symptom severity, which has been validated against the clinician-administered Yale-Brown Obsessive-Compulsive Scale (YBOCS). The OCI-R is widely-used to assess for OCD symptoms in nonclinical samples (Goodman et al., 1989). The scale measures symptom severity overall and in six specific symptom clusters (checking, hoarding, neutralizing, obsessing, ordering, and washing). Higher scores suggest greater symptom severity (overall and for individual symptom subdomains), with scores of 15-19, 20-34, and ≥35 indicating mild, moderate, and severe symptoms, respectively. Prior research found a cutoff of 21 was optimal for distinguishing individuals with OCD from non-anxious controls (Foa et al., 2002), although higher cutoffs have also been proposed (Abramovitch et al., 2020). Consistent with our prior survey work (Patel et al., 2017), we used a cutoff of 21 to define clinically significant OCD given our goal of recruiting individuals with a range of symptom severities. As a conservative measure, we also conducted a sensitivity analysis using a higher cutoff as described below.

b) Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU; Cuttler & Spradlin, 2017): The DFAQ-CU is a 33-item scale evaluating patterns of cannabis use, forms of cannabis used (e.g., cannabis flower, concentrates, edibles), and methods used to ingest cannabis (e.g., cigarettes, pipes, vaping). The DFAQ-CU includes frequency and quantity subscales; higher scores indicate more frequent and greater quantity of cannabis used. The measure also queries participants about their knowledge of the THC and CBD content of the products they typically use.

c) Cannabis Use Disorder Identification Test, Revised (CUDIT-R; Adamson et al., 2010): This 8-item scale asks about symptoms of cannabis use disorder (CUD) over the past 6 months (e.g., failure to meet responsibilities). Higher scores suggest greater CUD symptomatology; scores ≥8 indicate problematic cannabis use, and scores ≥12 suggest probable CUD.

d) Yale-Brown Obsessive-Compulsive Challenge Scale (YBOC-CS): The YBOC-CS is a 10-item Likert scale asking about current OCD symptoms that was previously used in pharmacological challenge studies of ketamine (Rodriguez et al., 2011, 2013) and our human laboratory study of cannabis (Kayser, Haney, et al., 2020). In this survey, participants were asked to indicate how cannabis typically affects their OCD symptoms with regard to each of the ten items queried by the YBOC-CS (e.g., time spent, degree of control over, and overall severity of obsessions and compulsions).

2.3 Sample

Participants were included in final analyses if they met all three of the following criteria: a) met OCD criteria, based on self-reported professional diagnosis or an OCI-R score≥21, b)

reported they had used cannabis at least once, and c) completed all required (i.e., non-qualitative) survey items.

2.4 Data Analysis

Statistical analyses were performed using SPSS25 (SPSS Statistics for Windows, Version 25.0, IBM Corp. Armonk, NY). Little's Missing Completely at Random (MCAR) test was non-significant (p=.273), suggesting data were unlikely to be missing at random, and the overall amount of missing data was low (<5%, with individual models missing between 4.7 and 10.1% of observations). Thus, pairwise deletion was used to account for missing data (Tabachnick, B. G. & Fidell, 2019). We computed descriptive statistics for demographic characteristics, psychiatric/medical history and comorbidity, OCD symptom severity, CUD symptoms, cannabis use patterns, and self-reported response to cannabis (i.e., YBOC-CS). We used multivariate linear regression to test the hypothesis that demographic variables and/or OCD symptom dimensions would predict participants' subjective response to cannabis. We also computed bivariate correlations (for continuous variables) and chi-square statistics (for categorical variables) between OCD- and cannabis-related outcomes to test the hypothesis that OCD symptoms would be associated with increased cannabis use and CUD symptoms. Finally, we used multiple logistic regression to test the hypothesis that cannabis use would predict whether participants were currently receiving evidence-based treatment for OCD. Considering recent literature proposing an OCI-R cutoff of 27 to establish OCD diagnosis, we conducted a sensitivity analysis by re-computing the above statistics in the subset of participants with OCI-R scores ≥27. As this did not change the overall outcomes of any of our analyses, all results hereafter reflect the entire group of participants who met inclusion criteria. All statistical tests were two-tailed and conducted using α=0.05; given the exploratory nature of this study, no corrections were made for multiple comparisons.

3. Results

3.1 Demographics

Of the 1476 individuals who provided consent, 1096 started the survey (response rate: 74.2%). Of those 1096, 601 participants met eligibility criteria (i.e., likely OCD diagnosis, at least one lifetime cannabis use episode, and survey completion). Demographic characteristics of participants are presented in Table 1; there were no significant differences in demographic characteristics between the 1096 who started the survey and the 601 who met eligibility criteria and were included in subsequent analyses.

The 601 eligible participants included residents of 47/50 US states as well as DC, Puerto Rico, and the US Virgin Islands. Cannabis' legal status has recently changed in several of these states. Based on state policies at the time this survey was administered, 44.0% of responses were from states where cannabis was fully-legal (i.e., both recreational and medicinal use had been legalized), 41.3% from states where only medicinal use was legal, and 14.7% from states where cannabis use was fully-illegal. The five most-represented states included those where cannabis was fully-legal (California, Michigan), only medicinal use was legal (New York, Florida), and cannabis was fully-illegal (Texas).

3.2 OCD diagnosis and symptom severity

The 601 participants were 28.6 years old on average (SD 8.6, range 18-72), with a female:male ratio of approximately 1:1; most participants were white and non-Hispanic. Mean OCI-R score was 33.4 (SD 13.1, median 33.0. Mean age of OCD symptom onset was 9.9 years (SD 5.1, median 9.0). Of the 601 participants, 522 (86.9%) were eligible based on OCI-R scores ≥21, while 79 (13.1%) scored <21 but were eligible based on a previous OCD diagnosis from a mental health professional. In total, 238 of the 601 eligible participants (39.6%) reported a prior OCD diagnosis, which they received on average at age 19.0 years (SD 6.6, median 18.0).

3.3 Psychiatric and Medical Comorbidities

Table 2 depicts rates of self-reported comorbid conditions. Most participants reported at least one medical or psychiatric diagnosis aside from OCD. The most commonly-endorsed psychiatric comorbidities were generalized anxiety disorder, major depressive disorder, and posttraumatic stress disorder (PTSD); chronic pain, migraine, and asthma were the most common medical comorbidities.

3.4 Treatment Utilization

As shown in Table 2, fewer than half of participants reported currently receiving treatment for OCD, and the most frequently endorsed current treatment was “alternative treatments” (e.g., mindfulness meditation, yoga, herbal supplements). More than half (n=315, 53.8%) reported lifetime medication use, including 236 participants (39.3%) who received serotonin reuptake inhibitors (SRIs, including SSRIs and clomipramine). The most frequently-endorsed lifetime psychotherapy treatment was CBT (but without exposure) in 257 participants (42.8%); only 99 participants (15.5%) endorsed lifetime EX/RP. About a quarter (n=160 participants, 26.6%) endorsed at least one psychiatric hospitalization.

3.5 Cannabis Use Patterns

As shown in Table 3, of the 601 participants, 539 reported using cannabis at least one day over the past month (mean: 20.1 days, SD 11.8, range 0-31), and 344 (57.3%) reported using cannabis at least daily. On average, participants reported that onset of their OCD symptoms preceded their first cannabis use episode (ages 9.9±5.4 vs. 17.3±4.2, respectively).

Table 3 also depicts the methods and formulations of cannabis that participants endorsed using. Participants were queried about both their primary (i.e., most commonly-used) methods/formulations and any others they used at least 25% of the time. Of the 601 participants, the most common primary method was vaporizing (endorsed by around one-third), followed by joints/blunts (endorsed by around one-fifth). Cannabis flower was the most commonly primary formulation (endorsed by nearly 65%), followed by cannabis concentrates (endorsed by about 25%).

For formulations used at least 25% of the time, participants were asked about their knowledge of the typical THC and CBD content of products they used. Responses were grouped into high (i.e., >10%), low (i.e., <10%), or unknown THC/CBD concentrations. Of the 42.1% of participants who used edibles (n=251), nearly 75% reported being unaware of

their typical THC/CBD contents; thus we focused on cannabis flower (n=472) and cannabis concentrate users (n=379). The most common THC concentration reported by both cannabis flower and cannabis concentrate users was high-THC (by 59.2% and 69.7%, respectively), followed by "I don't know" (by 36.2% and 25.6%, respectively). Around a third of concentrate users (n=126 [33.2%]) reported using products with extremely high THC contents (>80%). Regarding CBD concentrations, cannabis flower users most commonly reported "I don't know" (45.7%) followed by low-CBD (33.6%); reports from concentrate users were evenly divided between "I don't know" and low-CBD (37.4 vs. 37.9%, respectively).

3.6 Medicinal Cannabis Use

Of the 601 participants, 203 (33.8%) reported having a physician's recommendation to use cannabis; indications included OCD, anxiety, PTSD, depression, insomnia and pain. However, only 66 (11.0%) reported using cannabis exclusively medicinally: 447 (74.3%) reported both medicinal and recreational use, and 88 (14.6%) reported only recreational use. Of the 601 participants, 175 (29.1%) reported they used cannabis specifically to manage OCD symptoms.

3.7 Subjective Cannabis Effects

On the YBOC-CS, most participants reported that cannabis typically improved their obsessions n=457 [68.3%]), but to varying degrees ("a little better", n=225 [37.4%]; "a lot better", n=188 [31.3%]). Similarly, most reported that cannabis improved their compulsions (n=393 [65.4%]; "a little better", n=220 [36.6%]; "a lot better", n=173 [28.8%]). A subset reported that cannabis worsened obsessions (n=104, 17.3%) or compulsions (n=81, 13.8%). Fifty (8.3%) and 127 (21.1%) reported that cannabis had no effect on overall obsessions and compulsions, respectively.

Correlation analysis revealed significant positive associations between subjective cannabis effects (i.e., YBOC-CS scores, with higher scores indicating greater perceived benefit) and all OCI-R subdomains except obsessing (all correlations > 0.10, all P's < .005). Multivariate linear regression revealed two significant predictors of YBOC-CS scores: Total medical comorbidities, an increase in which was associated with greater perceived benefit, and the obsessing symptom subdomain, for which higher scores were associated with less perceived benefit (Table 4; see Supplemental Materials for detailed results of bivariate correlations and regression analyses).

Qualitative reports described a range of cannabis effects on OCD symptoms, though most focused on its subjective benefits. 17 participants (2.8%) described integrating cannabis into psychotherapy treatment (for example, using before EX/RP sessions). Figure 1 includes selected examples representing the range of responses.

3.8 Problematic Cannabis Use

Of the 601 participants, 253 (42.1%) met CUD criteria (CUDIT-R≥12), and 394 (65.6%) for problematic cannabis use (CUDIT-R≥8). Participants meeting CUD criteria were less likely to be in treatment (n=78, 31%; χ^2=7.4, df=1, p=.007) and less likely to have ever received

psychiatric medications (n=133, 53%; χ^2=11.9, df=1, p<.001) or CBT (n=33, 13%, χ^2=4.8, df=1, p=.028). They were more likely to be male (n=140, 55%; χ^2=17.5, df=2, p<.001) and to endorse comorbid substance use disorder (n=41, 16.2%; χ^2=4.0, df=1, p=.006) and migraine (n=35, 14%; χ^2=6.54, df=1, p=.011). There were no correlations between total OCD symptoms and cannabis use frequency or CUD symptoms as assessed by total CUDIT-R scores. Given that frequent cannabis use may not be problematic *per se*, we also computed correlations without the CUDIT-R frequency items (i.e., only items 3-8). This did not change our findings; thus, subsequent analyses included the CUDIT-R total score. There were significant negative correlations between several individual OCD symptom subdomains and individual CUDIT-R item scores. The exception to this was with hoarding symptoms, which were positively correlated with the CUDIT-R frequency items; details in Supplemental Materials).

We used multiple logistic regression to explore whether demographic, OCD-related, and cannabis-related predictors affected participants' current treatment status (i.e., in OCD treatment vs. not; Table 5). The odds of being in treatment for OCD decreased with more frequent cannabis use (p=0.003); in contrast, earlier age of OCD symptom onset (p<0.001) and higher scores on the obsessing OCI-R subdomain (p<0.001) increased the likelihood of current OCD treatment.

4. Discussion

To our knowledge, this is the first study to assess patterns of cannabis use in a large sample of individuals with a diagnosis of OCD (based on a prior diagnosis by a healthcare profession or well-established cutoff on the OCI-R, a validated self-report form). There were five major findings. First, individuals with OCD who use cannabis were willing to provide very detailed information regarding their patterns of cannabis use in an online survey. In this sample, participants most commonly used inhalation methods (i.e., smoking or vaporization) to ingest cannabis and most often used cannabis flower over other formulations. Most participants reported either using products with high-THC/low-CBD concentrations or being unaware of the THC/CBD content of the products they used. Second, nearly 90% reported using cannabis for medicinal purposes, despite the fact that only about a third had a physician's recommendation to do so. Further, 29% said they used cannabis specifically to manage OCD symptoms. Third, most participants reported that cannabis improved their OCD symptoms, although greater severity of obsessions was associated with less perceived benefit. Fourth, our sample experienced high rates of cannabis-associated problems: 42% met criteria for CUD, and nearly 70% for problematic cannabis use. Finally, most participants were not currently receiving evidence-based OCD treatment, and the likelihood of this treatment decreased as cannabis use frequency increased.

Americans increasingly use cannabis for both recreational and medicinal purposes (Lin et al., 2016). Like all psychotropic agents, cannabis has the potential to cause beneficial or harmful effects; yet unlike most medical interventions, medicinal cannabis use often occurs without physician oversight or regard to state policies (Azcarate et al., 2020). Cannabis users increasingly report medicinal use to alleviate psychiatric symptoms (including OCD symptoms; Mauzay et al., 2021) and some describe using cannabis as a substitute for

psychotropic medications (Corroon et al., 2017). Yet, a 2019 meta-analyses including 83 studies found insufficient evidence to support treating any psychiatric condition with cannabinoids (Black et al., 2019). Meanwhile, both acute and chronic cannabis use has been linked to adverse psychiatric consequences (De Aquino et al., 2018; Hindley et al., 2020). In this context, there is a pressing public health need to understand how cannabis interacts with psychiatric illnesses like OCD. The present survey was designed with this need in mind.

In this first exploration of the methods and formulations by which individuals with OCD use cannabis, participants most commonly reported using inhalation methods to ingest cannabis flower, patterns of use that reflect findings from other studies of cannabis users (Azcarate et al., 2020; Sexton et al., 2016b; Spindle et al., 2019). Notably, some participants reported using high-potency cannabis products (i.e., containing high THC and low CBD); these included nearly a third of concentrate users who reported using products containing >80% THC. These data are consistent with findings from large epidemiological studies showing increasing use of high-THC cannabis products in the US (ElSohly et al., 2016; Hasin, 2018a), which is potentially concerning given that these products are associated with greater risk for adverse psychiatric consequences (Hindley et al., 2020). Because of our design (e.g., recruiting participants from online venues), it is unclear to what extent this reflects the broader population of adults with OCD who use cannabis. Nonetheless, our findings indicate that clinicians should ask about cannabis use in their patients with OCD and consider counseling cannabis users about potential risks associated with high-potency cannabis products.

As in other studies of cannabis users (Lin et al., 2016; Turna et al., 2019; Wall et al., 2019), most participants endorsed a mix of medicinal and recreational use. One-third of participants had a physician's recommendation to use cannabis for indications including anxiety and OCD; 29% of participants (including those with and without a physician's recommendation) used cannabis specifically to treat OCD symptoms. These findings are notable given that OCD is not currently an indication for medicinal cannabis in any state ("State Medical Marijuana Laws," 12/21/2020), and around 15% of participants resided in states where cannabis was fully-illegal. Discretionary cannabis recommendations (i.e., for indications beyond those specifically approved by state law) are currently permitted in at least nine states and may explain some of our findings. However, recent surveys of medicinal cannabis users suggest that the majority of such use may occur without a physician's recommendation or knowledge (Azcarate et al., 2020; Turna et al., 2020). Thus, it is reasonable to propose that our results also reflect self-medication of OCD symptoms with cannabis, either outside of a medical context or possibly in individuals with a physician's recommendation for a condition other than OCD.

As noted in the Introduction, in an observational study using a mobile app of 87 medicinal cannabis users with self-reported OCD, participants generally reported acute improvements in OCD symptoms following cannabis use (Mauzay et al., 2021). Consistent with these findings, more than 60% of participants in the present online survey indicated that cannabis typically improved their obsessions and compulsions (as measured by the YBOC-CS). Although prior research suggests that cannabis effects may vary with gender (Z. D. Cooper & Craft, 2018a) and age (Gorey et al., 2019), we did not find that these variables predicted

YBOC-CS scores. However, as hypothesized, we did find that greater severity of obsessions (assessed via the OCI-R) predicted worse perception of cannabis effects. Moreover, increased severity of obsessing correlated with less frequent cannabis use. One explanation for these findings could be that cannabis adversely affects obsessions. In this case, patients with prominent obsessions may perceive fewer benefits and thus use less often. Obsessional individuals might also be more likely to seek evidence-based care, perhaps due to the nature of obsessions themselves, or if self-medication of these symptoms with cannabis is ineffective; indeed, we found that participants with increased obsessions were more likely to be in treatment. As others have noted (Spradlin et al., 2017), a third possibility is that obsessional individuals ruminate about adverse cannabis effects and overreport these problems. Regardless of the explanation, our results provide further evidence supporting a link between obsessing and adverse cannabis effects from (and less frequent use of) cannabis.

Counter to our initial hypothesis, we found no correlation between OCD symptom severity (measured by the OCI-R) and problematic cannabis effects (measured by the CUDIT-R). This contrasts with prior survey findings (Spradlin et al., 2017), which could possibly be due to differences in sample: All participants included in our analysis met criteria for OCD, compared to only 13% of participants in the prior study. Nonetheless, our participants experienced substantial cannabis-related impairment in functioning, with nearly half meeting criteria for CUD, and close to 70% for problematic cannabis use (based on their CUDIT-R score). Alarmingly, the CUD rate we observed was over twice the rate for all lifetime cannabis users (19.5%) reported by the 2012-2013 National Epidemiologic Survey on Alcohol and Related Disorders (Hasin et al., 2016). Though not an epidemiological study and prone to recruitment bias, this survey raises a possibility that future studies should examine: That compared to the general population, those with OCD may be more susceptible to developing cannabis-associated problems. Our data suggest that clinicians treating patients with OCD should monitor for and provide additional counseling about the potential risk for CUD and other harms related to cannabis use (particularly when obsessive symptoms are prominent).

Confirming our hypothesis, more frequent cannabis use decreased participants' likelihood of currently receiving treatment for OCD in this sample. Furthermore, although nearly 75% of participants reported a lifetime history of psychiatric treatment, a minority had ever received first-line OCD treatments, including SRIs in only 39.3% and EX/RP in only 15.9%. Why participants were not receiving treatment is unclear. One interpretation is that some individuals with OCD attempt to manage their symptoms with cannabis in lieu of pursuing evidence-based treatments, which aligns with our finding that most participants perceived cannabis as benefitting their OCD symptoms. Alternatively, cannabis use may interfere with receipt of evidence-based treatment, for example when cannabis is an exclusion criterion for enrolling in treatment (as is the case in some specialty programs; Storch & Kay, 2019) or if CUD symptoms limit patients' ability to seek out or engage in care (e.g., inability to follow through with therapy appointments). Given the risks associated with untreated OCD and cannabis-related problems, our findings suggest that providers of OCD treatment may need to re-evaluate "zero-tolerance" policies around cannabis use. Instead, harm reduction strategies or CUD treatments could be integrated with existing approaches. Indeed, effective

treatment models for individuals with OCD and comorbid substance use already exist (Fals-Stewart & Schafer, 1992); expanding these could improve access to care for individuals with OCD and cannabis misuse.

Unexpectedly, around 3% of participants indicated using cannabis during psychotherapy, including before exposure exercises. Though beyond the scope of this survey, understanding the prevalence and motivations for this use in patients with OCD has important treatment implications. For example, if patients use cannabis to cope with exposure-related anxiety, this may become an avoidance behavior that undermines the mechanisms associated with this treatment. Yet there is evidence that THC can facilitate at least one of these mechanisms (i.e., extinction learning, Raber et al., 2019). Thus, cannabinoids delivered concurrently with exposure-based treatment might actually augment its effects in some contexts (as our preliminary study of nabilone in patients with OCD supports (Kayser, Raskin, et al., 2020). Future research should examine how cannabis use impacts the mechanisms and clinical efficacy of exposure treatment.

Strengths of this study include a large sample size of adults meeting OCD criteria (n=601) and use of well-validated measures of OCD symptoms (the OCI-R) and cannabis use (the DFAQ-CU and CUDIT-R). Nonetheless, interpretation of our findings is limited due to our use of a cross-sectional survey design relying on self-reports, without independent confirmation of OCD diagnosis, treatment history, or cannabis use. Moreover, because we recruited participants from online forums, our findings (e.g., that most participants perceived cannabis as beneficial towards their OCD symptoms) could reflect selection bias of individuals who would complete such a study. Perhaps related to this recruitment strategy, participants were predominantly white, non-Hispanic, and highly educated, which may impact the sample's generalizability. Finally, expectancy bias (to which subjective cannabis effects are notoriously susceptible; see Chait et al., 1988; Fillmore, Mulvihill, & Vogel-Sprott, 1994; Kirk, Doty, & De Wit, 1998) may have affected our data.

5. Future Directions

These survey results suggest that cannabis use may be associated with a range of positive and negative subjective effects in individuals with OCD, may be used instead of evidence-based OCD treatments, and may lead to problematic cannabis use and/or CUD. As cannabis use among the general population grows increasingly common (both in the US and worldwide; Hasin, 2018b), use by individuals with OCD is almost certain to expand as well. Thus, improving our understanding of cannabis' potential risks and benefits to those with OCD is crucial. Future research is needed to determine if our survey results are replicable in a larger, more nationally-representative sample. Placebo-controlled trials will be critical in order to objectively test the acute and chronic effects of different cannabis preparations in patients with OCD while accounting for expectancy effects. Similarly, controlled studies are needed to dissect the effects of different cannabis constituents (e.g., THC/CBD) on OCD symptoms. Investigators must also clarify why cannabis users are not accessing OCD treatment, how cannabis use interacts with evidence-based OCD care, and what explains the link between obsessing symptoms and adverse cannabis effects. Finally, it is time to develop effective treatment models for patients with both OCD and problematic cannabis use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In an internet survey, we examined patterns of cannabis use in adults with OCD (n=601)
- Participants reported experiencing both subjective benefits and harms from cannabis use
- Participants with more severe obsessions perceived fewer benefits from cannabis and used less often
- More frequent cannabis use reduced participants' odds of receiving evidence-based OCD treatment
- We discuss implications for treating cannabis users with OCD and topics for future research

Domain	Category	Sample quotes
Effects on Symptoms	**Improved**	"After using a small amount, I relax and am able to not focus on the obsessions. My anxiety drops significantly."
		"Aids me in redirecting my attention elsewhere"
		"It neutralizes or pauses my compulsions and allows me to be kinder"
	Worsened	"Brings about lots of bad thoughts and anxiety"
		"Marijuana, over time, has made my OCD much worse."
		"Severe panic attacks and dissociation, paranoia, and makes OCD a lot worse"
	Varying	"I find different strains of cannabis (indica vs. sativa) have drastically different effects. Indica usually improves my OCD symptoms while sativa makes it much worse."
		"Cannabis can be hit or miss with the OCD dependent on dosage. Too much and it can actually increase it."
		"Indica causes me to obsess over all the conversations I've had throughout the day. Sativa keeps my mind alert and less obsessive."
Effects on Treatment	**Use with EX/RP[a]**	"It helps me have more self-awareness and relax enough to do EX/RP."
		"I take small doses (exactly one puff from a pipe) of marijuana for exposure-response prevention therapy to practice feeling anxiety."
	Use with other treatments	"Cannabis makes it easier for me to use CBT[b] & DBT[c] skills to help cope with my obsessive thoughts. I'm more relaxed so I can talk myself through the intrusive thoughts."

Figure 1. Sample responses to open-ended questions about cannabis effects[a]

[a]EX/RP, exposure and response prevention; [b] CBT, cognitive behavioral therapy; [c]DBT, dialectical behavior therapy

TABLE 1.

DEMOGRAPHIC CHARACTERISTICS[a]

Variable	Participants,[b] n=601
Age	28.6±8.6, 18-72
Gender	
Female	283 (47.1)
Male	288 (47.9)
Transgender/Other	30 (5.0)
Single	329 (54.7)
Education	
<High School	9 (1.6)
High School Graduate	82 (13.6)
Attended College (≥1 year)	408 (67.6)
Attended Grad School (≥1 year)	103 (17.2)
Employment	
Working	363 (60.4)
Student	119 (19.8)
Homemaker, Retired	29 (4.9)
Disabled	34 (5.7)
Unemployed	56 (9.3)
Hispanic	36 (6.4)
Race	
White	498 (82.9)
Black	13 (2.2)
Asian	18 (3.0)
Other	72 (11.9)

[a]Values shown as means (±SD), range; for frequencies, as n (%)

[b]Includes participants who met OCD criteria (OCI-R≥21 or prior professional diagnosis), endorsed lifetime cannabis use, and completed required survey sections

TABLE 2.

CLINICAL CHARACTERISTICS (N=601)[a]

Variable	Value, n (%)	
Mean OCI-R Score	33.4±13.9, 1-72	
Age of OCD Symptom Onset	9.9±5.1, 1-30	
Age of first cannabis use	17.3±4.2, 6-46	
Psychiatric Comorbidity - any	481 (80.0)	
Generalized anxiety disorder	334 (55.6)	
Major depressive disorder	225 (37.4)	
Post-traumatic stress disorder	166 (27.6)	
Social anxiety disorder	151 (24.1)	
Personality disorder	110 (18.3)	
Eating disorder	100 (16.6)	
Panic disorder	96 (16.0)	
Substance use disorder	72 (12.0)	
Bipolar affective disorder	59 (9.8)	
Autism spectrum disorder	41 (6.8)	
Primary psychotic illness	18 (3.0)	
Mean # of Psychiatric Comorbidities	2.43 (SD: 2.03)	
Medical Comorbidity - any	361 (60.1)	
Chronic pain	131 (21.1)	
Migraine	110 (18.3)	
Asthma	94 (15.6)	
Thyroid disease	38 (6.3)	
Mean # of Medical Comorbidities	1.09 (SD: 1.26)	
Treatment History (N=601)	**Current**	**Lifetime**
Any Treatment	226 (37.6)	450 (74.9)
Medications	188 (31.3)	315 (52.4)
SRIs (SSRIs or clomipramine)	155 (25.8)	236 (39.3)
Psychotherapy	100 (16.6)	334 (55.5)
Residential	4 (0.7)	68 (11.3)
Transcranial Magnetic Stimulation	2 (0.3)	10 (1.8)
Alternative (mindfulness meditation, yoga, herbal supplements)	162 (27.0)	360 (59.9)
Lifetime Psychotherapy Treatment (N=334)	**Value, n (%)**	
Exposure and response prevention	99 (16.5)	
Cognitive therapy (without exposure)	257 (42.8)	
Acceptance and commitment therapy	67 (11.1)	
Psychodynamic psychotherapy	35 (5.8)	

[a]Includes only analyzed participants

TABLE 3.

PATTERNS OF CANNABIS USE (N=601)

Variable	Value[a]	
Mean cannabis use days (past month)	20.1±11.8, 0-31	
Mean CUDIT-R Score	11.5±6.1, 0-29	
CUDIT-R Item Scores (scale of 0-4)		
1. Frequency of use (past month)	3.2±1.2, 0-4	
2. Hours intoxicated per day	1.7±1.2, 0-4	
3. Unable to stop using	0.7±1.3, 0-4	
4. Failure to meet expectations	0.5±0.8, 0-4	
5. Time spent getting, using or recovering	0.9±1.3, 0-4	
6. Memory or concentration problems	1.2±1.4, 0-4	
7. Use in dangerous situations (e.g., driving)	0.8±1.3, 0-4	
8. Desire to reduce or stop use	2.3±1.7, 0-4	
Primary method used		
Vaporizing	183 (30.4)	
Joints/Blunts	105 (17.5)	
Pipes	113 (18.8)	
Bongs (water pipes)	104 (17.3)	
Edibles	41 (6.8)	
Primary formulation used		
Cannabis flower	388 (64.6)	
Concentrates	149 (24.8)	
Edible forms	34 (5.7)	
Typical THC content	**All cannabis flower users[b], n=472**	**All concentrate users[b], n=379**
“I don’t know”	171 (36.2)	97 (25.6)
High THC (>10%)	279 (59.2)	264 (69.7)
Low THC (<10%)	22 (4.6)	18 (4.7)
Typical CBD content		
“I don’t know”	212 (45.7)	136 (37.4)
High CBD (>10%)	96 (20.7)	90 (24.7)
Low CBD (<10%)	156 (33.6)	138 (37.9)

[a]Values shown as means (±SD), range; for frequencies, as n (%)

[b]Subset of participants who reported using this formulation at least 25% of the time, shown as n (%)

TABLE 4.

Multivariate Linear Regression Model for Prediction of Subjective Cannabis Effects[a]

Variable[b]	Effect on Slope		
	β	t	p
Age	0.049	1.014	0.311
Gender	0.014	0.310	0.757
Age of onset	−0.080	−1.728	0.085
Total Medication Trials	0.023	0.470	0.638
Total Medical Comorbidities*	0.128	2.564	0.011
Total Psychiatric Comorbidities	0.009	0.181	0.856
Checking	0.035	0.651	0.515
Hoarding	0.021	0.385	0.700
Neutralizing	0.079	1.506	0.133
Ordering	0.043	0.736	0.462
Washing	0.076	1.461	0.145
Obsessing*	−0.126	−2.472	0.014

*p < .05

[a]based on YBOC-CS scores; higher score=greater perceived benefit

[b]Variables of *a priori* interest (age, gender, OCI-R subscales) and those correlated with YBOC-CS at p<.1 were entered simultaneously into the model

TABLE 5.

Multiple Logistic Regression Model for Prediction of Treatment Status[a]

Variable[b]	B	SE	OR	95% CI for OR	
				Lower	Upper
Age	−0.02	0.01	0.98	0.96	1.01
Age of onset **	−0.09	0.02	0.92	0.88	0.95
Total Medical Comorbidities	0.02	0.09	1.02	0.86	1.22
Total Psychiatric Comorbidities **	0.16	0.06	1.17	1.05	1.31
Checking	−0.06	0.04	0.95	0.95	1.02
Hoarding	0.01	0.04	1.01	0.94	1.09
Neutralizing	0.04	0.03	1.04	0.98	1.11
Ordering	−0.01	0.05	0.99	0.90	1.09
Washing	−0.01	0.03	0.99	0.93	1.06
Obsessing **	0.19	0.04	1.21	1.13	1.31
Cannabis use frequency **	−0.06	0.02	0.94	0.90	0.98
%Medicinal (vs. recreational) use	−0.00	0.00	1.00	0.99	1.00

* $p < .05$

** $p < .005$

[a] Treatment status coded as a binary outcome (0=not currently in treatment, 1=currently in treatment)

[b] Variables with p<.1 on independent t-tests were forwarded stepwise into the logistic regression model

5. Letters of support provided by physicians with knowledge of the disease or condition.

The OMCIA has included a letter of support from Dr. John Dunne.

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 OCD. Patients often report symptom and functional improvement in certain co-morbidities in addition to their qualified conditions as serendipitous outcomes, including OCD symptoms.

I support the proposal to add obsessive compulsive disorder as a qualifying condition for medical marijuana under Ohio's Medical Marijuana Control Program.

Patients suffering from OCD are treated by a combination of cognitive therapy and prescription medications. As with many prescription medications, they yield unwanted side effects. The side effects can include nausea, vomiting, insomnia, headache, agitation, and discontinuation syndrome should the patient need to taper off a medication due to lack of efficacy.

The body's natural endocannabinoid system contains CB1 receptors which assist in regulating cell signaling. Agonists bind to these receptors, and can either increase or decrease signaling, depending on dose, sensitivity, and location of the receptors . One such agonist is THC, which can induce a calm feeling when it binds with CB1 receptors.

OCD affects the regions of the brain which are associated with stress reactions, fear conditioning, anxiety and habitual behavior. CB1 receptors are found in high density in these same regions. This correlation indicates that activation of these receptors may help ease OCD symptoms. Treatment with medical marijuana therefore offers a therapy targeting a currently overlooked pathophysiologic pathway with success highlighted in the briefings coming from Minnesota.

Please feel free to call me if you have any questions!

Kind regards, **John L. Dunne, DO**