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Specific Disease or Condition:
Generalized Anxiety Disorder (GAD)

Information from experts who specialize in the disease or condition.
File larger than 3MB

Relevant medical or scientific evidence pertaining to the disease or condition.
See Attached

- Question 2 GAD (3).pdf

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

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.
File larger than 3MB

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 file

- Question 5 GAD (2).pdf

Question 1

Information from experts who specialize in the disease or condition

Contents

Overview

General Anxiety Disorder (GAD) is a debilitating condition that has proven difficult to treat. The burden created by GAD has been compared to that of major depression.

As recently as March of 2018, the New Jersey Department of Health determined that GAD and anxiety as a broader set of conditions are so debilitating, and evidence of medical marijuana's effectiveness so persuasive, that they add anxiety to the state's qualifying conditions list.

GAD has also been shown to have a significant impact on society at large. The social routines of patients suffering from GAD and those around them can be severely interrupted. Additionally, work productivity has been shown to decrease in those with GAD creating an economic consequence for society when treatment isn't adequate.

The attached documents seek to explain New Jersey's reasoning for adding anxiety as a qualifying condition and explain the burden of GAD.

Research Article

GENERALIZED ANXIETY DISORDER: PREVALENCE, BURDEN, AND COST TO SOCIETY

Hans-Ulrich Wittchen, Ph.D.*

Generalized anxiety disorder (GAD) is a prevalent and disabling disorder characterized by persistent worrying, anxiety symptoms, and tension. It is the most frequent anxiety disorder in primary care, being present in 22% of primary care patients who complain of anxiety problems. The high prevalence rate of GAD in primary care (8%) compared to that reported in the general population (12-month prevalence 1.9–5.1%) suggests that GAD patients are high users of primary care resources. GAD affects women more frequently than men and prevalence rates are high in midlife (prevalence in females over age 35: 10%) and older subjects but relatively low in adolescents. The natural course of GAD can be characterized as chronic with few complete remissions, a waxing and waning course of GAD symptoms, and the occurrence of substantial comorbidity particularly with depression. Patients with GAD demonstrate a considerable degree of impairment and disability, even in its pure form, uncomplicated by depression or other mental disorders. The degree of impairment is similar to that of cases with major depression. GAD comorbid with depression usually reveals considerably higher numbers of disability days in the past month than either condition in its pure form. As a result, GAD is associated with a significant economic burden owing to decreased work productivity and increased use of health care services, particularly primary health care. The appropriate use of psychological treatments and antidepressants may improve both anxiety and depression symptoms and may also play a role in preventing comorbid major depression in GAD thus reducing the burden on both the individual and society. Depression and Anxiety 16:162–171, 2002. *© 2002 Wiley-Liss, Inc.*

Key words: *generalized anxiety disorder; prevalence; health care utilization; comorbidity*

INTRODUCTION

Generalized anxiety disorder (GAD) is a persistent and often severe mental disorder of the anxiety spectrum, characterized by persistent (6 months or more), excessive worrying, anxiety, tension associated with symptoms of hypervigilance, and other somatic symptoms of anxiety. The symptomology is associated with substantial and enduring subjective suffering, and the feeling of loss of control over the worrying and symptoms as another criterion. Clinical reports suggest that fewer than 20% of sufferers experience complete remission of their symptoms, and typically patients will have had their symptoms for between 5 and 10 years before they are diagnosed and effectively treated [Ballenger et al., 2001; Kessler et al., 2001a; Rogers et al., 1999]. Patients with GAD have been found to be frequent utilizers of primary care resources rather than mental health specialist settings and have been associated with over-utilization of general health care resources [Maier et al., 2000; Roy-Byrne and Katon, 1997; Wittchen et al., 2000; Wittchen et al., 2002]. Further primary care studies conducted in the early

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1990s have suggested that GAD is rarely recognized and diagnosed, and if it is diagnosed it is usually not, or only inappropriately, treated [Üstün and Sartorius, 1995]. This is particularly significant as GAD is associated with a substantial degree of social disability [Wittchen et al., 2000].

Yet, there has been some debate concerning the nosological status of GAD because of past reports of its low diagnostic reliability using standard criteria [DiNardo et al., 1993] and the fact that clinical studies have found that GAD is usually seen in comorbid presentations with major depression. Furthermore, there have been reports that pure GAD is both an extremely rare phenomenon with few indications of disorder-specific impairments (for examples, see discussions in Kessler et al., 2001a; Noyes et al., 2001]. However, one needs to take into account that these reservations against GAD, being an independent clinical disorder of critical significance, are based on studies that have mostly used older diagnostic criteria for GAD and/or stem from highly selective clinical samples that might suffer considerable selection bias.

Since the current diagnostic definition of GAD is a relatively recent addition to diagnostic classification systems, few studies have up to now reconsidered the nature and true burden of GAD, as defined by the current DSM-IV criteria, on the individual and society. This paper aims to address the question "what is the prevalence, level of disability and burden to society associated with GAD, as defined by DSM-IV criteria?"

PREVALENCE

The concept and diagnostic criteria of GAD have changed significantly since it was first codified in the Diagnostic and Statistical Manual of Mental Disorders [American Psychiatric Association, 1994] in 1980 and to date there are still small differences in the criteria used in the USA and Europe. In the USA and in research, the DSM-III-R/DSM-IV criteria prevail, whereas in Europe the use of the 10th International Classification of Diseases [ICD-10; World Health Organization (WHO) 1992], which has broader criteria, is preferred at least in routine clinical settings. However, it is remarkable that despite the many changes in diagnostic criteria and the differences between these two diagnostic classification systems, the reported lifetime prevalence rates for GAD are remarkably consistent. This is in contrast to the considerable variance observed with other psychiatric disorders, such as depression and phobias.

COMMUNITY STUDIES

The US National Comorbidity Survey [NCS: Kessler et al., 1994] and the German National Health Interview and Examination Survey, Mental Health Supplement [GHS; Carter et al., 2001; Jacobi et al., 2002] are the largest community epidemiological studies of GAD to date. and, together, include over 69,400 patients. The 12-month and lifetime prevalence rates of GAD (DSM-III-R) in the NCS were estimated to be 3.1% and 5.1%, respectively. The lowest lifetime prevalence rate was found in the 15–24 year age group (2.0%), while the highest rate was reported for the 45–55 year age group (6.9%) [Table 1; Wittchen et al., 1994]. This survey also demonstrated that women were twice as likely to have GAD than their male counterparts, with total lifetime prevalence rates of 6.6% and 3.6%, respectively [Wittchen et al., 1994]. The prevalence rate increased to 10.3% for women aged ≥45 years, but was unchanged for men aged ≥45 years (3.6%).

TABLE 1. Twelve-month and lifetime prevalence in the NCS of GAD in males and females by age group [Wittchen et al., 1994]

Age (yr)	Male (%)	Female (%)	Total (%)
12-month prevalence			
15–24	1.3	1.5	1.4
25–34	3.2	5.0	4.1
35–44	2.3	4.5	3.4
≥45	0.9	6.3	3.5
Total	2.0	4.3	3.1
Lifetime prevalence			
15–24	1.5	2.5	2.0
25–34	4.7	7.1	6.0
35–44	4.6	7.2	5.9
≥45	3.6	10.3	6.9
Total	3.6	6.6	5.1

These findings are relatively consistent with findings from a previous GAD community survey that used earlier diagnostic criteria and different instruments [see review by Carter et al., 2001]. The most recent epidemiological study using DSM-IV criteria [GHS; Carter et al., 2001] has reported slightly lower 12-month prevalence rates for GAD than the NCS (12-month prevalence 1.5% vs. 3.1%). However, this finding was found to be entirely due to methodology because the inclusion of subjects with lifetime GAD and partially remitted subthreshold GAD accounts for this difference. The highest rates were again found in women and older subjects [Carter et al., 2001].

Although in the past there was some speculation about GAD being a characteriological disorder [Akiskal, 2001] being best grouped under DSM axis II personality disorders, there has been little supporting evidence to date. Reports concerning the prevalence of GAD as defined by the DSM-III-R and the more stringent DSM-IV criteria in children and adolescents have generally found low rates of GAD in this age group [Müller, 2001, doctoral dissertation; Wittchen et al., 1998]. The prospective-longitudinal 5-year Early Developmental Stages of Psychopathology (EDSP) study in adolescents and young adults [Wittchen et al., 1998], which to our knowledge is the only DSM-IV-based study of this sort, examined the prevalence of GAD and patterns of age of onset among subjects aged

14–24 years at intake. This study found that GAD is rare in children and adolescents and that unlike most anxiety disorders, onset of GAD before the age of 25 years was uncommon. These findings are in agreement with those of most of the previous adult studies that report age of first onset data as well as surveys in children.

PRIMARY CARE

There is consistent evidence that patients with GAD are highly prevalent in primary care settings [Ormel et al., 1994; Schonfeld et al., 1997]. The international WHO multi-center study on Psychological Problems in General Health Care (PPGHC) assessed GAD using ICD-10 criteria with the Composite International Diagnostic Interview [CIDI; WHO, 1991] and estimated the current prevalence of GAD across centers to be approximately 8% of all primary care attenders [Üstün and Sartorius, 1995]. This was confirmed in a more recent reanalysis [Maier et al., 2000]. Of those patients visiting primary care physicians for a psychological problem, 25% presented with pure GAD in the absence of any comorbid psychiatric disorder [Maier et al., 2000]. In a subset of almost 2,000 individuals attending five of the European centers in this study [Weiller et al., 1998], 22% of all primary care patients who complained of any anxiety problems were found to have GAD. In this analysis, the overall current prevalence of GAD among primary care attenders was 8.5% with a further 4.1% of individuals having sufficient clinical problems to justify a diagnosis of subthreshold GAD.

The most recent primary care study of over 500 primary care centers and over 20,000 primary care attenders (Generalised Anxiety Disorder and Depression in Primary Care [GAD-P] study) has confirmed these findings on the basis of DSM-IV criteria for GAD [Hoyer et al., 2001; Wittchen et al., 2001; Wittchen et al., 2002]. The point prevalence of threshold GAD was estimated to be 5.3%, with highest estimates in those primary care attenders aged 35–60 years. The study also confirmed, even more impressively than the report by Weiller et al., [1998], that GAD is a) the most frequent anxiety disorder seen in primary care (more than 50% of all anxiety disorders), b) rarely correctly diagnosed (only 28% were correctly diagnosed as having GAD by their GP), and c) rarely appropriately managed in terms of type and duration of pharmacological and non-pharmacological treatments [Wittchen et al., 2001].

These findings of increased prevalence of GAD in primary care compared to the general population are in contrast to most other anxiety disorders where the prevalence rate in the general population is much higher than in primary care. This suggests, in line with previous speculations [Schonfeld et al., 1997] that GAD patients are high utilizers of primary care resources (Fig. 1).

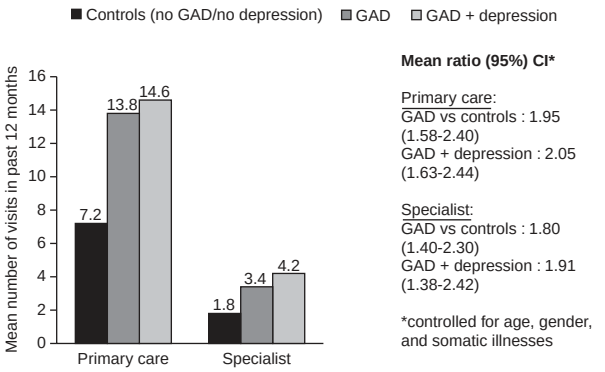

Figure 1. Increased utilization rates of primary care attenders with GAD (n=14,532) [Wittchen et al., 2001].

COMORBIDITY

A consistent finding in clinical and epidemiological studies of GAD is the high proportion of comorbidity (Table 2), with common comorbid diagnoses including major depression, panic disorder, social and specific phobia, and post-traumatic stress disorder (PTSD). However, there is no remarkable association with substance use disorders. As many as 66% of patients with current GAD have an additional concurrent psychiatric diagnosis and they almost invariably (90%) have a lifetime history of another psychiatric diagnosis [Wittchen et al., 1994]. The GHS confirmed these findings and reported that comorbidity of DSM-IV GAD includes other anxiety disorders in 55% of cases and depression in 59% of cases [Carter et al., 2001]. Brawman-Mintzer and colleagues [1993] pointed out in this respect that 42% of patients with GAD had experienced at least one major depressive episode during their lifetime. Data from the GHS showed a similar pattern; 40.5% of GAD patients had comorbid current major depression, 59% had comorbid 12-month major depression, and 60% had comorbid lifetime major depression [Carter et al., 2001].

TABLE 2. Comorbidity of current and lifetime DSM-III-R-GAD [Noyes, 2001]

Comorbid disorder	Current GAD (%)	Lifetime GAD (%)
Mania	12.1	10.5
Major depression	38.6	62.4
Dysthymia	22.1	39.5
Panic disorder	22.6	23.5
Agoraphobia	26.7	25.7
Simple phobia	24.5	35.1
Social phobia	23.2	34.4
Alcohol	11.2	37.6
Drug	5.1	27.6
Any of the above	66.3	90.4

GAD, generalized anxiety disorder.

TABLE 3. Proportion of NCS and DSM-III-R disorders with lifetime comorbidity and proportion of temporally primary cases[†]

Disorder	Proportion with lifetime comorbidity (%)	Proportion of temporally primary disorders (%)
Mood disorders		
Mania	99.4	20.2
Dysthymia	91.3	37.7
Major depressive episode	83.1	41.1
Any mood disorder	82.2	—
Anxiety disorders		
Panic disorder	92.2	23.3
Generalized anxiety disorder	91.3	37.0
Agoraphobia	87.3	45.2
Simple phobia	83.4	67.6
Social phobia	81.0	63.1
Post-traumatic stress disorder	81.0	52.1
Any anxiety disorder	74.1	—

[†]Adapted from Kessler RC. 1997. The prevalence of psychiatric comorbidity. In: Wetzler S, Sanderson WC, editors. Treatment strategies for patients with psychiatric comorbidity. New York: John Wiley & Sons. Reproduced by permission of the publisher.

Even slightly higher comorbidity rates have been reported for clinical samples [Noyes, 2001; Roy-Byrne and Katon, 1997]. Although these high rates of anxiety-mood disorder comorbidity have stimulated some controversy over whether GAD should be regarded as a distinct disorder or should more appropriately be conceptualized as a prodromal, residual stage or as a severity marker of depression, there has been little supporting evidence for the latter. Kessler et al. [2001a] have reviewed the available evidence for this controversy and come to the conclusion that GAD and depression are distinct disorders based on the following findings: 1) twin studies do not support the lumping of both conditions, 2) exceedingly high comorbidity rates are confined to selected clinical studies with potential patients' self-selection bias that have used early definition of GAD and not DSM-IV position, 3) conditional rates of comorbidity among GAD cases are not higher than those observed for other disorders, and 4) there is an abundance of studies revealing that pure and comorbid presentations differ considerably with regard to their clinical and other correlates (Table 3). For example, 50% of all adult GAD cases were found to be temporally primary to mood disorders [Fava et al., 2000; Wittchen et al., 2000]. Comorbidity, especially with depression, significantly lowers the probability of GAD being successfully diagnosed and treated and patients experience more severe symptoms. Comorbid, as opposed to pure, GAD is associated with increased disability and dysfunction, and has a worse prognosis and impairment [Bakish, 1999; Wittchen et al., 2000]. Thus, there is considerable evidence that GAD is a distinct disorder that deserves special research and clinical attention. There is also a need for further studies that provide a better and fuller understanding of the pathogenic and clinical management implications of these patterns of comorbidity.

INDIVIDUAL BURDEN OF DISABILITY

Another key finding that provides further evidence for GAD being a particularly clinically significant mental disorder in itself was the recent demonstration that GAD is associated with a significant burden of disability for individuals, even if they do not have a comorbid condition. This is most notable in terms of diminished functioning both socially and at work. General population studies have considered the degree of impairment caused by pure GAD. The NCS and Midlife Development in the United States Survey both reported that the level of impairment associated with DSM-III-R GAD is substantial and comparable to that of pure major depression [Table 4; Kessler et al., 2001a, 1994, 1997].

A combined analysis of data from these two studies confirmed their findings and showed that even "pure" GAD was associated with marked impairment in role functioning and social life [Kessler et al., 1999]. Moreover, this impairment was equivalent to that caused by major depression (Fig. 2). The highest levels of impairment were seen when GAD was comorbid with major depression (Figure 3).

TABLE 4. Odds ratios of 12-month GAD with major depression without GAD in predicting impairment[†]

Impairment	GAD without MD		MD without GAD		Risk of GAD alone relative to MD alone	
	NCS	MDUSS	NCS	MDUSS	NCS	MDUSS
Fair or poor perceived mental health	6.0*	4.8*	3.3*	5.2*	1.6	0.8
High level of work impairment	3.5	3.5	3.5*	8.5*	0.9	0.5
High level of social impairment	2.5*	1.2	2.0*	1.6*	1.5	1.0

[†]Adapted from Kessler RC, DuPont RL, Berglund P, Wittchen H-U. 1999. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 156: 1915–1923. Reprinted by permission of the publisher.
*Significant at the 0.05 level, two-sided test
NCS, National Comorbidity Survey [Kessler et al., 1994]; MDUSS, Midlife Development in the United States Survey [Kessler et al., 1999]; GAD, generalized anxiety disorder; MD, major depression.

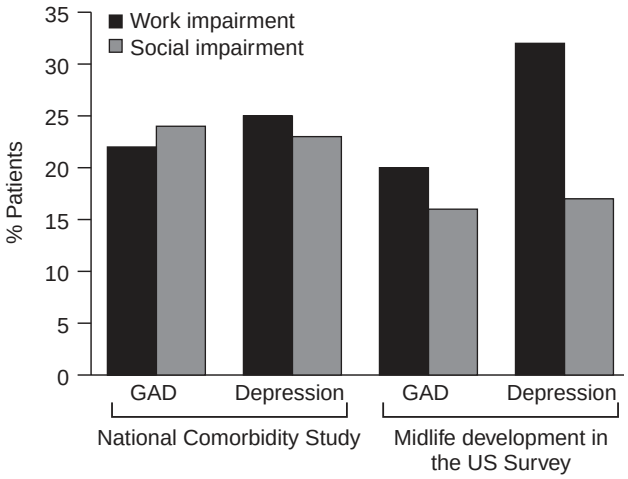

Figure 2. Work and social impairment in GAD and depression [Kessler et al., 1999].

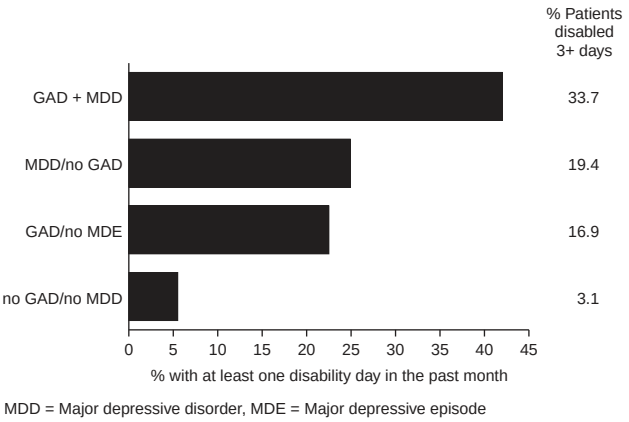

Figure 3. Impairment associated with DSM-III-R GAD [Kessler et al., 1999].

Similar findings were recently reported for DSM-IV GAD from the GHS [Wittchen et al., 2000], which also confirmed similar findings with regard to work productivity as well as other measures of impairment and quality of life [Figure 4; Wittchen et al., 2000].

In the PPGHC study, patients with GAD (and subthreshold GAD) showed greater severity of symptoms and had a greater degree of disability than primary care subjects with no current psychiatric symptoms [Weiller et al., 1998]. Twenty-seven percent of all GAD sufferers reported moderate or severe social disability (assessed by the Brief Disability Questionnaire) and this proportion rose to 59% when GAD was comorbid with major depression.

COST TO SOCIETY

While the level of social disability associated with GAD is as severe as that seen with chronic somatic diseases [Kessler et al., 2001a; Maier et al., 2000], GAD also has a major impact on society in terms of decreased work productivity and increased health care utilization.

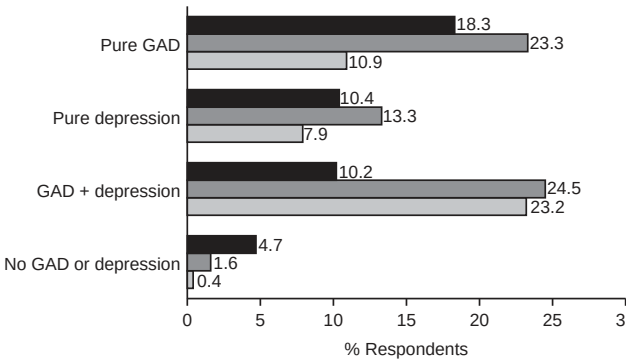

Figure 4. Overall work productivity reductions in pure and comorbid 12-month GAD [Wittchen et al., 2000]. Black bars, 0–10%; gray bars, 11–49%; light gray bars ≥50%.

Impact on work productivity. GAD is associated with a significant economic burden owing to particularly decreased work productivity [Kessler et al., 1999; Greenberg et al., 1999; Souêtre et al., 1994; Judd et al., 1998]. A recent analysis using data from the GHS study (see above) considered disability in terms of reduced work productivity in individuals with pure GAD and GAD comorbid with major depression [Wittchen et al., 2000]. Approximately 34% of patients with 12-month pure GAD, 21% of those with depression, and 48% of those with comorbid GAD and depression showed a reduction in work productivity of 10% or more and a reduction of at least 50% in activity during the past month was reported by approximately 11% of respondents with pure GAD and 8% of those with pure major depression (Fig. 4). Thus, GAD is associated with considerable impairment even when no comorbid depression is present. Of those individuals with comorbid GAD and depression, 23% had experienced reductions of at least 50% in the activities of the previous month. In the PPGHC study, the mean number of workdays lost to disability was 4.6 for pure GAD and rose to 8.0 when GAD was comorbid with major depression [Weiller et al., 1998].

Further evidence has been presented by an Australian study, which reported that the burden of mental disorders was third after the burden of heart disease and cancer and, of these mental disorders, the two most relevant were GAD and depression [Andrews et al., 2000]. This was confirmed by Kessler et al. [2001b; Table 5].

This indicates that the presence of GAD is a significant factor that leads to complete disability, diminished productivity at work and that the burden of GAD on society is at least equivalent to, if not greater than, the burden caused by depression.

Health care utilization. The high prevalence of GAD in the primary care setting, compared with the general population, suggests that patients with the disorder are likely to be high users of health care

TABLE 5. Prevalence of 30-day work impairment for selected conditions in the Midlife Development in the United States Survey [Kessler et al., 2001b][†]

Condition	Prevalence of condition (%)	Any work impairment days (%)	Mean number of impairment days	Average per capita number of work impairment days
Physical conditions				
Arthritis	19.4	38.8	8.3	3.2
Hypertension	18.2	34.6	9.0	3.1
Asthma	12.6	44.7	7.7	3.5
Diabetes	5.6	40.2	7.6	3.1
Ulcer	4.4	52.7	10.9	5.8
Mental/substance disorders				
Major depression	14.1	51.9	8.3	4.3
Panic attacks	6.8	56.4	9.5	5.3
Alcohol dependence	4.3	37.1	4.3	1.6
Generalized anxiety disorder	3.3	61.3	9.8	6.0
Drug dependence	2.0	60.8	8.1	4.9

[†]From Kessler RC, Mickelson KC, Barber C. 2001. The effects of chronic medical conditions on work impairment. In: Rossi AS, editor. Caring and doing for others: social responsibility in the domains of the family, work and community (John D. and Catherine T. MacArthur Foundation series.). Chicago: University of Chicago Press. Reproduced by permission of the publisher.

services and particularly primary care health services [Maier et al., 2000; Weiller et al., 1998]. According to the most recent primary care study [Wittchen et al., 2002], patients with pure GAD reported a two-fold higher than average number of visits to primary care doctors compared with depressed patients and significantly more visits to non-mental health specialists in the previous 12 months, even when controlling for the presence of physical illnesses. Similarly, GAD ranks third among anxiety disorders (after PTSD and panic disorder) in the rate of use of primary care physicians' time [Kessler et al., 1999]. Approximately one third of patients with GAD seek medical help for their somatic GAD symptoms [Judd et al., 1998], most commonly from primary care physicians. Comorbidity with GAD is reported to increase the rate of help-seeking behavior by more than 50% [Bland et al., 1997].

It has been reported that the specialists seen most often by GAD patients are gastroenterologists [23%; Kennedy and Schwab, 1997]. This was significantly greater than for patients with other anxiety disorders (16% panic disorder, 3% obsessive compulsive disorder; $P < .05$). Only 10% of patients with GAD had seen a psychiatric specialist. These observations were attributed to the considerable overlap between the anxiety symptoms of GAD and the symptoms associated with other conditions, for example, irritable bowel syndrome [Kennedy and Schwab, 1997]. Fifty percent of patients with GAD had seen 1–2 medical specialists (other than primary care physicians) in the preceding year, while 10% had visited 3–5 specialists [Kennedy and Schwab, 1997]. These results show that many patients with GAD visit a number of physicians before they are definitively diagnosed and treated.

It is noteworthy that, despite the high primary care utilization rates of GAD, sufferers are rarely specifically diagnosed and treated for their disorder either directly by the primary care doctor or after referral to mental health specialists. In the NCS conducted in the early 1990s, only 48% of all pure GAD subjects had received health care intervention at some point in their life, and only 25% had at some point taken medication for their GAD symptoms. The recent GAD-P study (conducted during the year 2000) confirmed this finding and revealed that despite high utilization rates in primary care, less than 10% of GAD patients receive adequate non-pharmacological or pharmacological treatments for their disorder [Wittchen et al., 2001].

Economic burden. The economic cost of anxiety disorders has been examined [DuPont et al., 1996; Greenberg et al., 1999; Rice and Miller, 1998] in elaborate and complex secondary data analyses. These studies indicated that the annual cost of anxiety disorders was \$42–47 billion in the USA in 1990. The three largest components of the total cost comprised \$23 billion (54%) in non-psychiatric medical treatment, \$13 billion (31%) in psychiatric treatment, and over \$4 billion (10%) in indirect workplace costs. Prescription pharmaceutical costs were a minor factor, accounting for less than \$1 billion (2%) of the total cost of anxiety disorders [Greenberg et al., 1999].

The \$4 billion indirect workplace costs reflect an average annual (1990) cost in the workplace of \$256 per affected worker [Greenberg et al., 1999]. A total of 88% of this cost per individual was attributed to lost productivity while at work, as opposed to actual absence from work. Therefore, work productivity may provide a more accurate assessment of the economic cost of GAD than absence from work [Greenberg et al., 1999].

Primary care patients with DSM-III-R anxiety or depressive disorders have been reported to have

markedly higher associated costs ($2,390/patient) than patients with subthreshold disorders ($1,098/patient) or those with no anxiety or depressive disorder ($1397/patient) [Simon et al., 1995]. These cost differences reflected greater utilization of general medical services rather than higher treatment costs.

It is to be expected that the high prevalence of GAD comorbid with depression would lead to increased economic costs. An evaluation of the direct and indirect health care costs in GAD patients found that over 60% were experiencing one or more symptoms of comorbidity that resulted in a high rate of health care utilization that was affected by both the level of comorbidity and symptom severity [Souêtre et al., 1994]. In GAD patients, hospitalizations were significantly more prevalent in those with comorbidity than in those without (11.8% vs. 5.1%, respectively; $P<.001$), with internal medicine and emergency admission being the most frequently used services [Souêtre et al., 1994]. Hospitalization costs accounted for 35% of total costs and over 53% of direct health care costs in patients with comorbidities. The economic cost was also increased in GAD patients with comorbidity in terms of increased absenteeism from work (33.6% with comorbidity vs. 26.6% without; $P<.05$). Absenteeism from work accounted for 34.4% and 33.1% of total costs for patients with and without comorbidity, respectively.

REDUCING THE BURDEN

The debate that existed concerning the status of GAD as a discrete anxiety disorder has meant that less attention has been focused on identification of adequate treatment for the disorder than for other anxiety disorders. Improving the recognition and treatment of GAD is key to reducing the burden of the disorder on the individual and society. The challenges of GAD as a chronic, and after several years, usually complex disorder with a substantial degree of impairment, disability, and comorbid complications are a) its early recognition before substantial complications develop and b) appropriate combined acute and long-term management strategies to reduce the suffering caused by the GAD symptoms and comorbid presentations as well as reducing the associated disability as a major source of relapse. Thus therapeutic interventions should aim at reducing the core symptoms of GAD, the prevalence of comorbidity, and the associated disabilities.

In addition to several well-established, effective non-pharmacological, mostly cognitive-behavioral treatments, there are various traditional drug treatments, most of which have significant limitations, as well as several new drug therapies of first choice.

Benzodiazepines have traditionally been used to treat acute anxiety disorders but they are not ideal for the treatment of chronic GAD. Following long-term therapy, benzodiazepines have the potential to produce dependency and withdrawal symptoms [Lydiard et al., 1997]. Initial findings in patients with GAD generally showed that buspirone was as efficacious as the benzodiazepines in treating anxiety disorders [Petracca et al., 1990; Strand et al., 1990] but appeared to lack the side effects and withdrawal symptoms [Laakman et al., 1998]. Although buspirone is effective in most (but not all) studies of GAD [Davidson et al., 1999; Lydiard, 2000], its lack of efficacy against comorbid conditions is the main reason for it not being recommended as a first-line treatment for GAD [Ballenger et al., 2001].

The use of buspirone for the treatment of anxiety disorders is limited to short-term treatment only and therefore is inadequate for the treatment of GAD. In a placebo-controlled study to investigate the use of both buspirone and hydroxyzine in patients with GAD, a significant difference was shown only between hydroxyzine and placebo with respect to improvement of the primary efficacy measurement (improvement on the Hamilton Anxiety Scale). However, both buspirone and hydroxyzine were shown to be more effective than placebo for the secondary efficacy measurement (improvement in CGI and HAD scale ratings) [Lader and Scotto, 1998]. Treatment with benzodiazepines or buspirone is ineffective when comorbid depression is present [Bakish, 1999; Lydiard et al., 1987].

There is evidence that the tricyclic antidepressants (TCAs) are at least as effective as benzodiazepines in the treatment of GAD and may be superior in long-term therapy [Kahn et al., 1986; Hoehn-Saric et al., 1988; Rickels et al., 1993]. The tertiary TCAs, which have dual serotonergic-noradrenergic effects (e.g., imipramine and amitriptyline), appear to be consistently effective in the treatment of anxiety [Feighner, 1999]. However, side effects, such as anticholinergic events, preclude the use of TCAs in many patients, namely, the elderly or those with cardiovascular disease.

Clinical studies have shown that the selective serotonin reuptake inhibitor (SSRI) paroxetine and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine are as effective in the treatment of GAD as they are for most other anxiety disorders studied so far [Bellew et al., 2001; Davidson et al., 1999; Davidson, 2001; Feighner, 1999; Gelenberg et al., 2000; Pollack et al., 2001; Rocca et al., 1997], resulting in a reduction of the symptoms of anxiety and depression. An important advantage of these drugs is that it is useful in the treatment of the depression and anxiety disorders frequently comorbid with GAD, such as panic disorder, social anxiety disorder, or OCD [Ballenger et al., 2001]. Paroxetine, which has proven efficacy across the spectrum of depression and anxiety disorders (panic disorder [Lecrubier et al., 1997], OCD [Zohar and Judge, 1996], social anxiety disorder [Lydiard and Bobes, 2000], and PTSD [Beebe et al., 2000]), has also been shown to be effective in patients with GAD [Bellew et al., 2000; Pollack et al., 2001; Rocca et al., 1997] and has been the first SSRI to be

specifically licensed for the treatment of GAD. A large clinical program involving 1,264 patients in three 8-week studies has shown that paroxetine significantly reduces HAM-A total scores compared with placebo and reduces the core GAD symptoms (worry, anxiety, and tension). Paroxetine treatment results in a significant improvement in quality of life in GAD [Pollack et al., 2001]. The EuroQol visual analogue scale (EQ-5D VAS) provides a measure of quality of life by assessing general well-being and the mean change from baseline in EQ-5D VAS scores was significantly greater with paroxetine than with placebo [Bellew et al., 2000].

Controlled studies have also demonstrated that the SNRI, venlafaxine extended release (XR) (which is also licensed for GAD) are effective in both the short- and long-term treatment of GAD [Allgulander et al., 2001; Davidson et al., 1999; Gelenberg et al., 2000; Rickels et al., 2000; Silverstone and Salinas, 2001].

In the first of these studies, the mean adjusted HAM-A anxious mood and tension scores were significantly lower for both doses of venlafaxine XR at week 8 compared with placebo [$P < .05$; Davidson et al., 1999]. However, the adjusted mean total HAM-A scores for all the treatment groups compared to placebo were not significantly different.

In the study by Rickels et al. [2000], venlafaxine XR 75, 150, and 225 mg/day over 8 weeks were significantly more effective than placebo in the treatment of GAD in 377 outpatients without major depressive disorder.

The study by Gelenberg et al. [2000] evaluated flexible doses of venlafaxine XR over 6 months. The results showed that the efficacy of venlafaxine XR 75-225 mg/day could be sustained in 238 patients with GAD over a 28-week maintenance period. Similarly, in the 24-week placebo-controlled study by Allgulander et al. [2001], venlafaxine XR 37.5, 75, and 150 mg/day were significantly more effective than placebo in the treatment of GAD in 541 outpatients.

The placebo-controlled study by Silverstone and Salinas [2001] compared the efficacy of venlafaxine XR (75–225 mg) over 12 weeks in patients with major depression and patients with comorbid GAD. In the comorbid patients, venlafaxine significantly decreased both HAM-D and HAM-A scores compared with placebo.

The rapidly increasing evidence that SSRIs and SNRIs are highly effective treatments for GAD and are also equally effective in the treatment of major depression and the other anxiety disorders (which frequently comorbid with GAD) suggests that these strategies are the drug treatments of first choice for current practice. They also have the potential greatly to reduce the individual and economic burden of GAD.

CONCLUSIONS

GAD is a recognizable and distinct anxiety disorder that is associated with a significant burden of disability on the individual, the magnitude of which is at least equivalent to that of major depression [Kessler et al., 1999; Wittchen et al., 2001]. However, a comprehensive and sound estimation of the burden of GAD on the individual and society is complicated by the high prevalence of comorbid disorders. Patients with comorbid GAD and depression are particularly likely to demonstrate disability and dysfunction. The presence of GAD in other somatic and mental disorders seems to magnify the disability found for the other condition per se. Further investigations into the associated burden of GAD as well as a change in the current approach to the recognition and treatment of the disorder are necessary.

GAD reduces work productivity and increases the utilization of health care services [Greenberg et al., 1999; Souêtre et al., 1994], and comorbidity, particularly with depression, further increases levels of impairment and cost [Bakish, 1999; Greenberg et al., 1999; Souêtre et al., 1994; Weiller et al., 1998]. In addition, patients with GAD who present to medical practitioners with somatic symptoms may not be diagnosed as suffering from a psychiatric condition, leading to increased medical utilization until the true condition is revealed [Lydiard, 2000].

Although there is growing emphasis on the identification of new agents for the treatment of GAD, further research on the response of comorbidity to management is crucial. Of the current drug treatment options, the SSRI paroxetine and the SNRI venlafaxine are the most convenient treatment to use in the primary care setting and is specifically licensed for the treatment of GAD (DSM-IV definition). Both agents have proven efficacy across the spectrum of depressive and anxiety disorders that are frequently comorbid with GAD (panic disorder, social anxiety disorder, obsessive-compulsive disorder, and PTSD; Brawman-Mintzer et al., 1993; Ballenger et al., 2001; Davidson, 2000].

Prompt recognition and effective treatment of GAD are central to reducing the burden of this chronic, prevalent, and disabling condition. Greater availability of effective outpatient treatment for GAD will improve symptoms and functionality, reduce disability and health care utilization, and could substantially reduce the economic and social burden of this common and disabling disorder.

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Lt. Governor

SHEREEF M. ELNAHAL, MD, MBA
Acting Commissioner

March 22, 2018

Re: Final Agency Decision: Petitions to Establish Additional Debilitating Medical Conditions under the New Jersey Medicinal Marijuana Program

Dear Petitioners:

This letter sets forth the basis, rationale and final decision in the matter of the Department of Health's (Department) Request for Petitions to establish additional deliberating medical conditions under the New Jersey Medicinal Marijuana Program (MMP). As explained in detail below, I am granting the petitions seeking to add chronic pain conditions that are related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety as debilitating medical conditions under the MMP. However, I am denying the petitions seeking to add asthma and chronic fatigue syndrome to the MMP.

In reaching this decision, I considered the Request for Petitions, the petitions submitted in response to the Request, the MMP panel's recommendations, written and oral public comments received regarding various petitions, as well as the requirements of the New Jersey Compassionate Use Medical Marijuana Act (the Act), N.J.S.A. 24:6I-1 et seq., and the regulations promulgated thereunder. The referenced materials are incorporated herein and made a part of this final decision.

The Request for Petitions

On July 5, 2016, the Department published the Request for Petitions in the New Jersey Register advising that from August 1, 2016 to August 31, 2016, it was accepting petitions to establish additional medical conditions as "debilitating" under the MMP. 48 N.J.R. 1395(a). The Request for Petitions stated that the Department was seeking petitions in accordance with the Act, which authorizes the Department to include additional debilitating medical conditions under the MMP.

In the Request for Petitions, the public was advised that submitted petitions were required to include the following information, pursuant to N.J.A.C. 8:64-5.3:

(1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;

(2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;

(3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting, or otherwise severely impair the patient's ability to carry on activities of daily living;

(4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;

(5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and

(6) Letters of support from physicians or other licensed health care professional knowledgeable about the condition.

The Department also crafted a Petition Form that petitioners could use for their submissions. The form detailed the above-listed criteria, which each petitioner needed to provide in order for his or her submission to be accepted and considered.

In addition to publishing the request for petitions in the New Jersey Register, the Department also posted it on its website.

Completeness Review

At the close of the petition submission period, the Department received sixty-eight petitions. Thereafter, the Department reviewed each petition to determine whether it contained the information that was required for it to be accepted for consideration. From its review, the Department determined that twenty-three petitions did not meet the criteria for consideration.[1] Accordingly, the Department denied these petitions under separate cover on December 7, 2016, pursuant to N.J.A.C. 8:64-5.3(b). The remaining forty-five petitions met the criteria for consideration and were accepted.

Statutory and Regulatory Criteria

The Act charges the Department with the responsibility of administering the State's MMP, including establishing a registry of qualifying patients and primary care givers. To qualify as a MMP patient, an individual must suffer from one of the debilitating medical conditions set forth in the Act. The Act defines a "debilitating medical condition" as:

(1) one of the following conditions, if resistant to conventional medical therapy: seizure disorder, including epilepsy; intractable skeletal muscular spasticity; post-traumatic stress disorder; or glaucoma;

[1] Legislation was enacted during the pendency of the petitions, which added post-traumatic stress disorder to the list of conditions that qualify as debilitating under the MMP. As a result, the petitions seeking to add this condition to the MMP were deemed moot and not forwarded to the Panel for consideration.

(2) one of the following conditions, if severe or chronic pain, severe nausea or vomiting, cachexia, or wasting syndrome results from the condition or treatment thereof: positive status for human immunodeficiency virus; acquired immune deficiency syndrome; or cancer;

(3) amyotrophic lateral sclerosis, multiple sclerosis, terminal cancer, muscular dystrophy, or inflammatory bowel disease, including Crohn's disease; [or]

(4) terminal illness, if the physician has determined a prognosis of less than 12 months of life.

[N.J.S.A. 24:6I-3.]

In addition to the conditions listed in the Act, the Legislature authorized the Department to establish additional medical conditions as debilitating under the MMP. Ibid. Consistent with its statutory authority, the Department promulgated rules that outline the process for expanding the list of medical conditions that qualify as "debilitating" under the MMP. See N.J.A.C. 8:64-1.1 et seq. Pursuant to these rules, I am required to take into consideration the following factors in order to determine whether a condition should be added to the MMP as a "debilitating" medical condition that is likely to benefit from the use of medical marijuana to treat or alleviate the debilitating effect of the condition:

(1) The extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition;

(2) If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition;

(3) The extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living;

(4) The availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof;

(5) The extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof; and

(6) Letters of support from physicians or other licensed health care professionals knowledgeable about the condition.

[N.J.A.C. 8:64-5.3]

The MMP Review Panel Meetings, Public Comments and Panel Recommendations

On May 11, 2017, the MMP Review Panel, which is a panel assembled by the Department to review and make recommendations on petitions seeking to add conditions to the MMP, met to

review and hear public comments on the forty-five accepted petitions. At the meeting, the Panel acknowledged that they reviewed the material submitted with the petitions and that they also conducted their own independent analysis and research for each condition. During the meeting, the Panel also advised that it grouped the petitioned conditions into seven categories, namely chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, anxiety, asthma and chronic fatigue. After offering a panel discussion on each condition and hearing public comments from two individuals, both of whom expressed support for the MMP, the Panel voted on each petition. Based upon a majority vote of the members who were present at the meeting, the Panel recommended that chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety be approved as debilitating conditions under the MMP and recommended denial of asthma and chronic fatigue.

After the meeting, the Chairman of the Panel reduced the Panel's initial recommendations to writing and submitted it to the Department's Commissioner for consideration. In the initial recommendation letter, the Panel advised that it was recommending that the Commissioner add chronic pain related to musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety to the MMP because these conditions are debilitating and medicinal marijuana was more likely than not to have the potential to be beneficial to treat or alleviate the debilitation associated with each condition.

As for asthma and chronic fatigue, the Panel recommended that these conditions not be added to the MMP because medical marijuana was not likely to have the potential to be beneficial to treat or alleviate the debilitation associated with the conditions.

After receiving the Panel's initial recommendation letter, it was posted on the Department's website for a 60-day public comment period to provide the public with an opportunity to submit written comments on the recommendations. At the time the comment period closed, the Department received approximately sixty comments, which were generally supportive of the MMP.

During the 60-day comment period, the Department's MMP Review Panel also convened a public hearing on September 18, 2017, which provided the public with an additional opportunity to comment on the recommendations. During this public hearing, the Panel heard from seven individuals. The comments provided by the commenters did not express any disagreement with the Panel's recommendations.

Upon the conclusion of the public comment period, the Panel reconvened for a final meeting on the petitions. At the meeting, which was held on October 26, 2017, the Panel further deliberated its recommendations on the petitioned conditions, taking into consideration the petitions, information submitted with the petitions, public comments, the factors outlined in N.J.A.C. 8:64-5.3, each member's own research or that done by others, as well as each member's education and training, in order to determine whether any changes should be made to the Panel's initial recommendations. In so deliberating, the Panel discussed each condition in turn and permitted additional public comment on the conditions. Based upon the Panel's extensive and thorough discussions, the majority of the Panel members present at the meeting voted to uphold their initial recommendations on the conditions. As such, the Panel's initial recommendations converted to the Panel's final recommendations to the Commissioner, pursuant to N.J.A.C. 8:64-5.3(f).

Findings and Decisions on the Petitions

For the reasons that follow, I am granting the petitions seeking to add chronic pain that is related to musculoskeletal disorders, chronic pain conditions that are of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety as debilitating medical conditions under the MMP and denying the petitions seeking to include asthma and chronic fatigue syndrome under the MMP. My decision is consistent with the Panel's recommendations. In reaching my decision, I considered the statutory and regulatory criteria articulated above, the Panel's recommendations and their supporting materials, the petitions with supporting information, public comments and the transcripts of the Panel's meetings, which provides the Panel members' detailed discussions on each condition.

Granted Petitions

Chronic Pain associated with a Musculoskeletal Disorder

Based upon my independent review of the petitions, I am granting those seeking to add chronic pain associated with a musculoskeletal disorder to the MMP.[2] In coming to this conclusion, I reviewed this condition against the six regulatory criteria cited above and found that it meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain associated with a musculoskeletal disorder is a valid condition. According to the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), chronic pain associated with a musculoskeletal disorder is pain that persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing, and includes injury and inflammatory conditions "that cause pain in the body's joints; ligaments; muscles; nerves; tendons; and structures that support the limbs, neck, and back."[3] Moreover, as noted by the Panel, the World Health Organization's International Classification of Diseases, as clinically modified by the NCHS (ICD-10-CM), uses unique alphanumeric codes to identify known diseases and other health problems and lists multiple codes for chronic pain.[4] Given the fact that chronic pain associated with a musculoskeletal disorder has a common medical definition and maintains several ICD-10-CM codes, which entities covered by the Health Insurance Portability and Accountability Act must use for processing claims pursuant to rules promulgated by the U.S. Department of Health and Human Services, I find that chronic pain associated with a musculoskeletal disorder is a valid condition recognized by the medical community. See 45 C.F.R. 162.

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[2] Thirty-five of the petitions received by the Department concern various forms of chronic pain. After reviewing these petitions, the Panel determined that they fell into two categories: chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin. Based upon my review of this matter, I find that the Panel made the appropriate categorizations of these petitions. Thus, I agree with the Panel that the chronic pain conditions sought to be added to the MMP should be generally labeled as chronic pain associated with a musculoskeletal disorder and chronic pain of a visceral origin, rather than the unique, individual conditions set forth in each chronic pain petition. The list of petitions that fall into each category are set forth in the Panel's recommendation letter, which is incorporated herein by reference.

[3] See https://www.cdc.gov/nchs/data/nhsr/nhsr098.pdf (last visited March 13, 2018). See also https://www.cdc.gov/drugoverdose/prescribing/guideline.html (last visited March 13, 2018).

[4] See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. As set forth in the petitions and acknowledged by the Panel, the generally accepted treatments for chronic pain associated with a musculoskeletal disorder are opioids and non-steroid anti-inflammatory drugs (NSAIDs), both of which can have significant side effects. I agree. According to the Centers for Disease Control and Prevention (CDC), NSAIDs, such as ibuprofen, are a common treatment for chronic pain associated with a musculoskeletal disorder.[5] The CDC also recognizes opioids, such as oxycodone and hydrocodone, as a common and medically accepted treatment for chronic musculoskeletal pain.[6] Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community and relate to a patient's suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic pain associated with a musculoskeletal disorder itself as well as the treatment for this condition cause severe suffering for patients inflicted with this condition. As the name suggests, a patient with chronic pain associated with a musculoskeletal disorder experiences just that - pain. Specifically, musculoskeletal chronic pain can cause widespread or localized pain that may worsen with movement, stiffness or achiness, fatigue, and/or muscle twitches.[7] Thus, the condition itself is the main culprit for the suffering experienced by patients with this disorder. While chronic pain, in and of itself, causes extensive pain, the treatment for chronic pain associated with a musculoskeletal disorder can also cause significant suffering. Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness[8]. And, opioids can cause constipation, nausea, respiratory depression, dependency, sedation and dizziness.[9] All of these side effects can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that musculoskeletal chronic pain as well as the therapies to treat this condition cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic musculoskeletal pain that cause the patient suffering, namely NSAIDs and opioids, are essentially the most viable conventional medical therapies offered for this condition, which was noted by the Panel. As such, I find that there is an absence of effective alternative medical therapies to the conventional therapies currently prescribed for chronic musculoskeletal pain that cause patients to suffer.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical

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[5] See https://www.cdc.gov/drugoverdose/pdf/nonopioid_treatments-a.pdf (last visited March 13, 2018).
[6] See https://www.cdc.gov/drugoverdose/opioids/index.html (last visited March 13, 2018).
[7] See https://my.clevelandclinic.org/health/diseases/14526-musculoskeletal-pain (last visited March 13, 2018).
[8] See https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids (last visited March 13, 2018).
[9] See Footnote 6.

cannabis can relieve the chronic pain associated with a musculoskeletal disorder. Specifically, there are several peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, as well as a significant number of clinical trials, which found that the use of medical marijuana was effective in relieving chronic pain.[10] As such, I find that there is general acceptance in the medical community that medicinal cannabis can alleviate the suffering caused by chronic musculoskeletal pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic musculoskeletal pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain related to a musculoskeletal disorder is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain related to a musculoskeletal disorder should be added to the MMP.

Chronic Pain Conditions of a Visceral Origin

From my detailed review of the petitions, I am granting those seeking to add chronic pain conditions of a visceral origin to the MMP. In coming to this conclusion, I reviewed the petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

For the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic pain of a visceral origin is a valid condition. Chronic pain of a visceral origin is commonly defined by the medical community as pain that arises from the internal organs of the body and persists beyond the usual course of an acute condition, which is typically three months or more or past the time for normal healing.[11] Specifically, visceral pain is pain that results from the activation of nociceptors located in most viscera (internal organs of the body, specifically those within the chest (as the heart or lungs) or abdomen (as the liver, pancreas or intestines)) and the surrounding connective tissue.[12] Moreover, as noted by the Panel, there are multiple ICD-10-CM codes for chronic pain of a visceral origin, such as codes for pancreatitis, pain related to neurogenic bladder and bowel dysfunction, and irritable bowel syndrome. Because there is a common medical definition for chronic visceral pain as well as many ICD-10-CM codes for this condition, I find that chronic pain of a visceral origin is a valid and recognized medical condition.

As for the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community

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[10] See, e.g., The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017) (http://nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx) (last visited March 13, 2018); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, British Journal of Clinical Pharmacology (2001) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008/) (last visited March 13, 2018).

[11] See https://medical-dictionary.thefreedictionary.com/visceral+pain (last visited March 13, 2018).

[12] See https://www.merckmanuals.com/professional/neurologic-disorders/pain/overview-of-pain (last visited March 13, 2018).

and other experts as valid treatments for the condition. Like chronic musculoskeletal pain, chronic pain of a visceral origin is generally treated with opioids and NSAIDs, which, as I stated above, can have severe side effects. Indeed, the CDC advises that NSAIDs and opioids are the most common forms of treatment for chronic pain.[13] Thus, I find that the treatments for chronic pain, namely NSAIDs and opioids, are recognized and accepted by the medical community as the treatments for chronic visceral pain and relate to a patient's suffering.

Regarding the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the chronic pain condition itself as well as the treatments for this condition cause severe suffering for patients stuck with this disorder. Specifically, visceral pain due to an obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites.[14] Visceral pain that is caused by an injury of organ capsules or other deep connective tissues may be more localized and sharp.[15] As such, the actual condition is the main cause for the suffering experienced by patients with this disorder. Although chronic pain itself causes severe pain, the treatment for this condition can also result in significant suffering. As I outlined above, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness. And, opioids can cause constipation, nausea, respiratory depression, dependency, sedation and dizziness. So, the condition itself as well as the side effects from the medications used to treat this condition can prevent a patient from engaging in activities of daily living and eviscerate one's quality of life. Accordingly, I find that both the condition of chronic pain as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatments for chronic pain that cause the patient suffering, which are NSAIDs and opioids, are the only viable conventional medical therapies offered for this condition.[16] Therefore, I find that there is a lack of medically-accepted, alternative medical treatments to the conventional therapies currently recommended for chronic pain of this nature.

As for the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, the Panel concluded that there is comprehensive research demonstrating that the use of medicinal cannabis can alleviate the pain associated with chronic pain. As stated above, there are peer-reviewed publications in leading medical journals, including a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, and a number of clinical trials that found that the use of medical marijuana was effective in relieving chronic pain. As such, I find that the medical community has generally accepted the use of medicinal marijuana as a likely effective treatment for alleviating the suffering caused by chronic pain.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic

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[13] See footnotes 5 and 6.
[14] See footnote 12.
[15] Ibid.
[16] Ibid.

visceral pain under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of chronic pain of a visceral origin is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that chronic pain of a visceral origin should be added to the MMP.

Tourette's Syndrome

After a careful review of the petition seeking to add Tourette's Syndrome (TS) to the MMP, I have decided to grant this petition. In formulating this determination, I reviewed the condition against the six regulatory criteria cited above and found that its meets the requirements for inclusion in the MMP.

Under the first factor, I must determine whether the condition is generally accepted in the medical community as a valid medical condition. I find that TS meets this requirement. Specifically, TS is commonly defined by the medical community as a neurological disorder characterized by repeated involuntary movements (motor tics) and uncontrollable vocal sounds (vocal tics), with symptoms usually manifesting before the age of eighteen.[17] Moreover, a CDC study found that "1 of every 360 (0.3%) children 6 – 17 years of age in the United States have been diagnosed with TS based on parent[al] report[s]," with boys being "three to five times more likely to have TS than girls."[18] Accordingly, I find that TS is a valid and recognized medical condition.

Regarding the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. According to the petition and as acknowledged by the Panel, the generally accepted treatments for TS are medication and behavioral treatments, which can help manage the tics.[19] As noted by the Panel, there is no one primary medication to treat TS and, as a result, there is a varying approach to how it is addressed.[20] Most medications prescribed for TS have not been approved by the U.S. Food and Drug Administration (FDA) for treating tics and the medications that are approved fall into the category of anti-psychotics, which can have serious adverse side effects that include weight gain, stiff muscles, tiredness, restlessness, and social withdrawal.[21] As such, I find that the treatments for the symptoms of TS are recognized and accepted by the medical community as the treatments for this condition and relate to a patient's suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both TS itself as well as co-occurring conditions and the treatments for this condition cause severe

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[17] See http://www.merckmanuals.com/professional/pediatrics/neurologic-disorders-in-children/tic-disorders-and-tourette-syndrome-in-children-and-adolescents (last visited March 13, 2018).

[18] See https://www.cdc.gov/ncbddd/tourette/data.html (last visited March 13, 2018).

[19] See https://www.cdc.gov/ncbddd/tourette/treatments.html (last visited March 13, 2018).

[20] In Re: Medicinal Marijuana Review Panel Transcript. 55: 4 -6. October 25, 2017.

[21] See footnote 19.

suffering for patients inflicted with this condition. While the tics caused by TS clearly impair a patient's ability to carry on his or her activities of daily living, the co-occurring conditions that arise with this disorder can be equally if not more devastating to the patient. According to the National Institute of Neurological Disorders and Stroke, many individuals with TS experience additional neurobehavioral problems that often cause more impairment than the tics themselves. These include inattention, hyperactivity and impulsivity (attention deficit hyperactivity disorder — ADHD), problems with reading, writing, and arithmetic, and obsessive-compulsive symptoms such as intrusive thoughts/worries and repetitive behaviors.[22] Thus, TS itself along with its co-occurring conditions negatively impact a patient's quality of life. Additionally, as I noted above, the pharmacological treatments for TS can cause serious side effects that negatively impact an individual's quality of life. As recognized by the Panel, TS is difficult to treat and very debilitating.[23] I concur. As such, I find that both the condition of TS as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must analyze the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the only FDA-approved therapies for TS are anti-psychotic medications. While these medications have an 80% rate of tic suppression, which was noted by the Panel, the medications have serious side effects that can include weight gain and social withdraw. And, although behavioral therapy is a treatment that teaches people with TS ways to manage their tics, it is not a cure for tics. As such, the conventional therapies for TS, which are pharmaceutical and behavioral treatment, may not fully suppress or manage tics and the presence of TS may severely impair the patient's ability to carry on activities of daily living. Accordingly, I find that there is a lack of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for TS that cause suffering for some patients.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is research establishing that the use of medical cannabis can relieve the symptoms associated with TS. Evidence on the use of cannabis for effective symptomatic treatment of movement disorders, including TS, dates to the late 1990s with the work of Dr. Kirsten Müller-Vahl of the Hannover Medical School in Hannover, Germany.[24] Dr. Müller-Vahl's studies demonstrated improvements in global functioning and tic severity scores with cannabis use. Specifically, Dr. Müller-Vahl conducted a clinical survey among sixty-four TS patients of whom seventeen had reportedly consumed cannabis and approximately 82% of these patients reported a reduction in symptoms.[25] Subsequent studies of single cases confirmed that administration of 10mg of tetrahydrocannabinol (THC), which is one of the active chemical compounds in cannabis, led to an 80% reduction in tics and a simultaneous increase in the attention of patients.[26] And, a randomized, placebo-controlled six-week trial of up to 10mg THC

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[22] https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Tourette-Syndrome-Fact-Sheet (last visited March 13, 2018).

[23] In Re: Medicinal Marijuana Review Panel Transcript. 54:11. October 25, 2017.

[24] Müller-Vahl, K R., et al. "Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol." American Journal of Psychiatry 156.3 (1999): 495-495 .

[25] See http://researchfeatures.com/2017/06/01/cannabis-based-medication-tourettes-syndrome/ (last visited March 13, 2018).

[26] Ibid.

per day confirmed the previous findings.[27] Furthermore, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect.[28] Moreover, several states, such as Minnesota and Illinois, have approved medical marijuana specifically for the treatment of TS. Even more, a recent systematic review and meta-analysis published in the Journal of the American Medical Association (JAMA) in 2015 suggests there is some evidence that cannabinoids may improve symptoms of TS.[29] While the 2015 JAMA review suggests that marijuana may only have a minimal effect on relieving the symptoms of TS, the fact that the study evidenced some relief, even with the limited number of clinical trials available on the medical benefits of marijuana due to the legal restrictions surrounding cannabis, shows promise that marijuana is effective for this condition. As such, I find that the totality of the above research exhibits a general consensus in the medical community that marijuana is likely to alleviate some of the suffering caused by TS.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of TS under the MMP, I find that the petition was submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of TS is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that Tourette's Syndrome should be added to the MMP.

Migraine

After a thorough review of the petitions, I am granting those seeking to add migraine to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that migraine meets this criteria. According to the Merck Manual, migraine is an episodic primary headache disorder.[30] Symptoms typically last four to seventy-two hours and may be severe.[31] Pain is often unilateral, throbbing, worsen with exertion, and accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before but sometimes after the headache.[32] And, there are approximately 28 million individuals living with migraines in the United States.[33] As such, I find that migraine is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments

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[27] Ibid.

[28] See https://www.nap.edu/read/24625/chapter/6?term=tourette#104 (last visited March 13, 2018).

[29] See https://media.jamanetwork.com/news-item/mixed-findings-regarding-quality-of-evidence-supporting-benefit-of-medical-marijuana/ (last visited March 13, 2018).

[30] See http://www.merckmanuals.com/professional/neurologic-disorders/headache/migraine (last visited March 13, 2018).

[31] Ibid.

[32] Ibid.

[33] https://www.hopkinsmedicine.org/otolaryngology/_docs/Migraine%20patient%20handout.pdf (last visited March 13, 2018).

causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. As stated in the petitions and recognized by the Panel, the generally accepted treatments for migraines are NSAIDs, triptans, opioids and/or ergots (ergot alkaloids), all of which can have significant side effects.[34] Specifically, prolonged use of NSAIDs can cause gastritis, ulcerative disease, heartburn, nausea, vomiting and dizziness.[35] Side effects of triptans include nausea, dizziness, drowsiness and muscle weakness.[36] Furthermore, triptans should not be used by those who have a past history of, or risk factors, for heart disease, high blood pressure, high cholesterol, angina, peripheral vascular disease, impaired liver function, stroke or diabetes.[37] Ergots may worsen nausea and vomiting related to migraines, and it may also lead to medication-overuse headaches.[38] And, as outlined above, opioids have serious side effects including addiction and nausea.[39] Thus, I find that the treatments for migraine, namely NSAIDs, triptans, opioids and ergots, can cause a patient to suffer and are accepted by the medical community as the treatments for this condition.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the migraine condition itself as well as the treatments for this condition cause severe suffering for patients. As stated above, the condition itself causes intense pain, nausea and sensitivity to light, sound, or odors. In fact, the pain and sensitivity may become so intense that the patient may have no other option than to rest in a dark, quite room until the migraine passes.[40] Thus, the migraine condition causes severe suffering.

The same holds true for migraine treatments. The side effects caused by the treatments for migraines can be equally if not worse than the symptoms produced by this condition. Specifically, the treatments, which include opioids and triptans, can cause nausea, dizziness, and muscle weakness and may even cause rebound symptoms that are more intense than the original onset of the migraine.[41] Thus, the migraine condition as well as side effects accompanying the treatment for this condition impair or even prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. With this, I find not only that the migraine condition in and of itself causes a patient severe suffering but that the therapies to treat it also cause significant suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. The treatments for migraine that cause the patient suffering, namely

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[34] https://www.hopkinsmedicine.org/otolaryngology/_docs/Migraine%20patient%20handout.pdf (last visited March 13, 2018). See also https://www.mayoclinic.org/diseases-conditions/migraine-headache/diagnosis-treatment/drc-20360207 (last visited March 13, 2018).

[35] See https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids (last visited March 13, 2018).

[36] See http://www.headaches.org/2007/10/25/triptans/ (last visited March 13, 2018).

[37] Ibid.

[38] See https://www.drugs.com/mcd/migraine (last visited March 13, 2018).

[39] See footnote 6.

[40] https://www.hopkinsmedicine.org/otolaryngology/_docs/Migraine%20patient%20handout.pdf (last visited March 13, 2018).

[41] Ibid.

NSAIDs, triptans, opioids and ergots, are the conventional medical therapies offered for this condition. Furthermore, as noted by the Panel, the conventional therapies are ineffective for some patients, leaving them with a decreased ability to function and a decreased quality of life. Alternatives such as biofeedback, ice packs, acupressure, aromatherapy, adequate sleep, smoking cessation, avoiding any food and environmental triggers are available and may alleviate migraine symptoms.[42] However, these alternative treatments usually do not treat all of the symptoms associated with a migraine and do not necessarily alleviate the patient's suffering caused by the migraine. Therefore, patients that are not responsive to conventional or alternative therapies may suffer constant unrelenting pain, which produces mental and physical debilitation. As such, I find that there are serious limitations with the medically-accepted, alternative medical therapies and the conventional therapies currently prescribed for migraine.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there is extensive research establishing that the use of medical cannabis can relieve the pain associated with migraine. There are studies which found that the use of medical marijuana was effective in decreasing the frequency of migraine headaches and relieving migraine pain.[43] Most notably, a recent study recommended that prospective studies should be conducted to explore a cause-and-effect relationship and the use of different strains, formulations, and doses of marijuana to better understand the effects of medical marijuana on migraine headache treatment and prophylaxis.[44] A majority of the Panel agreed that a review of the literature suggests that marijuana might alleviate some of the symptoms caused by a migraine with less side effects than commonly accepted medical treatment. Based upon this research, I find that there is generally accepted evidence in the medical community that medicinal cannabis can alleviate the suffering caused by migraine.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of migraine under the MMP, I find that the petitions were submitted with support from physicians and an advanced practice nurse. Indeed, one petition was submitted by a board certified anesthesiologist. Thus, I find that this requirement is met.

Based upon the above analysis, I find that the condition of migraine is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that migraine should be added to the MMP.

Anxiety

Based upon my independent review of the petitions, I am granting those seeking to add anxiety to the MMP. In coming to this conclusion, I reviewed these petitions against the six regulatory criteria cited above and found that the condition meets the requirements for inclusion in the MMP.

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[42] Ibid. See also https://migraine.com/complimentary-and-alternative-therapies/ (last visited March 13, 2018).
[43] Ethan B. Russo, Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes, Cannabis and Cannabinoid Research, 20a6, 1,1, 154. See https://www.liebertpub.com/doi/10.1089/can.2016.0009 (last visited March 13, 2018).
[44] See https://www.ncbi.nlm.nih.gov/pubmed/26749285 (last visited March 13, 2018).

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that anxiety satisfies this criteria. Specifically, the American Psychiatric Association defines anxiety and anxiety disorders as conditions characterized by excessive fear and behavioral disturbances.[45] Anxiety results from anticipation of a future threat and may be associated with symptoms of muscle tension, vigilance in preparation for future danger, and overly cautious or avoidant behaviors.[46] Additionally, there are multiple ICD-10-CM codes for anxiety disorders.[47] Because anxiety maintains a common definition in the medical community and has ICD-10-CM codes, I find that anxiety is a valid and recognized medical condition.

Under the second factor, I must consider whether the treatments for the condition, rather than the condition itself, are causing the patient's suffering and the extent to which the treatments causing the patient suffering are generally accepted by the medical community and other experts as valid treatments for the condition. From my review of this condition, the generally accepted treatments for anxiety are dependent on the symptoms and the severity of the particular disorder. Mild and moderate forms of anxiety may not require a pharmacologic intervention, but may necessitate other forms of treatment, such as meditation, mindfulness, breathing techniques as well as psychotherapy (counseling) or cognitive therapy.[48] The most common classes of medications used to combat anxiety disorders are antidepressants, anti-anxiety drugs, and beta-blockers.[49] Antidepressants are safe and effective but they may be risky for children, teens, and young adults.[50] Antidepressants also come with a "black box" warning – the FDA's strongest warning - advising that some people may have suicidal thoughts or make suicide attempts while taking the medication.[51] The most common anti-anxiety medications are called benzodiazepines. As noted by the Panel, the common sides effects of benzodiazepines include headache, confusion, tiredness, and in some causes nightmares and memory impairments.[52] And, benzodiazepines carry a risk of dependence and addiction.[53] Furthermore, the FDA notes that the number of patients who were prescribed both an opioid analgesic and benzodiazepine increased by 41% between 2002 and 2014.[54] As a result, the FDA requires black box warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines to inform the patient about the serious risks associated with using these medications at the same time.[55] Thus, I find that the treatments for anxiety are recognized and accepted by the medical community as the treatments for this condition and relate to the suffering of the patient.

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[45] See https://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.dsm05 (last visited March 13, 2018).
[46] Ibid.
[47] See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited March 13, 2018).
[48] See https://adaa.org/finding-help/treatment# (last visited March 14, 2018).
[49] Ibid.
[50] See https://www.mayoclinic.org/diseases-conditions/teen-depression/in-depth/antidepressants/art-20047502 (last visited March 14, 2018).
[51] Ibid.
[52] See https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml (March 14, 2018).
[53] Ibid.
[54] See https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm (last visited March 14, 2018).
[55] Ibid.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that both the anxiety condition itself as well as the treatments for this condition cause severe suffering for patients. Specifically, anxiety may lead to problems that negatively impact an individual's activities of daily living and quality of life and may lead to suicide and depression. Anxiety disorders can also cause significant distress or interfere with social, occupational, and other areas of functioning. In fact, an estimated 31.1% of U.S. adults experience an anxiety disorder at some time in their lives.[56] Medications, in some instances, may exacerbate the symptoms and are associated with debilitating side effects that can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that both the condition of anxiety as well as the therapies to treat it cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. As discussed above, mild and moderate forms of anxiety may be treated with meditation, mindfulness, breathing techniques as well as counseling or cognitive therapy that can be effective. Progression to medication therapy may be initiated; however, in both instances, one must consider the therapeutic response. Failure to respond to therapies or side effects associated with treatments may result in significant impacts on quality of life. As such, I find that there is an absence of medically-accepted, alternative medical therapies to the conventional therapies currently prescribed for migraine that cause suffering.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that cannabis is generally accepted as an effective treatment for anxiety. The Panel discussed medical evidence that cannabis may exacerbate anxiety symptoms or that an effect related to cannabis may be associated with anxiety, such as dependence and cravings. Literature suggests that individuals with anxiety sensitivity may be more likely to turn to cannabis as a mechanism for coping with stress, which may in turn lead to problematic use behaviors.[57] However, the Panel further discussed a review published by the National Academies of Sciences, Engineering, and Medicine in 2017, which found that there is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, which was assessed by a public speaking test utilizing individuals with social anxiety disorders.[58] On balance, the Panel recommended adding anxiety as an allowable condition under the MMP as research suggests that it could be helpful to some patients with this condition. I agree. While marijuana may not be effective for all anxiety sufferers, there is research evidencing that it may be helpful to some, especially those with social anxiety disorders. Thus, I find that there is acceptance in the medical community that marijuana is likely to relieve the suffering associated with some anxiety conditions. However, like any medical condition, the use of medical marijuana to treat anxiety must be explored by the

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[56] See https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml (last visited March 13, 2018).

[57] Anxiety Sensitivity and Distress Intolerance as Predictors of Cannabis Dependence Symptoms, Problems, and Craving: The Mediating Role of Coping Motives. Farris SG, Metrik J, Bonn-Miller MO, Kahler CW, Zvolensky MJ. J Stud Alcohol Drugs. 2016 Nov;77(6):889-897.

[58] The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research, National Academies Press (2017); Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials, British Journal of Clinical Pharmacology (2001).

medical professional treating the patient to determine whether it is the best and most appropriate course of treatment for the patient.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of anxiety under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of anxiety is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition. As such, I find that anxiety should be added to the MMP.

Denied Petitions

Asthma

After carefully reviewing the petition seeking to include asthma as a debilitating condition under the MMP, and in accordance with the Panel's recommendation, I am denying the request. In coming to this conclusion, I reviewed the petition against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that asthma meets this requirement. The CDC defines asthma as a chronic lung disease[59] that "causes repeated episodes of wheezing, breathlessness, chest tightness, and nighttime or early morning coughing."[60] Moreover, the Department recognizes asthma as a chronic medical condition with approximately 600,000 adults and 167,000 children suffering from this condition in New Jersey.[61] Thus, I find that asthma is generally accepted by the medical community as a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. In the petition, the petitioner asserts that the use of albuterol to treat asthma causes an individual to experience an increased heart rate and shakiness and that the use of corticosteroids to treat asthma can cause the patient to become addicted to the drug. While corticosteroids and bronchodilators, such as albuterol, are generally accepted treatments for asthma, I do not find that the average patient suffers from the use of these medications. As stated by the Panel, there are several treatments for asthma that are not only effective but also provide minimal side effects. Specifically, asthma is generally treated with inhaled, oral and intravenous corticosteroids and bronchodilators.[62] Common side effects associated with the use of corticosteroids include acne, weight gain and upset stomach.[63] However, these side effects rarely occur with the short-term use of these medications, such as when they are used for acute asthma episodes.[64] While the use of corticosteroids is accepted

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[59] See https://www.cdc.gov/asthma/stateprofiles/asthma_in_nj.pdf (last visited March 13, 2018).
[60] See https://www.cdc.gov/asthma/default.htm (last visited March 13, 2018).
[61] See http://www.nj.gov/health/fhs/chronic/asthma/in-nj/ (last visited March 13, 2018).
[62] See https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660 (last visited March 13, 2018).
[63] See https://my.clevelandclinic.org/health/diseases/16864-treating-the-inflammation-of-asthma (last visited March 13, 2018).
[64] Ibid.

by the medical community as valid treatments for asthma, I do not find that these treatments cause the vast majority of patients to experience suffering from their use.

The same holds true for bronchodilators. While bronchodilators can cause nervousness or shakiness, headache, throat or nasal irritation, muscle aches and, in rare instances, a rapid heart rate or heart palpitations, these side effects can be greatly reduced and even eliminated by changing the delivery method of the medication and/or reducing the dosage.[65] Although these side effects could potentially cause a patient to suffer, they can be effectively decreased and even eliminated through medication management. As such, I find that the treatments for asthma do not cause an average asthma patient to experience suffering.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that asthma can cause severe suffering. Specifically, when asthma is not well-controlled, it can severely impair a patient's ability to engage in his or her activities of daily living, such as limiting the patient's physical activity, cause sleep disturbances and can even result in death. Accordingly, I find that asthma can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While asthma cannot be cured, it can be well-controlled with self-management education, adequate pharmacological management, and avoidance of exposure to environmental triggers.[66] Specifically, asthma is commonly and effectively treated with bronchodilators and corticosteroids, which are widely available to patients and have little side effects.[67] Thus, I find that the conventional medical treatments for asthma are effective and easily attainable by patients.

Regarding the fifth factor, which whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for asthma. While the petitioner points to a study published in the New England Journal of Medicine in 1973, which suggests that marijuana dilates the airway for a short period of time, the study did not evaluate the effect marijuana has on patients suffering from asthma. In fact, the study utilized thirty-two male subjects with no serious medical conditions and advised that "further investigation is required to determine . . . the effects of marijuana smoking and oral THC on the airway of asthmatic subjects." As such, I find that this study does not support the proposition that marijuana is an effective treatment for asthma.

Even more, physicians with the American Thoracic Society recently published an article in the American Journal of Respiratory and Critical Care Medicine advising that marijuana can worsen existing lung conditions and specifically noted that "marijuana smoke can cause an

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[65] See https://www.mayoclinic.org/diseases-conditions/asthma-attack/expert-answers/albuterol-side-effects/faq-20058088 (last visited March 13, 2018).

[66] See https://www26.state.nj.us/doh-shad/topic/Asthma.html (last visited March 13, 2018).

[67] See Footnote 62.

asthma attack leading to hospitalization and even death."[68] Thus, the medical community appears to be opposed to the use of marijuana as a treatment for asthma. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for asthma, and neither I nor the Panel found any reliable trials or research in support of this, I find that the medical community is not in favor of using medicinal cannabis to alleviate the suffering associated with asthma.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of asthma under the MMP, I find that the petition only referenced the 1973 New England Journal of Medicine article and did not include any letters of support from healthcare professionals. While the journal article was authored by three physicians, I do not find that this lone article from 1973 on the general effects of marijuana on the airway constitutes support from a medical professional for the inclusion of asthma to the MMP. Additionally, there were no public comments from medical professionals supporting the inclusion of asthma under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the foregoing, I find that asthma can be debilitating if uncontrolled, but that marijuana is not likely to be a beneficial treatment for this condition or alleviate the debilitating effect of this condition. Indeed, as noted by the Panel, inhalation of smoke is a known trigger for asthma exacerbation and, as a result, smoking marijuana may actually increase the suffering of asthma patients rather than alleviate the suffering associated with this condition[69]. And, while I acknowledge that medicinal marijuana is available in non-smokable forms, I am not convinced that there is credible support for its use in treating asthma. Unless and until there is sufficient research and evidence demonstrating that the use of marijuana can be beneficial for an asthma patient, I find that asthma should not be added to the MMP.

Chronic Fatigue Syndrome

From my detailed review of the petition seeking to include chronic fatigue syndrome as a debilitating condition under the MMP, and in accordance with the Panel's recommendation, I have concluded that the petition should be denied. In coming to this conclusion, I reviewed the petition against the six regulatory factors cited above and found that the condition fails to meet the requirements for inclusion in the MMP.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that chronic fatigue syndrome meets this criteria. According to the CDC, chronic fatigue syndrome, also known as myalgic encephalomyelitis, is a "long-term illness that affects many body systems." [70] In addition to extreme fatigue, which may worsen with physical or mental activity, but does not improve with rest, an individual with this condition may experience insomnia, depression, joint and muscle pain and memory impairments.[71] In fact, there is an estimated 836,000 to 2.5 million individuals

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[68] Drake MD, Matthew G. and Slatore MD, Christopher G. "Smoking Marijuana and the Lungs." Am. J. Respir. Crit. Care Med., Vol. 195, P5-6 (2017).

[69] Ibid.

[70] https://www.cdc.gov/me-cfs/index.html (last visited March 13, 2018).

[71] https://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/symptoms-causes/syc-20360490 (last visited March 13, 2018).

affected with this condition in the United States.[72] Thus, I find that chronic fatigue syndrome is a valid medical condition.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. Unfortunately, there is neither a cure nor an FDA-approved treatment for chronic fatigue syndrome.[73] As a result, treatment is largely palliative as the treatment is tailored to relieve the symptoms experienced by each individual patient. For example, a patient experiencing depression as a result of chronic fatigue syndrome could be treated with an anti-depressant and a patient experiencing muscle and joint pain could be prescribed an NSAID to relieve the pain.[74] Moreover, the symptoms of chronic fatigue are oftentimes treated with nutritional supplements and complementary therapies, such as massage, meditation, tai chi and acupuncture, which may be helpful in increasing the patient's energy level and decreasing his or her pain.[75] But, these are not treatments for the actual condition but rather treatments for the symptoms associated with the condition. As such, I find that there is no treatment generally accepted in the medical community for this disease that causes suffering.

However, I do find that the above therapies prescribed by healthcare professionals to treat the **symptoms** associated with chronic fatigue syndrome are accepted by the medical community. While I find that the treatments for chronic fatigue symptoms are medically acceptable, the specific treatment prescribed depends on the type and severity of the symptoms presented and can range from anti-depressants and NSAIDs, which can have severe side effects for some patients and thereby cause suffering, to massage therapy and acupuncture, which have little to no side effects. Because there is a vast array of treatment options for chronic fatigue symptoms and no two patients are treated the same, I am unable to conclude that chronic fatigue patients generally suffer from the treatments they receive for their symptoms. However, individuals with severe forms of chronic fatigue syndrome may suffer from the treatments used to alleviate their symptoms.

As for the third factor, which is whether the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living, I find that chronic fatigue syndrome can cause severe suffering. Specifically, some individuals suffering from chronic fatigue syndrome can experience severe pain, gross memory loss and even such extreme fatigue that the patient is house-bound or even bed-bound, all of which greatly impacts a patient's ability to engage in activities of daily living and maintain a quality life. Accordingly, I find that chronic fatigue syndrome can cause a patient to experience severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. While chronic fatigue cannot be cured and there is no approved treatment for the condition, there is a wide array of pharmacological therapies available for alleviating the symptoms associated with this condition. Specifically, chronic fatigue symptoms

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[72] Wright Clayton, MD, Ellen, "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome An IOM Report on Redefining an Illness." JAMA (2015).

[73] https://www.cdc.gov/me-cfs/treatment/index.html (last visited March 13, 2018).

[74] https://www.cdc.gov/me-cfs/index.html (last visited March 13, 2018).

[75] Ibid.

can be effectively managed for some patients with NSAIDs, anti-depressants and sleep-aids, depending on the severity and type of symptoms presented. However, depending upon the patient, the pharmacological treatments for chronic pain symptoms may be effective but may also cause the patient to suffer from side effects. Thus, I find that there are available conventional medical therapies to alleviate a chronic fatigue patient's suffering, but those treatments may cause suffering for some patients.

Regarding the fifth factor, whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I agree with the Panel's conclusion that there are no reliable clinical trials or research supporting the proposition that medical cannabis is an effective treatment for chronic fatigue syndrome. While the petitioner points to studies suggesting that medical marijuana can alleviate an individual's pain, which is potentially one symptom a patient inflicted with chronic fatigue syndrome may experience, the studies fail to articulate that marijuana is an effective treatment for the condition of chronic fatigue syndrome as a whole. Because the petitioner failed to point to any evidence demonstrating that the medical community accepts medical marijuana as a treatment for the actual condition of chronic fatigue syndrome, and neither I nor the Panel found any credible clinical evidence in support of this, I find that there is a lack of support in the medical community for the use of medicinal cannabis to alleviate the suffering associated with chronic fatigue syndrome.

As for the final factor, which is whether there are letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of chronic fatigue under the MMP, I find that the petition only referenced the above-mentioned studies reflecting on the effectiveness of medical marijuana to treatment pain and did not include any letters of support from healthcare professionals to have chronic fatigue added to the MMP. Additionally, there was an absence of public comments from medical professionals supporting the inclusion of chronic fatigue under the MMP. Thus, I find that there is a lack of support from physicians or other health care professionals for this condition to be added to the MMP.

Based upon the above analysis, I find that chronic fatigue syndrome can be debilitating for some patients, but that medical marijuana is not likely to be a potentially beneficial treatment for the debilitating effect of this condition or the alleviation of the symptoms associated with this condition. Indeed, as noted by the Panel, this condition has been researched for years and there is yet to be found a solid elucidation of the etiology of this condition or the treatments that are effective for it.[76] Because there are still so many unknowns with this condition and there is no clinical evidence suggesting that marijuana would be beneficial as a treatment, I find that chronic fatigue syndrome should not be added to the MMP at this time.

Conclusion

Based upon the foregoing, I am adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, as well as Tourette's Syndrome, migraine, and anxiety to the MMP. However, asthma and chronic fatigue syndrome will not be added to the MMP.

In order to provide patients with relief as soon as possible from the suffering they are experiencing from these debilitating conditions, I am immediately adding chronic pain associated with musculoskeletal disorders, chronic pain of a visceral origin, Tourette's Syndrome, migraine, and anxiety to the MMP in advance of rule promulgation. While I am including these conditions

[76] https://www.ncbi.nlm.nih.gov/books/NBK293931/ (last visited March 13, 2018).

under the MMP, please note that this decision is not intended to be a blanket endorsement for every patient inflicted with a condition falling under the MMP to utilize medicinal marijuana as a treatment. As with any condition, the course of treatment must be determined by a medical professional after a thorough evaluation and discussion with the patient regarding the benefits and possible negative effects of the recommended therapy. Accordingly, I encourage patients to discuss the possibility of utilizing medical marijuana as a treatment for their debilitating conditions with the medical professionals treating them. I hope that this decision brings needed relief to those suffering with these conditions.

This is a final agency decision. You have the right to appeal this final agency decision within 45 days to the New Jersey Superior Court, Appellate Division, Richard J. Hughes Justice Complex, P.O. Box 006, Trenton, New Jersey 08625-0006.

Shereef M. Elnahal, MD, MBA
Acting Commissioner

Question 2

Relevant medical or scientific evidence pertaining to the disease or condition

Contents

Overview

General Anxiety Disorder (GAD) is a mental health disorder that can interfere significantly in a patients daily life

Generalized anxiety disorder symptoms can vary. They may include:

- Persistent worrying or anxiety about a number of areas that are out of proportion to the impact of the events
- Overthinking plans and solutions to all possible worst-case outcomes
- Perceiving situations and events as threatening, even when they aren't
- Difficulty handling uncertainty
- Indecisiveness and fear of making the wrong decision
- Inability to set aside or let go of a worry
- Inability to relax, feeling restless, and feeling keyed up or on edge
- Difficulty concentrating, or the feeling that your mind "goes blank"

Physical signs and symptoms may include:

- Fatigue
- Trouble sleeping
- Muscle tension or muscle aches
- Trembling, feeling twitchy
- Nervousness or being easily startled
- Sweating
- Nausea, diarrhea or irritable bowel syndrome
- Irritability

Treatments include:

- Psychotherapy including cognitive behavioral therapy
- Medication

GAD is a debilitating disease that is difficult to treat, and it is vital for a patient’s quality of life that they’re physician have access to all credible treatments, including medical marijuana.

Generalized Anxiety Disorder:

When Worry Gets Out of Control

NIH National Institute of Mental Health

WHAT IS GAD?

Occasional anxiety is a normal part of life. You might worry about things like health, money, or family problems. But people with generalized anxiety disorder (GAD) feel extremely worried or feel nervous about these and other things—even when there is little or no reason to worry about them. People with GAD find it difficult to control their anxiety and stay focused on daily tasks.

The good news is that GAD is treatable. Call your doctor to talk about your symptoms so that you can feel better.

What are the signs and symptoms of GAD?

GAD develops slowly. It often starts during the teen years or young adulthood. People with GAD may:

- Worry very much about everyday things
- Have trouble controlling their worries or feelings of nervousness
- Know that they worry much more than they should
- Feel restless and have trouble relaxing
- Have a hard time concentrating
- Be easily startled
- Have trouble falling asleep or staying asleep
- Feel easily tired or tired all the time
- Have headaches, muscle aches, stomach aches, or unexplained pains
- Have a hard time swallowing
- Tremble or twitch
- Be irritable or feel “on edge”
- Sweat a lot, feel light-headed or out of breath
- Have to go to the bathroom a lot

Children and teens with GAD often worry excessively about:

- Their performance, such as in school or in sports
- Catastrophes, such as earthquakes or war

Adults with GAD are often highly nervous about everyday circumstances, such as:

- Job security or performance
- Health
- Finances
- The health and well-being of their children
- Being late
- Completing household chores and other responsibilities

Both children and adults with GAD may experience physical symptoms that make it hard to function and that interfere with daily life.

> Symptoms may get better or worse at different times, and they are often worse during times of stress, such as with a physical illness, during exams at school, or during a family or relationship conflict.

What causes GAD?

GAD sometimes runs in families, but no one knows for sure why some family members have it while others don't. Researchers have found that several parts of the brain, as well as biological processes, play a key role in fear and anxiety. By learning more about how the brain and body function in people with anxiety disorders, researchers may be able to create better treatments. Researchers are also looking for ways in which stress and environmental factors play a role.

How is GAD treated?

First, talk to your doctor about your symptoms. Your doctor should do an exam and ask you about your health history to make sure that an unrelated physical problem is not causing your symptoms. Your doctor may refer to you a mental health specialist, such as a psychiatrist or psychologist.

GAD is generally treated with psychotherapy, medication, or both. Talk with your doctor about the best treatment for you.

Psychotherapy

A type of psychotherapy called cognitive behavioral therapy (CBT) is especially useful for treating GAD. CBT teaches a person different ways of thinking, behaving, and reacting to situations that help him or her feel less anxious and worried. For more information on psychotherapy, visit **http://www.nimh.nih.gov/health/topics/psychotherapies**.

Medication

Doctors may also prescribe medication to help treat GAD. Your doctor will work with you to find the best medication and dose for you. Different types of medication can be effective in GAD:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Other serotonergic medication
- Benzodiazepines

Doctors commonly use SSRIs and SNRIs to treat depression, but they are also helpful for the symptoms of GAD. They may take several weeks to start working. These medications may also cause side effects, such as headaches, nausea, or difficulty sleeping. These side effects are usually not severe for most people, especially if the dose starts off low and is increased slowly over time. **Talk to your doctor about any side effects that you have.**

Buspirone is another serotonergic medication that can be helpful in GAD. Buspirone needs to be taken continuously for several weeks for it to be fully effective.

Benzodiazepines, which are sedative medications, can also be used to manage severe forms of GAD. These medications are powerfully effective in rapidly decreasing anxiety, but they can cause tolerance and dependence if you use them continuously. Therefore, your doctor will only prescribe them for brief periods of time if you need them.

Don't give up on treatment too quickly. Both psychotherapy and medication can take some time to work. A healthy lifestyle can also help combat anxiety. Make sure to get enough sleep and exercise, eat a healthy diet, and turn to family and friends who you trust for support.

For basic information about these and other mental health medications, visit **http://www.nimh.nih.gov/health/topics/mental-health-medications**. Visit the Food and Drug Administration's website (**http://www.fda.gov/**) for the latest information on warnings, patient medication guides, or newly approved medications.

What is it like to have GAD?

"I was worried all the time and felt nervous. My family told me that there were no signs of problems, but I still felt upset. I dreaded going to work because I couldn't keep my mind focused. I was having trouble falling asleep at night and was irritated at my family all the time.

I saw my doctor and explained my constant worries. My doctor sent me to someone who knows about GAD. Now I am working with a counselor to cope better with my anxiety. I had to work hard, but I feel better. I'm glad I made that first call to my doctor."

Where can I find more information?

To learn more about generalized anxiety disorder, visit:

MedlinePlus (National Library of Medicine)
http://medlineplus.gov
(En Español: http://medlineplus.gov/spanish)

For information on clinical trials, visit:

ClinicalTrials.gov
http://www.clinicaltrials.gov
(En Español: http://salud.nih.gov/investigacion-clinica/)

For more information on conditions that affect mental health, resources, and research, visit the NIMH website (http://www.nimh.nih.gov).

National Institute of Mental Health (NIMH)
Office of Science Policy, Planning, and Communications
Science Writing, Press, and Dissemination Branch

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. QF 16-4677
Revised 2016

Question 5

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

To Whom It May Concern,

We, the undersigned physicians, support adding generalized anxiety disorder to the qualifying conditions list under Ohio's Medical Marijuana Control Program.

We have reviewed the available science, research and information on treating generalized anxiety disorder with medical marijuana and believe it to be an effective treatment, and that the benefits outweigh the risks.

Any physician who has treated a patient with generalized anxiety disorder understands the immense impact this condition can have on a person's quality of life. At its most severe, generalized anxiety disorder can leave a patient bedridden and unable to perform basic daily tasks.

Studies conducted by Tyrer and Baldwin in 2006 and Yonkers *et all* in 1996 have shown remission rates for generalized anxiety disorder are low.

Given the difficulty of treating this condition, and the detrimental nature of it on a patient's life, we believe adding medical marijuana to the list of treatment options is vital to patient wellbeing.

For these reasons, we ask that the State Medical Board of Ohio add generalized anxiety disorder as a qualifying condition under Ohio's Medical Marijuana Control Program.

Sincerely,

DocuSigned by:
FED24AE73239452...

Daniel Neides

MD

To Whom It May Concern,

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For these reasons, we ask that the State Medical Board of Ohio add generalized anxiety disorder as a qualifying condition under Ohio's Medical Marijuana Control Program.

Sincerely,

DocuSigned by:
Cynthia Taylor
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Cynthia Taylor

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Question 3

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

Contents

Overview

General Anxiety Disorder (GAD) is a mental health disorder characterized by excessive worry and other symptoms ranging from restlessness to irritability. For many patients, chronic GAD can be debilitating, and at its worst leave a patient unable to go about their daily life.

Treating GAD is complicated by the fact that it is often associated with other conditions and sufferers regularly go years without seeking treatment. Nonetheless, when patients do seek treatment, they're results vary based on a range of factors with only 50-60% responding clinically to therapy and even less entering remission.

Attached are two publications detailing both the difficulties in treating GAD and the success rates of current treatment options:

1. **Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care** – "Most clinical studies suggest that GAD is typically a chronic condition with low rates of remission over the short and medium-term. Evaluation of prognosis is complicated by the frequent comorbidity with other anxiety disorders and depression, which worsen the long-term outcome and accompanying burden of disability (Tyrer & Baldwin, 2006)."
2. **Achieving Remission in Generalized Anxiety Disorder** - "Between 50% and 60% of patients respond clinically to therapy, but only one-third to one-half attain remission or realize full recovery during the acute phase of treatment."

Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care.

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2 GENERALISED ANXIETY DISORDER

2.1. INTRODUCTION

Go to:

This guideline is concerned with the treatment and management of adults with a diagnosis of GAD in primary and secondary care. GAD is one of a range of anxiety disorders including panic disorder (with and without agoraphobia), PTSD, OCD, social phobia, specific phobias (for example, of spiders) and acute stress disorder.

GAD commonly coexists with other anxiety disorders and with depressive disorders, as well as a variety of physical health disorders. 'Pure' GAD in the absence of another anxiety or depressive disorder is less typical than comorbid GAD. This guideline is relevant to both people with pure and comorbid GAD. The NICE guideline on case identification and referral for common mental health disorders will provide further guidance on identification (NICE, 2011).

2.2. THE DISORDER

Go to:

2.2.1. Symptoms, presentation and patterns of illness

Anxiety is a prominent symptom of many psychiatric disorders but it is only comparatively recently that several distinct anxiety disorders have been recognised in classificatory systems. The key feature of GAD is worry and apprehension that is out of proportion to the circumstances. The worries are typically widespread, involve everyday issues and have a shifting focus of concern. The affected person finds the worries difficult to control, and this can result in decreased occupational and social functioning (Tyrer & Baldwin, 2006; Bitran *et al.*, 2009).

As well as worry that is excessive, generalised and difficult to control, people with GAD experience other psychological and somatic symptoms of anxiety. Psychological symptoms include irritability, poor concentration, increased sensitivity to noise and sleep disturbance, typically difficulty falling asleep. Somatic symptoms of GAD can manifest in many different ways. For example, an overactive autonomic nervous system can lead to sweating, dry mouth, palpitations, urinary frequency, epigastric discomfort and frequent and/or loose bowel motions, while hyperventilation may result in feelings of shortness of breath and dizziness. Increased muscle tension is a common accompaniment of persistent anxiety and may be experienced as restlessness, inability to relax, headaches and aching pains, particularly in the shoulders and back (Gelder *et al.*, 2006).

GAD is frequently comorbid with other mental disorders, which can complicate its presentation. The rates of comorbidity vary between studies with estimates of between 68 and 93% of comorbidity with another axis 1 mental health disorder (Carter *et al.*, 2001; Hunt *et al.*, 2002; ESEMeD/MHEDEA 2000 Investigators, 2004). Comorbid disorders that are particularly common include depressive disorders (specifically major depression and dysthymia), other anxiety disorders (especially panic disorder, social phobia and specific phobias) and somatoform disorders (Bitran *et al.*, 2009; Carter *et al.*, 2001; Hunt *et al.*, 2002; Grant *et al.*, 2005; Kessler *et al.*, 2005b). There is also significant comorbidity with substance misuse especially among men (Grant *et al.*, 2005; Kessler *et al.*, 2005b).

GAD also often co-occurs with physical health problems such as arthritis and gastrointestinal and respiratory disorders and may mimic the presentation of some

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physical conditions (for example, hyperthyroidism) (Culpepper, 2009; Roy-Byrne *et al.*, 2008; Sareen *et al.*, 2006). Due to the somatic symptoms of anxiety, which are central to GAD, and physical comorbidities, people with GAD who present in primary care may emphasise somatic problems or sleep disturbance, rather than excessive worry or psychological symptoms of anxiety (Rickels & Rynn, 2001).

2.2.2. Course and prognosis

Most clinical studies suggest that GAD is typically a chronic condition with low rates of remission over the short and medium-term. Evaluation of prognosis is complicated by the frequent comorbidity with other anxiety disorders and depression, which worsen the long-term outcome and accompanying burden of disability (Tyrer & Baldwin, 2006). In the Harvard-Brown Anxiety Research Program, which recruited participants from Boston hospitals, the mean age of onset of GAD was 21 years, although many participants had been unwell since their teens. The average duration of illness in this group was about 20 years and despite treatment the outcome over the next 3 years was relatively poor, with only one in four showing symptomatic remission from GAD (Yonkers *et al.*, 1996). The proportion of people who became free from all psychiatric symptomatology was smaller, about one in six. In people who remitted from GAD the risk of relapse over the next year was about 15%, increasing to about 30% in those who achieved only partial symptomatic remission (Yonkers *et al.*, 1996).

The participants in the above study were recruited from hospital services and may not be representative of GAD in general. In a naturalistic study in the UK, Tyrer and colleagues (2004) followed up people with anxiety and depression identified in psychiatric clinics in primary care and found that 12 years later 40% of those initially diagnosed with GAD had recovered, in the sense that they no longer met criteria for any *Diagnostic and Statistical Manual of Mental Disorders* 3rd edition (DSM-III; American Psychiatric Association [APA], 1980) psychiatric disorder. The remaining participants remained symptomatic, but GAD was still the principal diagnosis in only 3% of trial participants; in the vast majority conditions such as dysthymia, major depression and agoraphobia were now more prominent. This study confirms the chronic and fluctuating symptomatic course of GAD in clinically-identified people. It should be noted, however, that the majority of people with GAD in the community do not seek medical help for their symptoms (Wittchen & Jacobi, 2005), and the course of the illness in these circumstances is not established.

2.2.3. Disability and mortality

As is the case with major depression, GAD is associated with a substantial burden of disability, equivalent to that of other chronic conditions such as arthritis and diabetes (Wittchen, 2002). Outcome studies suggest that anxiety disorders are more chronic than other common mental disorders (Tyrer *et al.*, 2004) and there is evidence that comorbid depression and anxiety has a worse prognosis, with more associated disability and more persistent symptoms than either depression or anxiety disorders alone (Kroenke *et al.*, 2007). There is also evidence in the community that anxiety disorders are independently associated with several physical conditions, and this comorbidity is significantly associated with poor quality of life and disability (Sareen *et al.*, 2006). This morbidity comes with high associated health and social costs (Simon *et al.*, 1995).

Studies have shown that the presence of GAD is also associated with significant impairments in occupational and social functioning. For example, over 30% of people with GAD showed an annual reduction of work productivity of 10% or more compared with 8% of people with major depression. The figure for people with comorbid GAD and depression was over 45% (Wittchen *et al.*, 2000). A large part of the economic cost of anxiety disorders is attributable to the costs of non-medical psychiatric treatment. People with GAD have increased numbers of visits not only to primary care doctors but also to hospital specialists, particularly gastroenterologists (Kennedy & Schwab, 1997; Wittchen, 2002). This may be a consequence of the distressing somatic symptoms which many people with GAD experience.

GAD also carries a considerable cost in personal suffering – in the Harvard-Brown Anxiety Research Program noted above, one third of people had never married and unemployment was higher than average (Yonkers *et al.*, 1996). Suicidal ideation and suicide attempts are significantly increased in GAD compared with the general population, particularly in women, and this increase is still greater in the presence of comorbid major depression (Cougle *et al.*, 2009).

2.2.4. Incidence and prevalence

The estimated proportion of people in England with GAD was 4.4% in the most recent *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), a figure that has varied little across the three survey years 1993, 1997 and 2007. This figure is at the upper end of estimates of point and annual prevalence of 2.1 to 4.4% in English speaking countries (Grant *et al.*, 2005; Hunt *et al.*, 2002; Kessler & Wang, 2008) with lower rates of 0.8 to 2.2% reported from other European countries (Lieb *et al.*, 2005; Wittchen & Jacobi 2005). Worldwide estimates of the proportion of people who are likely to experience GAD in their lifetime vary between 0.8% and 6.4% (Lieb *et al.*, 2005; Grant *et al.*, 2005; Kessler & Wang, 2008).

Prevalence rates have generally been found to be between 1.5 and 2.5 times higher in women than men. In the *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), the rates were 3.4% for men and 5.3% for women. In terms of age, epidemiological studies have generally found GAD to be less common in older age groups (over 55 years) although there are some exceptions. Some studies have also found GAD to be less common in younger adults (younger than 35 years).

Evidence from the US on ethnicity and race differences in GAD rates is inconsistent, with studies finding increased (Blazer *et al.*, 1991), decreased (Grant *et al.*, 2005) and no difference (Wittchen *et al.*, 1994) in rates between white and one or more of black, Asian and Hispanic groups. Numbers of minority ethnic groups sampled in the *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009) were too small to draw conclusions about possible differences, although proportions of the black and South Asian groups with GAD in the sample (both male and female) were higher than the equivalent proportions for white interviewees.

Socioeconomic factors associated with GAD are lower household income (Grant *et al.*, 2005; McManus *et al.*, 2009), lack of tertiary qualifications (Hunt *et al.*, 2002) and unemployment (Hunt *et al.*, 2002). Divorce, separation and death of a partner are also associated with an increased likelihood of GAD.

2.2.5. Diagnosis

Diagnostic criteria and methods of classification of anxiety disorders have changed substantially over the years. Historically what we now consider to be GAD was subsumed under 'anxiety neurosis'. It first appeared as a separate diagnosis in 1980 with the introduction of DSM-III (APA, 1980). In DSM-III it was a residual category to be used only when an anxiety disorder could not be classified under another diagnosis. It was only with the DSM-III revision in 1987 (DSM-III-R; APA, 1987) that it became a well defined condition in its own right. DSM-III-R also changed the DSM-III minimum duration requirement from 1 month to 6 months and introduced excessive worry as a central feature. Some of the developments in DSM-III-R were later reflected in the *International Classification of Diseases – the Classification of Mental and Behavioural Disorders* 10th revision (ICD-10; World Health Organization [WHO], 1992), although without the same focus on worry. The introduction of DSM-IV in 1994 (APA, 1994) further streamlined and refined the criteria, in particular focusing less on somatic symptoms of anxiety and replacing the DSM-III-R criterion that the worry is 'unrealistic' with a criterion that the worry is 'difficult to control'.

DSM-IV and ICD-10 have overlapping but different diagnostic features for GAD. DSM-IV emphasises worry ('apprehensive expectation'), including the feature that the worry is difficult to control, while ICD-10 focuses more on somatic symptoms of

anxiety, particularly autonomic reactivity and tension. DSM-IV requires two major symptoms (6 months or more of excessive anxiety and worry, occurring on more days than not, about a number of events and activities and difficulty controlling the worry) and three or more additional symptoms from a list of six. ICD-10, as operationalised in the *ICD-10 Diagnostic Criteria for Research* (ICD-10-DCR; WHO, 1993), requires 6 months or more prominent tension, worry and feelings of apprehension, and four from a list of 22 symptoms, of which at least one must be from a list of four autonomic symptoms (palpitations, sweating, trembling, dry mouth).

In line with the previous guideline on GAD (NICE, 2004a) and other NICE guidelines on anxiety disorders and depression (NICE, 2005a, b; 2009b) the GDG used DSM-IV, rather than ICD-10 to define the diagnosis of GAD, because the evidence base for treatments nearly always uses DSM-IV.

As there is now greater recognition of the need to consider 'subthreshold' depression in terms of human and economic costs and the risk of future major depression (Rowe & Rapaport, 2006), there has also been recent attention given to subthreshold GAD. Relaxing the DSM-IV requirements of duration, excessive worry and/or three associated symptoms more than doubles the estimated prevalence of GAD (Ruscio *et al.*, 2007). Cases of subthreshold GAD have similar but reduced comorbidities, with persistence, impairment and sociodemographic correlates all being significantly associated with an elevated risk of subsequent psychopathology (Kessler *et al.*, 2005a; Ruscio *et al.*, 2007). The implication is that, in clinical practice, identification of subthreshold GAD may be helpful for prevention of future disorder.

2.3. AETIOLOGY

Go to:

The aetiology of GAD is multifactorial and involves psychological, social and biological factors. Interpretation of experimental data is complicated by changes in diagnostic practice and the frequent occurrence of comorbidity, particularly with major depression (Yonkers *et al.*, 1996). On the other hand, anxiety (or more precisely, fear) is readily modelled in animal experimental studies, and the brain circuitry relevant to fear has been characterised in both animals and humans (Engel *et al.*, 2009). One influential formulation ('the theory of triple vulnerability') regards GAD as arising from three distinct kinds of vulnerability: a generalised biological, a generalised psychological and a specific psychological vulnerability (Barlow, 2000; Bitran *et al.*, 2009).

Anxiety disorders run in families. For example, a family study found that the risk of GAD in first-degree relatives of people with GAD was five times that in control groups (Noyes *et al.*, 1987), although specific genes conferring vulnerability to GAD have not yet been reliably identified. Indeed the genes involved in the transmission of GAD appear to increase susceptibility to other anxiety disorders such as panic disorder and agoraphobia as well as major depression (Kendler, 1996; Hettema *et al.*, 2001; 2005). There is also genetic overlap between GAD and the temperamental trait of neuroticism, which is itself a predisposing factor for GAD (Hettema *et al.*, 2004). Overall the findings suggest that genetic factors play a significant though moderate role in the aetiology of GAD, that these factors predispose people to a range of anxiety and depressive disorders rather than GAD specifically, and that environmental factors are important in determining the nature of the emotional disorder experienced by a particular person.

Several environmental factors are known to predispose individuals to GAD. These can act remotely or as contemporaneous triggers to the disorder. For example, good parenting experiences are important in providing children with a secure base from which to explore the world, and problems in child-parent attachment have been linked to feelings of diminished personal control of potentially threatening events (Barlow, 2000). Such feelings could plausibly contribute to the risk of experiencing anxiety disorders. Studies suggest that adults with GAD report experiencing parental styles characterised by overprotection and lack of emotional warmth (Silove *et al.*, 1991). Similar findings have been reported in other anxiety disorders and depression (Parker *et al.*, 1995), which suggest that certain parenting

styles may act as a psychological vulnerability factor for a range of subsequent emotional disorders. Similar comments apply to other kinds of childhood adversity such as neglect, abuse, maternal depression and family disruption, which increase the risk of experiencing GAD in adulthood as well as other anxiety and depressive disorders (Brown & Harris, 1993; Halligan *et al.*, 2007; Safren *et al.*, 2002). More recent stressful life events are also known to be involved in the onset of emotional disorders including GAD (Roemer *et al.*, 1996). A study by Kendler and colleagues (2003) showed that stressful life events characterised by loss increased the risk of both depression and GAD; however, life events characterised by 'danger' (where the full import of the event was yet to be realised) were more common in those who subsequently developed GAD.

Particular coping and cognitive styles also predispose individuals to the development of GAD, although it is not always easy to distinguish predisposition from the abnormal cognitions seen in the illness itself. As noted above, it is believed that people who lack a sense of control of events and personal effectiveness, perhaps through early life experiences, are more prone to anxiety disorders (Barlow, 2000). Such individuals may also demonstrate trait-like cognitive biases in the form of increased attention to potentially threatening stimuli, overestimation of environmental threat and enhanced memory of threatening material. This has been referred to as the 'looming cognitive style', which appears to be a general psychological vulnerability factor for a number of anxiety disorders (Reardon & Nathan, 2007). More recent cognitive formulations have focused on the process of worrying itself, which is of central importance in the diagnosis of GAD. Studies suggest that people at risk of GAD use worry as a positive coping strategy to deal with potential threats, whereby the person worries until they feel reassured that they have appraised all possible dangers and identified ways of dealing with them. However, this can lead to 'worry about worry', when individuals come to believe, for example, that worrying in this way, while necessary for them, is also uncontrollable and harmful. This 'metacognitive belief' may constitute a transitionary stage between excessive, but normal, worrying and GAD (Wells, 2005).

Studies of both animal and human subjects suggest that the amygdala plays a central role in the processing of information relevant to threat and fear (Le Doux, 2000). Activation of the amygdala can occur prior to conscious appreciation of threat but there are strong connections between the amygdala and areas of prefrontal cortex involved in the conscious experience and regulation of emotion (Le Doux, 2000; Phillips *et al.*, 2003). Another structure involved in anxiety is the hippocampus, which is important in relating fearful memories to their environmental context (Fanselow, 2000). The hippocampus forms part of a 'behavioural inhibition system', which is activated by potential threats, and has the ability in these circumstances to suspend ongoing behaviours (Gray, 1982). Brain imaging studies of individuals with high trait anxiety and people with GAD have shown exaggerated responses in both the amygdala and prefrontal cortex during presentation of emotionally threatening stimuli (Bishop *et al.*, 2004; Nitschke *et al.*, 2009). It is therefore possible that pre-existing abnormalities in this circuitry might predispose people to GAD and other anxiety disorders.

The neural circuitry involved in fear and anxiety is modulated by brain neuro-transmitters and other chemical mediators including hormones (Dedovic *et al.*, 2009). A relevant hormonal system is the hypothalamo-pituitary-adrenal axis (HPA), which regulates cortisol secretion. Adversity experienced in childhood and current stresses can alter the pattern of cortisol secretion in adult life, and there is an extensive literature on the role of HPA axis dysfunction in major depression (for example, Pariante & Lightman, 2008). HPA axis activity in people with GAD has been much less studied but there is some evidence that GAD, like depression, is associated with excessive glucocorticoid secretion (Mantella *et al.*, 2008). The monoamine neurotransmitters, serotonin and noradrenaline, can alter fear processes in animals and have extensive inputs to the relevant neural circuitry, including the amygdala and the behavioural inhibition system (Bitran *et al.*, 2009; Garner *et al.*, 2009). In addition, selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of GAD (Baldwin *et al.*, 2005). Despite this there is only modest evidence that abnormalities in serotonin and noradrenaline are

involved in the pathophysiology of GAD, though more work needs to be carried out with ligand neuroimaging to resolve this issue (Garner *et al.*, 2009). In the same way, pharmacological manipulation of gamma-aminobutyric acid (GABA) neurones and their associated benzodiazepine receptors clearly have profound effects on the experience of fear and anxiety in animals and humans (Kalueff & Nutt, 2007) but again there is only modest evidence that abnormalities in GABA neurotransmission or benzodiazepine receptor function are involved in the aetiology of GAD (Garner *et al.*, 2009).

Overall there is good evidence that both genetic factors and early life difficulties can predispose people to a range of emotional disorders, including GAD. More specific risk factors for GAD, presumably occurring in combination with these more generalised vulnerabilities, include certain kinds of life events and particular individual cognitive styles involving the use of worrying as a coping strategy. The neural circuitry involved in fear and anxiety has been well delineated in brain imaging studies and abnormalities in both people with GAD and non-clinical subjects with high trait anxiety have been described in relevant brain regions. It seems likely that these neural changes are associated with abnormal cognitions, such as increased attention to threat, that are seen in people with GAD and those at risk of the disorder. There is much knowledge on how particular neuropharmacological manipulations can influence anxiety. While this information has proved helpful in developing pharmacological treatment, the role of neurotransmitters and other chemical mediators in the aetiology of GAD is currently unclear.

2.4. TREATMENT AND MANAGEMENT IN THE NHS

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2.4.1. Detection, recognition and referral in primary care

Relative to its prevalence in the community, GAD is more common in primary care occurring in about 5% of attendees, and is the most common anxiety disorder seen in this setting. A recent international review of some of the larger general population surveys reported 12-month prevalence rates of 5.6 to 18.1% for anxiety disorders, of which GAD and panic disorder together accounted for over half of the prevalence figures (Baumeister & Hartner, 2007).

General practitioner (GP) rates of diagnosis and treatment of anxiety disorders are much lower than expected from the prevalence figures (Wittchen & Jacobi, 2005). Wittchen and colleagues (2002) found that recognition rates by primary care practitioners were only 34.4% for pure GAD and 43% for GAD with comorbid depression. There are likely to be a variety of reasons why GPs are poor at recognising anxiety disorders in their patients. People with GAD may have symptoms of anxiety, worry, tension, irritability or tiredness, about which they feel reluctant to complain to their GP because they do not view these symptoms as being 'medical', or the GP may identify these as symptoms of a more general malaise and not specifically consider or ask about anxiety as a possible cause (Arroll & Kendrick, 2009). In addition, many people may present with somatic symptoms associated with their anxiety, considering these to be more legitimate or more troubling. It appears that people with anxiety disorders are often frequent users of primary care resources, but if the anxiety component of their problem is not detected they may not receive the correct treatment and may undergo unnecessary and costly investigations, in particular for their physical symptoms (Hales *et al.*, 1997). Recognition is increased by factors such as older age, presentation of other psychological problems, and enhanced knowledge, skills and attitudes of practitioners in primary care (Tylee & Walters, 2007).

There is evidence that GPs may not offer effective evidence-based treatments to people with anxiety disorders as often as may be indicated, and that the treatments offered are more likely to be pharmacological, rather than psychological therapies such as cognitive behavioural therapy (CBT) (Stein *et al.*, 2004) due to limited availability of such treatments, although this may be changing with increased access to psychological therapies through the Improving Access to Psychological Therapies programme (IAPT).[2] The majority of treatments offered for anxiety disorders are likely to be based in primary care and may involve the GP and/or a

low-intensity psychological therapist such as a primary care mental health worker or the practice counsellor. Self-help bibliotherapy and web-based interventions may be effective for some people with GAD, although referral to secondary care practitioners, such as a high-intensity psychological therapist, may occur for those more severely affected. Referral to secondary care psychiatric mental health services is likely to be rare and reserved for people with the most treatment-resistant symptoms and severe functional impairment.

In summary, there is evidence that GAD is currently significantly under-detected and under-treated in UK primary care settings. This is a potentially serious omission, given the functional impairment and chronicity that can be associated with this diagnosis, particularly when comorbid with depression or physical health problems. There needs to be an increased emphasis on encouraging people to actively present their anxiety symptoms, and for their GPs to be more attuned to this diagnosis (particularly in people known to have depression or a chronic physical health problem) and the need to provide effective evidence-based treatments as early as possible in the course of this disorder before it becomes a long-term problem.

2.4.2. Assessment and co-ordination of care

Primary care and mental health practitioners need to have skills in the identification of GAD and its differentiation from other anxiety and depressive disorders in order to assess GAD and provide appropriate treatment. Assessment involves evaluation of GAD symptoms, especially worry and somatic symptoms of anxiety, the duration of these symptoms, and the extent of the person's functional impairment and distress and their coping resources. Assessment also needs to include evaluation of the symptoms of other anxiety and depressive disorders (especially panic disorder, hypochondriasis, OCD, social phobia, major depressive disorder and dysthymic disorder) given both the overlap of symptoms (for differential diagnosis) and the comorbidity between GAD and these other disorders.

The majority of treatment takes place in primary care or is linked with primary care, usually by either being directly provided by GPs or by psychological practitioners in liaison with GPs. GPs are accordingly central to the coordination of care. Ensuring a clear collaborative treatment plan between GP and psychological practitioners is important. For a small minority of people with very severe disorders, treatment may be provided by a multi-professional team in secondary care with coordination of care through the Care Programme Approach (CPA).

2.4.3. Aims and non-specific effects of treatment and placebo

The aim of treatment for GAD is to relieve symptoms, restore function and prevent relapse. The latter goal is important because GAD manifests as a chronic, relapsing condition and recurrence of illness is common, even when short-term treatment has apparently been successful (Yonkers *et al.*, 1996). In clinical trials, the outcome of treatment is often determined on standardised rating scales and can be divided into 'response' (where the symptom score has dropped by at least 50%) and 'remission' (almost complete relief of symptoms). In the treatment of depression, remission rather than response is now seen as the preferred goal because people who are essentially asymptomatic have improved functional outcomes and less risk of relapse. It seems probable that similar considerations will apply to the treatment of GAD.

Many people with GAD have had symptoms for long periods of time. Nevertheless, in short-term studies of medication, pill placebo treatment in the context of the clinical care provided by a controlled trial is certainly beneficial for a proportion of people. For example, in a 12-week placebo-controlled trial of escitalo-pram and paroxetine, just over 40% of participants responded to placebo and about 30% reached remission (Baldwin *et al.*, 2006). In contrast, naturalistic follow-up studies of people with GAD in the community have found considerably lower remission rates than this, at about 15% a year (Yonkers *et al.*, 1996). This suggests that either GAD, despite its chronicity, can respond well to pill placebo and non-specific aspects of good clinical management, or that the people who participate in placebo-controlled trials are not typical of the broad range of people with GAD in the

community. In addition, it is not known whether people who respond to a placebo in the short-term will maintain this level of improvement whereas there is some evidence that continuing drug treatment that proved effective in the short-term can help prevent relapse (Baldwin *et al.*, 2005).

Non-specific effects of treatment are also important in assessing the benefits of psychological therapies such as CBT and applied relaxation. Often such treatments are assessed against 'waitlist' or 'treatment as usual' control groups, which means that the non-specific effects of factors such as increased professional support and instillation of hope will augment the specific effects of a particular therapy. Thus a meta-analysis showed that while CBT was superior to waitlist control in the treatment of GAD, its superiority to supportive psychological therapy could not be clearly demonstrated (Hunot *et al.*, 2007).

Consistent with this, a substantial number of other approaches have been employed to help people with anxiety disorders, such as exercise, prayer and homeopathic and herbal remedies (Jorm *et al.*, 2004). This suggests that numerous non-medical approaches, provided they carry meaning and hope for the person concerned, can enable individuals to use their own coping and healing capacities to overcome anxiety symptoms. At present it is not possible to identify those people who will respond to non-specific, as opposed to specific, pharmacological and psychological treatments. In the treatment of depression it appears that the response to placebo lessens as the condition becomes symptomatically more severe (Khan *et al.*, 2005); this means that the specific benefits of antidepressants are greater in the most severely ill people. Whether the same is true in people with GAD is not clear.

2.4.4. Pharmacological treatments

Placebo-controlled trials indicate that a wide range of medicines with differing pharmacological properties can be effective in the treatment of GAD (Baldwin *et al.*, 2005). Traditionally, benzodiazepine drugs, such as diazepam, were employed for this purpose but it became clear that their use was commonly associated with the development of tolerance and dependence (Royal College of Psychiatrists, 2005). For this reason they are now recommended only for short-term use (2 to 4 weeks). Another drug specifically licensed for the treatment of GAD is buspirone, which acts on a particular subtype of serotonin receptor. However, like benzodiazepines, buspirone is recommended for short-term use only (British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2009).

In recent years antidepressants such as SSRIs have been increasingly used to treat GAD (Baldwin *et al.*, 2005). Unlike benzodiazepines, antidepressants do not relieve anxiety from the beginning of treatment and a period of some weeks often needs to elapse before significant clinical improvement is seen. Tolerance and dependence do not seem to be a problem with antidepressant treatment, though it should be noted that, like benzodiazepines, antidepressants can cause discontinuation symptoms on abrupt withdrawal (MHRA, 2004). As well as SSRIs, serotonin noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, are also effective in GAD, as are the older and less selective tricyclic antidepressants (TCAs), such as imipramine. However, TCAs are not as well tolerated as newer antidepressant agents and are more dangerous in overdose (Baldwin *et al.*, 2005).

In addition to the antidepressants, other compounds also have efficacy in the treatment of GAD. These include the antihistamine hydroxyzine, and the anticonvulsant drug pregabalin, which binds to a subtype of calcium channel in the brain (Baldwin *et al.*, 2005). Both conventional antipsychotic drugs and the newer 'atypical' antipsychotic agents have also been used in the treatment in GAD, both as a sole therapy and as an 'add-on' to SSRI therapy when the latter has proved ineffective (Pies, 2009). However, the greater side-effect burden of antipsychotic drugs means that their use is currently restricted to people with refractory conditions, with prescribing guided by secondary care.

While many drug treatments have been demonstrated to be effective in GAD relative to placebo, there are very few comparative studies between active

pharmacological agents. In addition there are no reliable clinical or biological predictors of treatment response in individuals. For this reason the selection of pharmacological treatment is usually made on the basis of the side-effect profile and the history of medication response in a particular individual.

2.4.5. Psychological treatments

Developments in psychological treatments for GAD have tended to parallel changes in the conceptualisation and diagnostic criteria for GAD, moving from a more general approach to more specific interventions.

Early psychological treatments for GAD tended to involve non-specific interventions such as supportive psychotherapy and relaxation training. Initial cognitive behavioural packages for the treatment of GAD (Borkovec & Costello, 1993; Barlow *et al.*, 1992) focused on the treatment of persistent anxious arousal and often included a number of interventions such as applied relaxation, imagery rehearsal (imaginal practice of coping skills in response to anxiety), stimulus control (establishing increased control over worry) and cognitive approaches based on the work of Beck and colleagues (1985).

More recent adaptations of CBT have emphasised the specific role of worry in GAD and have tried to focus treatment more on the processes thought to underlie the disorder. An example of this is CBT targeting the intolerance of uncertainty (Dugas *et al.*, 2007) or the metacognitive therapy developed byWells (1999), which emphasises the importance of the beliefs people have about worry and attempts to modify these.

Borkovec and colleagues (2002) have augmented existing CBT protocols with interpersonal/psychodynamic strategies to address problematic relationship patterns often found in people with GAD and the implications of the avoidance theory of worry, suggesting that people with GAD worry in order to avoid experiencing negative emotions.

Other adaptations of CBT have integrated acceptance-based and mindfulness approaches into treatment for GAD, incorporating the acceptance and experience of frequently avoided emotions into treatment protocols (Orsillo *et al.*, 2003).

2.4.6. Stepped care

Stepped care (Scogin *et al.*, 2003) is a framework that is increasingly being used in the UK to specify best practice in the design of clinical pathways to care. Stepped care is designed to increase the efficiency of service provision and therefore benefit patient populations. The basic principle is that patients presenting with a common mental health disorder will 'step through' progressive levels of treatment as necessary, with the expectation that many of these patients will recover or improve while undergoing less intensive treatments. The key features of stepped care are that treatments delivered first should be the least restrictive and that the model is self-correcting. The definition of 'least restrictive' may refer to the impact on patients in terms of cost and personal inconvenience, but can also refer to the amount of specialist therapist time required (that is, treatment intensity). High-intensity treatments are reserved for patients who do not benefit from low-intensity treatments, or for those who can be accurately predicted to not benefit from such treatments. 'Self-correcting' in this context means that the decisions about treatment provision and the effects of treatment are monitored systematically, and changes are made ('stepping up') if current treatments are not achieving significant health gain. Thus, stepped care has the potential for deriving the greatest benefit from available therapeutic resources (Bower & Gilbody, 2005).

Successful implementation of a stepped-care model is crucial for effective implementation of the NICE guidelines (Lovell & Bee, 2008). There are two conceptualisations of the stepped-care model. The first is a sequential model, where all people move through the steps in a systematic way, regardless of severity, need or choice. All patients initially receive an evidence-based low-intensity treatment and only 'step up' if and when they have not benefited from the low-intensity treatments offered. The second model is a stratified or multiple-access

model, which allows patients to access more intensive treatment initially, without having received less intensive interventions first (Lovell & Richards, 2000). Stratified stepped-care models have been incorporated into previous NICE guidelines, where stratification has been determined by the person's degree of functional impairment (as in the NICE guideline on OCD and body dysmorphic disorder; NICE, 2005b) or severity of the disorder (as in the NICE guidelines on depression; NICE, 2009b; 2009c).

2.4.7. The economic cost of anxiety disorders – focus on generalised anxiety disorder

Anxiety disorders place a significant burden on individuals as well as on the health-care system. Andlin-Sobocki and colleagues (2005) estimated the cost of anxiety disorders in Europe using published epidemiological and economic data from 28 European countries. Data on healthcare resource utilisation (medication, hospitalisation and outpatient care) and productivity losses due to sick leave associated with anxiety disorders were based on a German national health survey. The estimated total cost of anxiety disorders in Europe was reported to reach €41 billion (2004 prices). The average annual additional cost per person with GAD (relative to a person without an anxiety disorder) was estimated at €1,628 in 2004; of this, 76% was associated with provision of healthcare services and the remaining 24% with productivity losses due to sick leave (Andlin-Sobocki & Wittchen, 2005). The additional per-person cost of GAD was found to be the highest among respective costs of other anxiety disorders, such as panic disorder, agoraphobia, social phobia and OCD.

Only limited data on the healthcare resource utilisation by people with anxiety disorders exist in the UK. According to the Hospital Episode Statistics, in the financial year 2007 to 2008, 8,682 admissions were reported for phobic and other anxiety disorders in England, resulting in 121,359 inpatient bed days; of these, 747 admissions and 16,733 bed days were attributed specifically to GAD (NHS, The Information Centre, 2009). According to the most recent *Adult Psychiatric Morbidity in England* survey (McManus *et al.*, 2009), only 34% of people with GAD were receiving any kind of treatment for their condition at the time of the survey. Of them, 53% were receiving medication, 21% counselling or other psychological therapy, and 26% a combination of drugs and psychological treatment. In addition, 1% of respondents with GAD reported that they had used inpatient services for their condition over the past 3 months, 8% had used outpatient services during the same period, while 25% had used community or day care services during the past year.

A number of studies have estimated the cost of anxiety disorders in the US. DuPont and colleagues (1998) estimated this cost at $46.6 billion in 1990, which accounted for 31.5% of the total cost of mental disorders in the country. The estimated cost was incurred by healthcare resource utilisation such as mental health services, medication, hospitalisation, nursing homes and outpatient visits (23.1%), productivity losses (76.1%) and, to a lesser extent, by provision of other services such as criminal justice services, incarceration, social welfare administration, as well as family care-giving (0.8%). Greenberg and colleagues (1999) provided a more up-to-date figure of the cost of anxiety disorders in the US, at $63.1 billion in 1998.

A retrospective, multivariate analysis of data derived from a large claims database in the US demonstrated that people with anxiety disorders are more likely to use outpatient mental health services compared with a control group; they are also more likely to visit medical specialists such as cardiologists and neurologists and to use hospital services, including accident and emergency services. Furthermore, compared with controls, people with anxiety disorders were found to miss more days of work or to have a short-term disability (Marciniak *et al.*, 2004). According to the same analysis, the total medical cost per person with any anxiety disorder was estimated at $6,475 in 1999 (Marciniak *et al.*, 2005). The multivariate model indicated that, controlling for demographics and other disease states, GAD was associated with an increase of $2,138 in the total medical cost per person.

An Australian study (Andrews *et al.*, 2004) estimated the total annual cost of routine treatment for GAD in Australia at AUS$112.3 million in 1997 prices, based on the results of a national survey of mental health and wellbeing, and an estimated treatment coverage of only 38%. By applying optimal treatment (as achieved by operationalising detailed clinical practice guidelines and expert reviews) and increasing treatment coverage to 70%, the total annual direct medical cost of GAD was expected to rise to AUS$205.1 million.

Anxiety disorders are associated with a wide range of comorbidities, which result in a substantial increase in total healthcare costs. Souêtre and colleagues (1994) estimated the total direct and indirect costs incurred by people with GAD, with and without comorbidities, using data on 999 people participating in a French cross-sectional study. Controlling for confounding variables, the prevalence of healthcare utilisation in terms of hospitalisation, laboratory tests and medications and the respective medical costs were found to be significantly higher in people with GAD and other comorbidities, as opposed to those with GAD without comorbidities. Moreover, comorbidities were associated with increased absenteeism from work. In particular, comorbid depression (Marciniak *et al.*, 2005; Wetherell *et al.*, 2007; Zhu *et al.*, 2009) and physical pain (Olfson & Gameroff, 2007; Zhu *et al.*, 2009) have been found to have a significant impact on treatment costs incurred by people with GAD.

Efficient use of available healthcare resources will maximise the health benefits for people with GAD and can potentially reduce costs to the healthcare system and society in the long term.

Footnotes

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Psychiatric Times

Achieving Remission in Generalized Anxiety Disorder

By Laura A. Mandos, PharmD, Jennifer A. Reinhold, PharmD, BCPS, BCPP and Karl Rickels, MD

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Anxiety, Sleep Disorders, Comorbidity In Psychiatry, Generalized Anxiety, Major Depressive Disorder

Generalized anxiety disorder (GAD) is a prevalent, chronic, debilitating mental illness associated with marked impairment in daily functioning.[1] An ongoing evolution of the definition of GAD has resulted in a bifurcation of the historical anxiety neurosis designation.[2] A diagnosis of GAD currently implies chronic,

In This Special Report:

excessive worry lasting at least 6 months and 3 of the possible 6 somatic or psychological symptoms (restlessness, fatigue, muscle tension, irritability, difficulty concentrating, and sleep disturbance).[3] GAD typically presents in an episodic pattern of moderate improvement or remission and relapse characterized by a chronic and complicated clinical course.

Chronic worry, a core component of GAD, is consistently found in 10% of the population, and this subset reports a level of anxiety and tension so significant that it markedly impairs daily function. Epidemiological studies, however, suggest a lifetime GAD prevalence of 4% to 7%, a 1-year prevalence of 3% to 5%, and a current prevalence of 1.5% to 3%.4 Discrepancies between the incidence of anxiety-related symptoms and potential subsequent underestimation of GAD prevalence may be attributed to DSM-IV diagnostic criterion of 6 months' duration of worry.

It is the robust association of GAD with psychological and physical comorbidities that potentially contributes to the complexity of the illness as well as the limited treatment success.[4,5] More than 90% of patients with GAD present with an additional psychiatric diagnosis. The ancillary condition is major depressive disorder (MDD) in 48% of patients.[4,6]

Three primary care studies found that pure GAD, defined as a current episode of GAD in the absence of any other mood, anxiety, or substance use disorder, was associated with meaningful levels of impairment in several life

Strategies for Assessing and Treating Comorbid Panic and Generalized Anxiety Disorder, by Kristalyn Salters-Pedneault, PhD

Can Anticonvulsants Help Patients With Anxiety Disorders? by Marco Mula, MD, PhD

SSRIs as Antihypertensives in Patients With Autonomic Panic Disorder, by Sean Hood, MBBS, MSc

Achieving Remission in Generalized Anxiety Disorder, by Laura A. Mandos, PharmD, Jennifer A. Reinhold, PharmD, and Karl Rickels, MD

domains.[7-10]Ormel and associates[7]
found that the mean numbers of disability days in the past month were much higher among primary care patients with pure GAD than among patients with none of the psychiatric disorders assessed in their survey. The 272 patients with pure GAD had more self-reported dysfunction in occupational role fulfillment and physical disability scores.

Remission/treatment goals

Traditionally, the goal of therapy has been to treat patients with GAD until a response is achieved. The response is either a clinically meaningful improvement in symptoms or a specific magnitude of change in a rating scale score from baseline. Given the extensive use of health care resources, the residual subsyndromal symptoms, and the substantial relapse rate of anxious patients, the goal of therapy has evolved to that of achieving remission.[11]

Remission is a dichotomous concept in that it is an absence or near absence of symptoms in addition to a return to premorbid functionality.[11,12] Between 50% and 60% of patients respond clinically to therapy, but only one-third to one-half attain remission or realize full recovery during the acute phase of treatment.13 Some patients may achieve “durable remission” within the first 4 to 8 weeks of therapy, which may indicate an eventual sustained remission (lasting 4 to 9 months after acute treatment).[12] Patients who achieve a sustained remission are less likely to experience relapse.[14]

Response to treatment and attainment of remission is comprehensively quantified both globally and specifically. The magnitude of treatment outcome is primarily measured by changes in the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global ImpressionImprovement (CGI-I) scale, and the total Sheehan Disability Scale (SDS). This multidimensional approach assesses disease-specific anxiety symptoms, quality of life, functioning, and nonspecific symptoms (avoidance).[12] Response generally is defined as at least a 50% reduction in HAM-A score from

baseline, and a “much improved” or “very much improved” rating on the CGI-I.[11,12,15,16] Remission is defined as a HAM-A score of 7 or less, with global recovery achieved at a CGI-I score of 1 (“not ill at all” or “borderline mentally ill”), and functional recovery at an SDS score of 5 or less.[14] For this designation of remission to be clinically meaningful, it must incorporate a time component. Remission is not static but rather should be sustainable over a considerable time—at least 8 consecutive weeks.[17]

Treatment options

The treatment of GAD involves a sequential process of first resolving the acute, symptomatic anxiety and then maintaining a longer-term constant suppression of chronic anxiety. Historically, benzodiazepines were the mainstay of GAD treatment, although the appropriateness of their use for long-term therapy is now under scrutiny.

Benzodiazepines indirectly affect the release and reuptake of monoamines via enhancement of the inhibitory effects of g-aminobutyric acid, thereby modulating fear, stress, and anxiety responses.[18] Benzodiazepines are indicated for the short-term management of the acute phase of anxiety (2 to 4 weeks) as well as any subsequent exacerbations of anxiety during stable treatment. Their rapid onset and tolerability make them conducive to alleviating anxious symptoms when immediate anxiolytic effects are desired.[19,20]

A randomized, double-blind study compared response rates among patients treated with imipramine, trazodone, and diazepam. Patients in the diazepam arm had the most significant improvement in anxiety ratings within the first 2 weeks. Within this group, 66% of patients completing the study reported moderate to marked global improvement.[21] Although more marked improvement was realized in the first 2 weeks of treatment with benzodiazepines, antidepressants consistently afforded the same efficacy as benzodiazepines or even surpassed them after 6 to 12 weeks of treatment, particularly in alleviating psychic symptoms.[21,22]

Aside from the obvious issue of potential dependence with prolonged use, benzodiazepines are not desirable as first-line therapy because of their potential for withdrawal syndromes and rebound effects on abrupt discontinuation.[6,23,24] Yet, primary care providers have traditionally used benzodiazepines as first-line treatment of acute anxiety.[20]

The anxiolytic buspirone has been used with moderate success but has not consistently demonstrated utility in any of the potentially comorbid conditions that can accompany GAD, with the exception of MDD.[25,26] A retrospective analysis demonstrated significant improvement in HAM-A and global improvement scores relative to baseline, and another study reported buspirone's failure to differ from placebo on numerous outcome measures.[22,27,28] In addition, buspirone was shown to be superior to placebo in improving anxiety symptoms as well as coexisting depressive symptoms in patients with GAD. The significant anxiolytic effect resulted in more than a 50% response rate, based on reductions in the HAM-A score.[29]

Buspirone exerts its effect by reducing serotonin (5-HT) release as a partial agonist at 5-HT1A receptors in the hippocampus and as a full agonist at the presynaptic serotonergic auto-receptors.[14,30] It has been shown to have comparable but slightly weaker efficacy than diazepam, clorazepate, lorazepam, and alprazolam and a slower onset of action.[6] Its utility is mainly associated with its propensity to relieve the cognitive aspects, but it lacks long-term efficacy, particularly in managing the behavioral and somatic manifestations.[14] In addition, patients who had been previously treated with benzodiazepines, especially recently, tend to have a muted response to buspirone (ie, a reduction in the anxiolytic effects).[31]

Tricyclic antidepressants (TCAs), such as imipramine, are typically more effective at attenuating the psychological symptoms of GAD as opposed to the somatic symptoms. Their inhibition of 5-HT and norepinephrine reuptake produces anxiolytic and antidepressant effects. According to a study conducted by Rickels and colleagues,[21] significant resolution of anxiety was achieved in

patients who took imipramine between weeks 2 and 8 of therapy, and it afforded effects slightly superior to those of trazodone. Psychic symptoms of tension, apprehension, and worry were most effectively reduced in the imipramine arm: 73% of patients achieved moderate to marked improvement.[21]

The SSRIs are generally regarded as first-line medications, according to domestic and international practice guidelines.[18,32] Paroxetine, specifically, is FDA-approved for the long-term treatment of depression as well as for GAD at dosages of 20 to 50 mg daily. While the 2- to 4-week delay in onset of therapeutic effect may be discouraging, significant reductions in “anxious mood” have been documented as early as 1 week into treatment.

Remission rates in paroxetine responders at 32 weeks, admittedly a selected population of patients who persevere with treatment, are as high as 73%; relapse rates are only 11%. SSRIs have a sustained therapeutic effect and afford additional incremental improvement over a 24-week period.[14,33] An 8-week, double-blind, placebo-controlled study examined paroxetine’s impact on HAM-A and SDS scores relative to baseline. The groups that received 20 mg and 40 mg of paroxetine demonstrated a statistically and clinically significant change in the HAM-A and psychic anxiety subscale relative to placebo.

In the intent-to-treat group, 62% in the 20-mg arm and 68% in the 40-mg arm met the criteria for response by week 8 ($P < .001$). Response rates were as high as 80% among patients who completed the study. Remission was achieved in 36% of the patients in the 20-mg group and 42% of the patients in the 40-mg group by week 8 ($P = .004$).[22]

An SSRI discontinuation syndrome, characterized by dizziness, insomnia, and flu-like symptoms, occurs in approximately 5% of patients on abrupt discontinuation or significant dose reduction.[32] This typically manifests within 1 to 7 days of discontinuation in patients who have been taking an

SSRI for at least 1 month.[34] Of the SSRIs, paroxetine is most often implicated in withdrawal symptoms: about 35% to 50% of patients experience discontinuation symptoms on abrupt cessation.[35] Reinstating the drug resolves symptoms of withdrawal relatively quickly.[36] Tapering the SSRI dosage before discontinuation reduces the likelihood of this syndrome.

A promising alternative in first-line treatment in GAD therapy are the serotonin-norepinephrine reuptake inhibitors, which have been studied in both short- and long-term efficacy trials. Venlafaxine XR at a dosage of 75 to 225 mg daily consistently demonstrated superior efficacy versus placebo in improving anxiety symptoms by measure of a reduction in HAM-A total scores.[37] The added benefit of venlafaxine's efficacy in treating symptoms of anxiety in patients with comorbid anxiety and depression, in addition to pure GAD, has elevated its status in the treatment algorithm. Response rates approach 70%, and remission rates are as high as 43% short-term and as high as 61% long-term.[14,38]

The comorbidity of nonspecific somatic pain complaints is common in patients with GAD, which translates into a compounded negative impact on quality of life. A majority of patients (60%) with GAD and concomitant pain report that they experience a moderate to severe change in their somatic symptoms on days when they feel more anxious or depressed.[39] Previous use of benzodiazepines was shown to reduce the probability of a response to venlafaxine in a study by Pollack and colleagues,[40] although there was no substantial impact on attaining long-term remission.

Abrupt discontinuation of venlafaxine also precipitates a discontinuation syndrome with similar or greater frequency than does paroxetine.[35] In addition, more diligent patient monitoring is required secondary to its propensity to precipitate hypertension.[32]

Duloxetine is indicated for the treatment of anxiety disorders, MDD, neuropathic pain, and fibromyalgia. Its dual impact on anxious symptoms and somatic pain resulted in 53% to 61% of treated patients who achieved a HAM-A score of 7 or less (symptomatic remission) and an about 47% who achieved an SDS score of 5 or less (functional remission).[1,41] There is a positive correlation between improvement in pain scores and reduction in SDS scores: most patients who achieved remission also reported greater improvements in visual analog pain scales.[39] Venlafaxine or an SSRI have been successfully used as initial monotherapy and long-term therapy; both have been shown to be equally effective.[32]

Patients with GAD are considerably more intolerant of normal uncertainty, which results in the formation of negative beliefs about uncertainty.[42] Thus, these patients could benefit from psychosocial therapy. Numerous psychosocial treatment options are available as monotherapy or as adjunctive therapy in combination with a pharmacological agent. A psychosocial therapy that specifically addresses these cognitive aspects and trains patients to develop and apply coping skills that address psychological and somatic symptoms may be useful.[43,44]

Overcoming the barriers to remission

A multitude of factors are responsible for worsened outcomes and reduced probability of achieving remission in patients with GAD. Stressful life events, anxiety sensitivity, negative affect, gender, subsyndromal symptoms, and comorbidities all have a palpable impact on the course of illness and outcome. Frequently, patients elect to not complete long-term treatment and thus, life stressors may perpetuate subsyndromal symptoms. Although GAD is characterized by alternating periods of quiescence and exacerbation, the presence of comorbid depression, panic, or any Axis I or Axis II disorder, and a higher initial symptom rating, greatly lessens the possibility of remission.[45-47] Pollack and colleagues[40] found that restlessness predicted a worse treatment outcome, while sleep disturbance was typically associated with a more optimistic outcome.

Most patients who present with GAD have been ill for an average of 15 years before seeking help. As evidenced consistently by the literature, patients with GAD may decide to discontinue medication once they experience some improvement of symptoms.[15] Unfortunately, once they respond positively to treatment, many patients will settle for that level of response instead of continuing therapy. This decision typically arises from fear of dependence on medication.[15] Discontinuation of medication may briefly elicit a mild improvement, secondary to the psychological empowerment of self-management, but it will frequently lead to relapse.[45] This drives the need for extensive patient education and clear, focused, patient-physician interactions.

Symptomatic remission traditionally precedes functional remission. Patient awareness of this fact should stem the inclination to discontinue therapy prematurely. Most of the first-line, long-term pharmacotherapies for GAD take 2 or more weeks to exert a full pharmacodynamic effect. The interval between the initial prescription of medication and a realization of effect may discourage adherence at an early stage. The likelihood of adherence can be increased by educating the patient about the expected onset of action and by prescribing a benzodiazepine at the start of long-term therapy.[48]

The majority of patients with GAD present to their primary care physician with a somatic complaint that is seemingly unrelated to GAD. This “masquerading” is another potential barrier to treatment.[4] The inadvertent misdiagnosis of GAD or failure to identify a comorbid disorder results in poor treatment outcomes. Patients who are adherent and do not respond partially or fully to an appropriate medication may need to be reevaluated by a psychiatrist. Reevaluation may well lead to an alternative diagnosis and treatment regimen. Patients who present with predominantly depressive symptoms may be inaccurately labeled as depressed and treated accordingly. Treatment of depressive symptoms alone will not attenuate the somatic or functional aspects of GAD.[49]

Owing to the cyclical pattern of exacerbation and quiescence, many patients present for care during episodic exacerbations when symptoms are most debilitating. The risk is that the perceived acute anxiety will be treated as such, and the underlying, chronic anxiety will not be appropriately resolved.[38] Inappropriate resolution of the chronic component of GAD will functionally impede remission and the prevention of relapse. Chronic pharmacotherapeutic treatment, as in MDD, is indicated for most patients who have GAD.

Whether early symptomatic improvement is a potential predictor of future response is currently being explored. A diminution in anxious symptoms within the first 2 weeks of drug therapy may predict remission. Pollack and colleagues[11] found that significant improvement by week 2 of treatment translated into an increased likelihood of a clinical HAM-A response and remission of functional disability (SDS). Even moderate symptomatic improvement early on yielded functional remission by the end of week 2.

Conclusions

A constellation of factors influence the likelihood of attaining remission of GAD. The frequent presence of psychiatric or physical comorbidities complicates the clinical picture. Depression is the most prevalent of the psychiatric comorbidities and, as a result, incomplete treatment or misdiagnosis of GAD is often a root cause for treatment failure. Patient nonadherence, high initial symptom ratings, and interpatient variability in clinical presentation of GAD all contribute to the modest remission rates. Perhaps the most consequential factor in determining the propensity for success of GAD treatment is the use of an appropriate drug for an appropriate length of time. The duration of treatment is proportional to the magnitude of the outcome and the potential for realizing symptomatic and functional remission.

While not achievable in all patients, remission is the most appropriate therapeutic goal for GAD. Patients with personality problems and a multitude of comorbidities for whom the illness provides

secondary gain may have difficulty in achieving remission. Although attaining remission is complicated by numerous treatment- and patient-related barriers, overcoming these challenges is feasible in the majority of patients. The diagnosis of GAD must be distinct from any other intervening psychiatric or somatic disorders. While the level of comorbidity is relatively high, the GAD diagnosis must be reliable and not confounded by other disorders. Treatment outcome goals must be clearly established in advance of therapy and should be based on the individual patient's needs.

Psychotropic drug therapy for appropriate treatment duration is the foundation of successful therapy. A single drug is typically initially prescribed for patients who have GAD. Inadequate responses to monotherapy may warrant the addition of a second pharmacological agent or psychotherapy. Augmentation of drug therapy with benzodiazepines for 3 to 4 weeks and then gradually tapering the benzodiazepine may further reduce the reemergence of anxiety symptoms.[6] Patients who demonstrate incomplete remission or lack of response need to be reevaluated in a timely manner to confirm the GAD diagnosis. In adherent patients for whom an appropriate duration of single drug therapy is unsuccessful, consider augmentation with a benzodiazepine or an anxiolytic with a different mechanism of action. The addition of a psychotherapeutic modality and/or a new pharmacological agent may generate additional benefit. Continuation of pharmacotherapy for 6 to 12 months beyond symptom resolution increases the likelihood of a sustained remission and decreases the likelihood of relapse.

Drugs Mentioned in This Article

Alprazolam (Xanax)
Buspirone (BuSpar)
Clorazepate (ClarazeCaps, others)
Diazepam (Valium)
Duloxetine (Cymbalta)

Imipramine (Tofranil)
Lorazepam (Ativan)
Paroxetine (Paxil)
Trazodone (Desyrel)
Venlafaxine (Effexor)

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Question 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

Contents

Key Findings

Marijuana's schedule I status makes studies on its medical use difficult to conduct. Because of this, evidence that medical marijuana is effective in treating generalized anxiety disorder is more limited than that of an FDA approved pharmaceutical, but significant evidence of medical marijuana's effectiveness can still be seen.

New Evidence

Cannabidiol in Anxiety and Sleep: A Large Case Series

CBD appears to be better tolerated than routine psychiatric medications. Furthermore, CBD displays promise as a tool for reducing anxiety in clinical populations.

Use of cannabidiol in anxiety and anxiety-related disorders

CBD has consistently demonstrated acute reduction in anxiety-related symptoms in patients, specifically within GAD and SAD. Additionally, the use of CBD for these disorders has shown increasingly minimal adverse effects compared with existing pharmacotherapy.

Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users

The vast majority of patients perceived symptom improvement with CMP (cannabis for medical purposes) use and did not believe CMP use was associated with impairment or an inability to control use.

Previously Submitted Evidence

Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD.

The Endocannabinoid System and the Brain

Cannabidiol, which does not bind to either CB1 or CB2, possesses anxiolytic and antipsychotic properties (Mechoulam et al. 2002) both in animals and in humans.

Anxiogenic-like effects of chronic cannabidiol administration in rats

Chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported. In addition, CBD decreased the expression of proteins that have been shown to be enhanced by chronic treatment with antidepressant/anxiolytic drugs.

Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow

These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

In agreement with the results obtained in animal models, clinical studies confirmed that CBD has anxiolytic properties

Cannabidiol as a Potential Treatment for Anxiety Disorders

Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders…

Cannabis Use in HIV for Pain and Other Medical Symptoms

Relief of symptoms of anxiety and depression was common, as was general symptom relief.

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report

Cannabidiol oil, an increasingly popular treatment of anxiety and sleep issues, has been documented as being an effective alternative to pharmaceutical medications. This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety …

Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics

37.8% of patients in this study reported a benefit of medical marijuana was a reduction in anxiety symptoms.

Therapeutic Benefits of Cannabis: A Patient Survey

Other reported therapeutic benefits [of cannabis] included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia.

Therapeutic Benefits of Cannabis: A Patient Survey – Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization

82.9% of patients studied reported relief from anxiety symptoms.

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

The myriad effects of CBD on 5-HT1A activity provide a strong rationale for this and other phytocannabinoids as base compounds for treatment of anxiety

Patient-Reported Symptom Relief Following Medical Cannabis Consumption

The first two regressions shown in Table 2 indicate that people with anxiety and depression report greater relief from using cannabis than people with chronic pain, and users with higher starting symptom levels report greater symptom relief.

Cannabidiol in Anxiety and Sleep: A Large Case Series

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ABSTRACT

Context: Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a "high." A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature.

Objective: To determine whether CBD helps improve sleep and/or anxiety in a clinical population.

Design: A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients.

Main Outcome Measures: Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.

Results: The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.

Conclusion: Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.

INTRODUCTION

The *Cannabis* plant has been cultivated and used for its medicinal and industrial benefits dating back to ancient times. *Cannabis sativa* and *Cannabis indica* are the 2 main species.[1] The *Cannabis* plant contains more than 80 different chemicals known as cannabinoids. The most abundant cannabinoid, tetrahydrocannabinol (THC), is well known for its psychoactive properties, whereas cannabidiol (CBD) is the second-most abundant and is nonpsychoactive. Different strains of the plant are grown containing varying amounts of THC and CBD. Hemp plants are grown for their fibers and high levels of CBD that can be extracted to make oil, but marijuana plants grown for recreational use have higher concentrations of THC compared with CBD.[2] Industrial hemp must contain less than 0.3% THC to be considered legal, and it is from this plant that CBD oil is extracted.[3]

Many different cultures have used the *Cannabis* plant to treat a plethora of ailments. Practitioners in ancient China targeted malaria, menstrual symptoms, gout, and constipation. During medieval times, cannabis was used for pain, epilepsy, nausea, and vomiting, and in Western medicine it was commonly used as an analgesic.[4,5] In the US, physicians prescribed *Cannabis sativa* for a multitude of illnesses until restrictions were put in place in the 1930s and then finally stopped using it in 1970 when the federal government listed marijuana as a Schedule I substance, claiming it an illegal substance with no medical value. California was the first state to go against the federal ban and legalize medical marijuana in 1996.[6] As of June 2018, 9 states and Washington, DC, have legalized recreational marijuana, and 30 states and Washington, DC, allow for use of medical marijuana.[7] The purpose of the present study is to describe the effects of CBD on anxiety and sleep among patients in a clinic presenting with anxiety or sleep as a primary concern.

CBD has demonstrated preliminary efficacy for a range of physical and mental health care problems. In the decade before 2012, there were only 9 published studies on the use of cannabinoids for medicinal treatment of pain; since then, 30 articles have been published on this topic, according to a PubMed search conducted in December 2017. Most notable was a study conducted at the University of California, San Diego's Center for Medicinal Cannabis Research that showed cannabis cigarettes reduced pain by 34% to 40% compared with placebo (17% to 20% decrease in pain).[8] In particular, CBD appears to hold benefits for a wide range of neurologic disorders, including decreasing major seizures. A recent large, well-controlled study of pediatric epilepsy documented a beneficial effect of CBD in reducing seizure frequency by more than 50%.[9] In addition to endorphin release, the "runner's high" experience after exercise has been shown to be induced in part by anandamide acting on CB1 receptors, eliciting anxiolytic effects on the body.[10] The activity of CBD at 5-HT_{1A} receptors may drive its neuroprotective, antidepressive, and anxiolytic benefits, although the mechanism of action by which CBD decreases anxiety is still unclear.[11] CBD was shown to be helpful for decreasing anxiety through a simulated public speaking test at doses of 300 mg to 600 mg in single-dose studies.[12-14] Other studies suggest lower doses of 10 mg/kg having a more anxiolytic effect than higher doses of 100 mg/kg in rats.[15] A crossover study comparing CBD with nitrazepam found that high-dose CBD at 160 mg increased the duration of sleep.[16] Another crossover study showed that

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plasma cortisol levels decreased more significantly when given oral CBD, 300 to 600 mg, but these patients experienced a sedative effect.[17] The higher doses of CBD that studies suggest are therapeutic for anxiety, insomnia, and epilepsy may also increase mental sedation.[16] Administration of CBD via different routes and long-term use of 10 mg/d to 400 mg/d did not create a toxic effect on patients. Doses up to 1500 mg/d have been well tolerated in the literature.[18] Most of the research done has been in animal models and has shown potential benefit, but clinical data from randomized controlled experiments remain limited.

Finally, the most notable benefit of cannabis as a form of treatment is safety. There have been no reports of lethal overdose with either of the cannabinoids and, outside of concerns over abuse, major complications are very limited.[19] Current research indicates that cannabis has a low overall risk with short-term use, but more research is needed to clarify possible long-term risks and harms.

Given the promising biochemical, physiologic, and preclinical data on CBD, a remarkable lack of randomized clinical trials and other formal clinical studies exist in the psychiatric arena. The present study describes a series of patients using CBD for treatment of anxiety or sleep disturbances in a clinical practice setting. Given the paucity of data in this area, clinical observations can be quite useful to advance the knowledge base and to offer questions for further investigation. This study aimed to determine whether CBD is helpful for improving sleep and/or anxiety in a clinical population. Given the novel nature of this treatment, our study also focused on tolerability and safety concerns. As a part of the evolving legal status of cannabis, our investigation also looked at patient acceptance.

METHODS

Design and Procedures

A retrospective chart review was conducted of adult psychiatric patients treated with CBD for anxiety or sleep as an adjunct to treatment as usual at a large psychiatric outpatient clinic. Any current psychiatric patient with a diagnosis by a mental health professional (psychiatrist, psychiatric nurse practitioner, or physician assistant) of a sleep or anxiety disorder was considered. Diagnosis was made by clinical evaluation followed by baseline psychologic measures. These measures were repeated monthly. Comorbid psychiatric illnesses were not a basis for exclusion. Accordingly, other psychiatric medications were administered as per routine patient care. Selection for the case series was contingent on informed consent to be treated with CBD for 1 of these 2 disorders and at least 1 month of active treatment with CBD. Patients treated with CBD were provided with psychiatric care and medications as usual. Most patients continued to receive their psychiatric medications. The patient population mirrored the clinic population at large with the exception that it was younger.

Nearly all patients were given CBD 25 mg/d in capsule form. If anxiety complaints predominated, the dosing was every morning, after breakfast. If sleep complaints predominated, the dosing was every evening, after dinner. A handful of patients were given CBD 50 mg/d or 75 mg/d. One patient with a trauma history and schizoaffective disorder received a CBD dosage that was gradually increased to 175 mg/d.

Often CBD was employed as a method to avoid or to reduce psychiatric medications. The CBD selection and dosing reflected the individual practitioner's clinical preference. Informed consent was obtained for each patient who was treated and considered for this study. Monthly visits included clinical evaluation and documentation of patients' anxiety and sleep status using validated measures. CBD was added to care, dropped from care, or refused as per individual patient and practitioner preference. The Western Institutional Review Board, Puyallup, WA, approved this retrospective chart review.

Setting and Sample

Wholeness Center is a large mental health clinic in Fort Collins, CO, that focuses on integrative medicine and psychiatry. Practitioners from a range of disciplines (psychiatry, naturopathy, acupuncture, neurofeedback, yoga, etc) work together in a collaborative and cross-disciplinary environment. CBD had been widely incorporated into clinical care at Wholeness Center a few years before this study, on the basis of existing research and patient experience.

The sampling frame consisted of 103 adult patients who were consecutively treated with CBD at our psychiatric outpatient clinic. Eighty-two (79.6%) of the 103 adult patients had a documented anxiety or sleep disorder diagnosis. Patients with sole or primary diagnoses of schizophrenia, posttraumatic stress disorder, and agitated depression were excluded. Ten patients were further excluded because they had only 1 documented visit, with no follow-up assessment. The final sample consisted of 72 adult patients presenting with primary concerns of anxiety (65.3%; n = 47) or poor sleep (34.7%; n = 25) and who had at least 1 follow-up visit after CBD was prescribed.

Main Outcome Measures

Sleep and anxiety were the targets of this descriptive report. Sleep concerns were tracked at monthly visits using the Pittsburg Sleep Quality Index. Anxiety levels were monitored at monthly visits using the Hamilton Anxiety Rating Scale. Both scales are nonproprietary. The Hamilton Anxiety Rating Scale is a widely used and validated anxiety measure with 14 individual questions. It was first used in 1959 and covers a wide range of anxiety-related concerns. The score ranges from 0 to 56. A score under 17 indicates mild anxiety, and a score above 25 indicates severe anxiety. The Pittsburg Sleep Quality Index is a self-report measure that assesses the quality of sleep during a 1-month period. It consists of 19 items that have been found to be reliable and valid in the assessment of a range of sleep-related problems. Each item is rated 0 to 3 and yields a total score from 0 to 21. A higher number indicates more sleep-related concerns. A score of 5 or greater indicates a "poor sleeper."

Side effects and tolerability of CBD treatment were assessed through spontaneous patient self-reports and were documented in case records. Any other spontaneous comments or complaints of patients were also documented in case records and included in this analysis.

Data Analysis

Deidentified patient data were evaluated using descriptive statistics and plotted graphically for visual analysis and interpretation of trends.

RESULTS

The average age for patients with anxiety was 34 years (range = 18-70 years) and age 36.5 years for patients with sleep disorders (range = 18-72 years). Most patients with an anxiety diagnosis were men (59.6%, 28/47), whereas more sleep-disordered patients were women (64.0%, 16/25). All 72 patients completed sleep and anxiety assessments at the onset of CBD treatment and at the first monthly follow-up. By the second monthly follow-up, 41 patients (56.9%) remained on CBD treatment and completed assessments; 27 patients (37.5%) remained on CBD treatment at the third monthly assessment.

Table 1 provides means and standard deviations for sleep and anxiety scores at baseline and during the follow-up period for adults taking CBD. Figure 1 graphically displays the trend in anxiety and sleep scores over the study period. On average, anxiety and sleep improved for most patients, and these improvements were sustained over time. At the first monthly assessment after the start of CBD treatment, 79.2% (57/72) and 66.7% (48/72) of all patients experienced an improvement in anxiety and sleep, respectively; 15.3% (11/72) and 25.0% (18/72) experienced worsening symptoms in anxiety and sleep, respectively. Two months after the start of CBD treatment, 78.1% (32/41) and 56.1% (23/41) of patients reported improvement in anxiety and sleep, respectively, compared with the prior monthly visit; again, 19.5% (8/41) and 26.8% (11/41), respectively, reported worsening problems as compared with the prior month.

These results demonstrated a more sustained response to anxiety than for sleep over time. Patient records displayed a larger decrease in anxiety scores than in sleep scores. The sleep scores demonstrated mild improvement. The anxiety scores decreased within the first month and then remained decreased during the study duration.

Table 1. Descriptive statistics for anxiety and sleep scores among adults using cannabidiol treatment

Parameter	HAM-A, mean (SD)	PSQI, mean (SD)
Anxiety (n = 47)		
Baseline	23.87 (9.87)	10.98 (3.43)
1-month follow-up	18.02 (7.56)	8.88 (3.68)
2-month follow-up	16.35 (8.80)	8.59 (2.91)
3-month follow-up	16.36 (9.80)	9.25 (2.46)
Sleep disorder (n = 25)		
Baseline	22.18 (7.55)	13.08 (3.03)
1-month follow-up	17.82 (9.72)	10.64 (3.89)
2-month follow-up	17.36 (10.91)	9.39 (3.81)
3-month follow-up	13.78 (7.86)	9.33 (4.63)

HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburg Sleep Quality Index; SD = standard deviation.

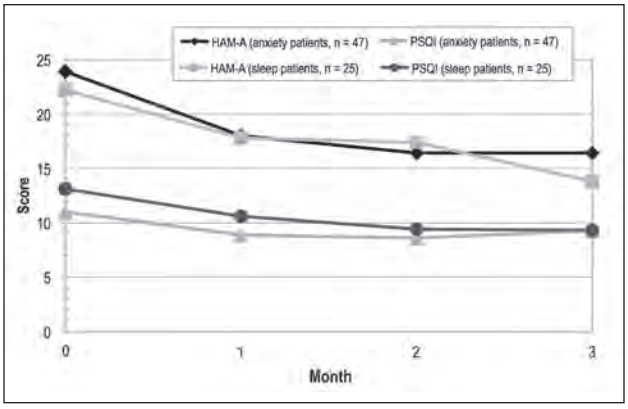

Figure 1. Mean anxiety and sleep scores for adults using cannabidiol treatment.
HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburg Sleep Quality Index.

CBD was well tolerated, with few patients reporting side effects. Two patients discontinued treatment within the first week because of fatigue. Three patients noted mild sedation initially that appeared to abate in the first few weeks. One patient with a developmental disorder (aged 21 years) had to be taken off the CBD regimen because of increased sexually inappropriate behavior. The CBD was held, and the behavior disappeared. The behavior reappeared on redosing 2 weeks later, and the CBD regimen was formally discontinued. The treating psychiatrist thought this was related to disinhibition because the patient's anxiety responded dramatically. One patient noted dry eyes. Reasons for patients not following-up at later assessment points are largely unknown but are probably because of standard attrition experienced in usual clinical practice. There was no evidence to suggest patients discontinued care because of tolerability concerns. The attrition rates were similar in nature and size to those found in routinely scheduled visits in this clinic.

The treatment with CBD was in general well accepted, as judged by the clinicians' and patients' responses. Four patients declined CBD treatment because of religious or ethical concerns about the relation to cannabis. Nearly all patients easily provided informed consent once the nature of the treatment was explained. Most patients appreciated the opportunity to try something natural and avoid further or initial psychiatric medication use.

DISCUSSION

In an outpatient psychiatric population, sleep scores displayed no sustained improvements during the 3-month study. Anxiety scores decreased fairly rapidly, and this decrease was sustained during the study period. These results are consistent with the existing preclinical and clinical data on CBD. CBD was well accepted and well tolerated in our patients. Side effects were minimal (mainly fatigue) and may be related to dosing.

The doses used in this study (25 mg/d to 175 mg/d) were much lower than those reported in some of the clinical literature (300 mg/d to 600 mg/d)[12-14,17] for 2 reasons. The first is that in our experience lower doses appear to elicit an adequate clinical

response. Second, the current retail cost of CBD would make the use of 600 mg/d cost prohibitive.

Study Limitations

These results must be interpreted cautiously because this was a naturalistic study, all patients were receiving open-label treatment, and there was no comparison group. Concurrent psychiatric medications were employed as in routine clinical care. This is both a limitation and strength, as very few publications exist in this population. Other researchers have noted that the large societal notoriety about cannabis and medical marijuana probably contributes to a larger-than-normal placebo effect.[20] Any study that explores efficacy in this therapy probably will struggle with a potentially inflated placebo effect that will make these determinations more difficult. Likewise, the clinical population in this case series is skewed younger than typical for our clinic, and future studies could explore the possible selection bias inherent in this treatment option. Most patients were also taking psychiatric medications and receiving other mental health services, such as counseling, which limits the ability to make any causal links to CBD treatment. Clinical attrition is evident in the dataset. The reason for this might be related to CBD ingestion or not, so the overall component remains unclear. Furthermore, patients at our clinic often express a desire to reduce or to avoid use of psychiatric medications, which may contribute to an enhanced placebo effect or additional bias. The length of clinical monitoring may help to decrease this concern. However, the clinical data in this analysis show a trend toward clinically significant relief of anxiety upon the start of CBD treatment.

Legality of Cannabidiol

The legality of CBD is not clear. Like the issues surrounding the legality of cannabis in general, CBD presents the clinician with a confusing state vs federal legal quandary, and this keeps the issue in question. CBD is legal in the 33 states that have legalized medical or recreational use of marijuana and in 17 other states that have legalized some form of CBD, according to the National Organization for the Reform of Marijuana Laws (NORML).[21] But like marijuana, it is still not legal at the federal level. The federal government has announced that it is not focused on this compound in terms of enforcement or interdiction.[22] However, CBD is interpreted by the Drug Enforcement Administration, Food and Drug Administration, and Congress to be a Schedule I substance, and therefore it is illegal in all 50 states.[23] Pragmatically, CBD is widely available on the Internet, with sales expected to reach $1 billion by 2020. Pending federal legislation to redefine the legal status of cannabis would clarify this complex issue. Canada's move to legalize cannabis in October 2018 further highlights the need for a speedy resolution to this question.[24]

CONCLUSION

Formal studies on efficacy and dose finding are much needed. Some urgency exists, given the explosion of lay interest in this topic and the rush to market these compounds. Current understanding of the physiology and neurologic pathways points to a benefit with anxiety-related issues. The results of our clinical report support the existing scientific evidence. In our study, we saw no evidence of a safety issue that would limit future studies. In this evaluation, CBD appears to be better tolerated than routine psychiatric medications. Furthermore, CBD displays promise as a tool for reducing anxiety in clinical populations, but given the open-label and nonrandomized nature of this large case series, all results must be interpreted very cautiously. Randomized and controlled trials are needed to provide definitive clinical guidance. ❖

Disclosure Statement

Dr Shannon has published several professional books on integrative mental health. Dr Shannon is a Principal Investigator for a Phase 3 study of 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy for severe posttraumatic stress disorder and receives compensation for his clinical work from the Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA. The other authors have no conflicts of interests to disclose.

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REVIEW

Use of cannabidiol in anxiety and anxiety-related disorders

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ABSTRACT

Objective: Cannabidiol (CBD) has a proposed novel role in the management of anxiety owing to its actions on the endocannabinoid system. The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in anxiety and anxiety-related disorders.
Data sources: A literature search was conducted on PubMed, Google Scholar, and International Pharmaceutical Abstracts from database inception through June 2019. A bibliographic search of relevant articles was also conducted.
Study selection: Articles published from case reports, case series, or randomized controlled trials on human subjects were included in the review if they examined the safety and efficacy of CBD therapy in anxiety and anxiety-related disorders.
Data extraction: Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes.
Results: Eight articles were included in the review: 6 small, randomized controlled trials; 1 case series; and 1 case report. These studies examined the role of CBD in the anxiety response of healthy volunteers; in generalized anxiety disorder; in social anxiety disorder; and in the anxiety component of posttraumatic stress syndrome. No articles that evaluated CBD in panic disorder, specific phobia, separation anxiety, and obsessive-compulsive disorder were identified. In the studies, CBD was administered orally as a capsule or as a sublingual spray and as either monotherapy or adjunctive therapy. Doses varied widely, with studies employing fixed CBD doses ranging from 6 mg to 400 mg per dose. Various anxiety assessment scales were used in the studies to assess efficacy, with CBD demonstrating improved clinical outcomes among the instruments. In general, CBD was well-tolerated and associated with minimal adverse effects, with the most commonly noted adverse effects being fatigue and sedation.
Conclusion: CBD has a promising role as alternative therapy in the management of anxiety disorders. However, more studies with standardized approaches to dosing and clinical outcome measurements are needed to determine the appropriate dosing strategy for CBD and its place in therapy.

Background

Anxiety is an adaptive, emotional response that naturally occurs as a result of a perceived threat.[1] Anxiety becomes maladaptive when it occurs excessively or inappropriately in the absence of relevant threatening stimuli.[1] The exact pathophysiology of anxiety-related disorders is unknown. However, results from neuroimaging and biochemical studies suggest that the variation between adaptive and maladaptive anxiety responses is modulated by regions of the limbic system—primarily the amygdala—and key neurotransmitters, such as dopamine (DA), norepinephrine (NE), γ-aminobutyric acid (GABA), and serotonin (5-HT).[2]

Within *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobia (SP), and separation anxiety are classified as anxiety disorders. Obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) share a common symptomatology of excessive anxiety; however, they are reviewed in their own respective chapters within *the DSM-5*, after the

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Key Points

Background:

- As a group, anxiety disorders and anxiety-related disorders are the most common psychiatric conditions in the United States. As such, they pose a serious disease burden to patients and the health care system because of decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.
- At present, the mainstay agents for treatment of anxiety have limitations in efficacy and are associated with a number of adverse effects, which suggests the need for new pharmacotherapies for these disorders.
- Cannabidiol (CBD) is a nonhallucinogenic chemical compound, derived from the plant *Cannabis sativa*, with a novel role in the management of anxiety.
- This article provides a review of evidence on the clinical efficacy and safety of CBD used to manage anxiety and anxiety-related disorders.

Findings:

- In the studies reviewed, CBD consistently demonstrated improved clinical outcomes in anxiety disorders, with a minimal adverse-effect profile.
- However, optimal dose, route of administration, and dosing strategy (acute vs. chronic use) of CBD in the management of anxiety disorders remain undetermined.
- Pharmacists have an essential role in advising patients and prescribers on the use of alternative therapies. Given the heightened popularity of CBD, it is crucial that pharmacists are knowledgeable about its benefits and are able to provide appropriate recommendations on the place in therapy of CBD in the treatment of common disorders, such as anxiety.

chapter on anxiety disorders. As a group, the anxiety disorders and anxiety-related disorders of PTSD and OCD are the most common psychiatric conditions in the United States.[3] Taken together, these disorders have an estimated lifetime prevalence of approximately 29% for U.S. adults.[3,4] As such, they pose a substantial disease burden to patients and the health care system because of their association with decreased well-being, physical impairment, loss of productivity, and increased health care utilization costs.[3,4]

At present, the primary pharmacologic treatment for anxiety and anxiety-related disorders involves the use of medications that modulate the activity of DA, NE, GABA, and 5-HT neurotransmitters. Benzodiazepines are prescribed commonly because of their modulation of GABA. Likewise, antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, 5-HT receptor antagonists, monoamine oxidase inhibitors, and buspirone are frequently used for their effects on DA, NE, and 5-HT. Less commonly prescribed agents for anxiety and anxiety-related disorders include second generation antipsychotics, anticonvulsants, and certain antihistamines, such as hydroxyzine. These pharmacotherapies have limitations in efficacy and are associated with a number of adverse effects (e.g., sexual dysfunction and potential for dependence and tolerance), which suggests the need for novel therapeutic modalities for management of anxiety and anxiety-related disorders.[5-7]

The endocannabinoid system (ECS) is a promising therapeutic target for anxiolytic-drug development owing to its purported role in modulating synaptic plasticity and neuronal activity involved in the anxiety response.[4,5,8-12] Primary activity of signaling within the ECS is thought to be because of the action on 2 known cannabinoid receptors, CB1 and CB2.[4,5,8-12] Cannabidiol (CBD), a chemical compound known as a phytocannabinoid, is derived from the plant *Cannabis sativa* and may have a role in the management of anxiety given its pharmacologic activity within the ECS.[4,5,8-12] Among the more than 400 chemicals produced by *C sativa*, delta-9-tetrahydrocannabinol (THC) and CBD are the major compounds.[4,5,8-12] THC is the most abundant psychoactive chemical and is primarily responsible for the well-known hallucinogenic effects of *C sativa*. In contrast, CBD is not psychoactive.[4,5,8-12]

In the literature, CBD has several proposed therapeutic effects accomplished through multiple mechanisms. Despite low affinity for CB1 and CB2 receptors, CBD has proposed indirect activity on the ECS through its action of inhibiting the inactivation of anandamide—a neurotransmitter within the ECS—which leads to activity on the CB1 receptor.[4,5,8-12] This mechanism, in conjunction with activity on 5-HT_{1A} receptors, is believed to be a key factor in the reported therapeutic effects of CBD in anxiety.[4,5,8-12] Available literature suggests a favorable adverse-effect profile of CBD and minimal drug interaction potential when compared with other therapeutic agents; however, it should be noted that there is a dearth of studies examining these parameters.[13]

CBD can be administered through various routes of administration and is currently available and marketed in numerous formulations, such as tinctures administered under the tongue, concentrated oil administered orally or topically, topical compounds such as ointments and creams, vaporized solutions, and infused beverages and food items. In the United States, there is only 1 Food and Drug Administration (FDA)-approved CBD product, Epidiolex, which is approved for treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.[14] All other cannabis-derived CBD products remain under the purview of the FDA regulation under the 2018 Farm Bill, and determination of the scope of this regulation is evolving.[15] With the dramatic increase in use of CBD products, it is prudent to assess the validity of therapeutic claims as well as the safety profile.[15] This information will be beneficial to clinicians when examining the risks and benefits of using CBD for pharmacologic activity in anxiety.

Objective

The purpose of this systematic review was to evaluate the current evidence on the safety and efficacy of CBD in the management of anxiety and anxiety-related disorders.

Methods

Data sources

This study was a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance statement.[16] A free text search of PubMed (January 1996-June 2019) was conducted. The term "cannabidiol" was combined with either "generalized anxiety disorder," or "social anxiety disorder," or "panic disorder," or "specific phobia," or "separation anxiety," or "post-traumatic stress disorder," or "obsessive compulsive disorder" with the Boolean operator AND. This free text search was duplicated on Google Scholar and International Pharmaceutical Abstracts. In addition, references of relevant articles were also reviewed.

Study selection

Articles were included in the review if they examined CBD treatment in diagnosed anxiety or anxiety-related disorders or if they evaluated the anxiety response in healthy volunteers. Animal studies, articles evaluating the psychosis components of PTSD and OCD, and studies evaluating the role of CBD in managing THC-related anxiety were excluded from review. In addition, editorials, commentaries, and letters to the editor were excluded. Two reviewers independently executed the search and screened articles for inclusion.

Data extraction

Two reviewers independently extracted the following data from the articles: year of publication; study design; patient characteristics (sex; type of anxiety disorder; use of concomitant anxiolytic therapy); dosing strategy and route of CBD administration; and safety and efficacy outcomes. Efficacy outcomes included scores on assessment scales for anxiety, such as the Screen for Anxiety-Related Disorders (SCARED), Hamilton Anxiety Rating Scale (HAM-A), Visual Analogue Mood Scale (VAMS), State-Trait Anxiety Inventory (STAI), Bodily Symptoms Scale (BSS), and Negative Self-Statements subscale (SSPS-N).

Results

Study characteristics

A total of 233 potentially relevant articles resulted from the search. Eight articles met criteria for full text review: 6 small, randomized controlled trials; 1 case series; and 1 case report (Figure 1). One article evaluating the role of CBD in the anxiety response of healthy volunteers, 1 assessing CBD in GAD, 1

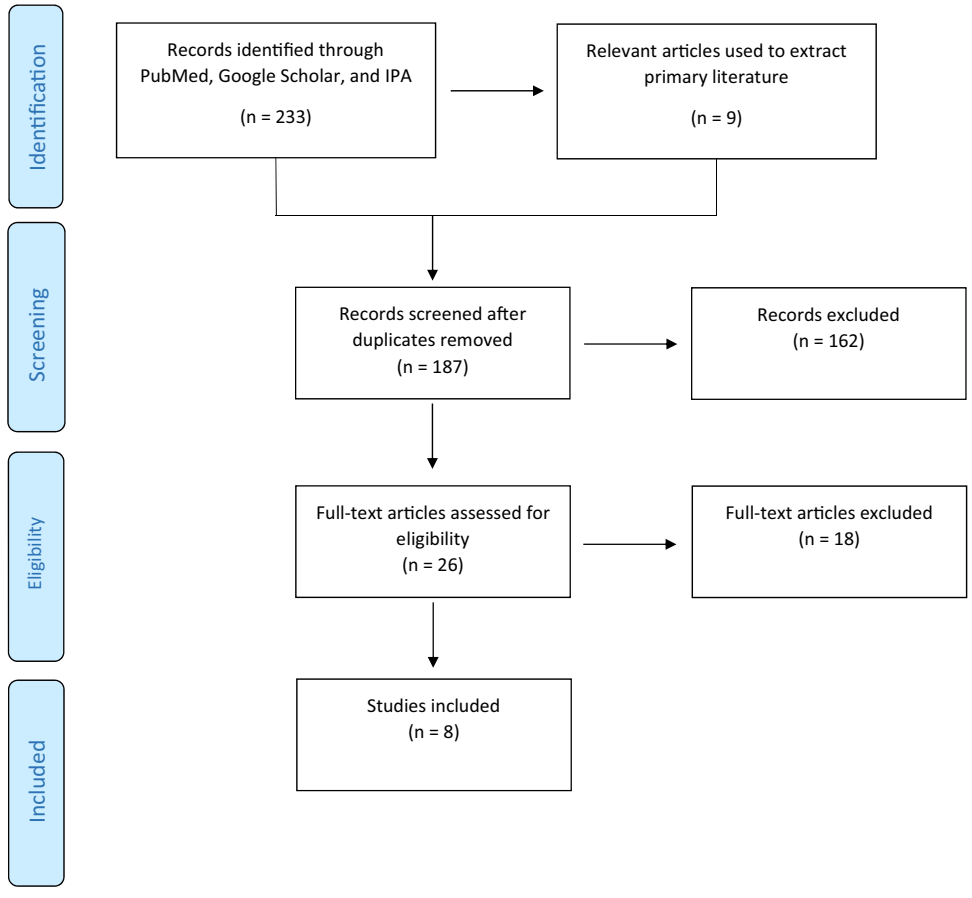

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. Abbreviation used: IPA, International Pharmaceutical Abstracts.

evaluating CBD in the anxiety response of PTSD, and 5 articles examining CBD in SAD were identified. No articles on the role of CBD in PD, SP, separation anxiety, or OCD management met the criteria for review. Table 1 summarizes the efficacy and safety outcomes of the studies.

Anxiety response in healthy volunteers: Effects of CBD on regional cerebral blood flow

Crippa et al.[17] conducted a double-blind, crossover study in 10 healthy male patients to evaluate the effect of CBD on neural activity of pathways that normally mediate anxiety, measured through neuroimaging. None of the patients nor their first-degree relatives had a history of psychiatric illness. The participants were separated into 2 groups of 5. Regional cerebral blood flow (rCBF) was measured at rest via single-photon emission computed tomography (SPECT), and each participant was evaluated on 2 occasions separated by 1 week. At the first session, 1 group received 400 mg of CBD while the other group received placebo, both administered as a gelatin capsule in double-blinded fashion. After 90 minutes, SPECT images were taken. In the second session, the procedure was repeated in a crossover design with those who received placebo being administered CBD and vice versa. VAMS was used to assess subjective feelings of anxiety along with physical sedation, mental sedation, and other attitudes and perceptions. VAMS scores were assessed at 30 minutes before CBD or placebo ingestion, at the time of ingestion, and at 60 and 75 minutes following ingestion. A significant reduction in subjective anxiety, measured through VAMS, was noted following CBD administration at all measurements ($P < 0.001$). In the investigators' comparison of rCBF measurements between CBD and placebo ingestion groups, a significantly ($P < 0.001$) increased uptake of the injected ethyl-cisteinate dimer into the medial temporal cortex along with VAMS findings

Table 1
Study summaries: Efficacy and safety of CBD in anxiety disorders

Citation	N	Classification	Study design	Subject(s)	CBD dose and route of administration	Acute versus chronic CBD dosing	Comparison anxiolytic with or without placebo	Measures of anxiety symptoms
Crippa et al., 2004[17]	10	Anxiety response in healthy volunteers	RCT; crossover	Healthy males without anxiety diagnosis	CBD 400 mg orally x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS
Shannon et al., 2019[19]	72	Anxiety response in patients with either GAD or insomnia diagnosis	Open-label, case series	GAD diagnosis (n = 47; 28 males; 19 females) Insomnia diagnosis (n = 25)	CBD 25–175 mg, dosed daily, oral capsules (n = 72)	Chronic	None	HAM-A
Shannon et al., 2016[20]	1	GAD	Case report	10-year-old female with anxiety diagnosis	Months 1–4: CBD 25 mg dosed daily, capsule Months 4–6: CBD 25 mg dosed daily, capsule; and CBD 6–12 mg as needed for anxiety, sublingual spray	Chronic and acute	None	SCARED
Zuardi et al., 2017[21]	59	Healthy volunteer model of SAD	RCT	Healthy males (n = 29) and females (n = 30)	CBD oral capsule x 1 dose: 100 mg (n = 11; 5 males, 6 females) 300 mg (n = 12; 6 males, 6 females) 900 mg (n = 12; 6 males, 6 females)	Acute	Placebo (n = 12; 6 males, 6 females) Clonazepam 1 mg (n = 12; 6 males, 6 females)	VAMS
Zuardi et al, 1993[23]	40	Healthy volunteer model of SAD	RCT	Healthy males (n = 18) and females (n = 22)	CBD 300 mg, oral gelatin capsule x 1 dose (n = 10)	Acute	Placebo (n = 10) Ipsapirone 5 mg (n = 10) Diazepam 10 mg (n = 10)	VAMS
Linares et al, 2019[24]	57	Healthy volunteer model of SAD	RCT	Healthy males	CBD oral capsule x 1 dose: 150 mg (n = 15) 300 mg (n = 15) 600 mg (n = 12)	Acute	Placebo (n = 15)	VAMS
Bergamaschi et al, 2011[25]	36	SAD diagnosis	RCT	SAD diagnosis (n = 24; 12 males, 12 females) Healthy control patients (n = 12; 6 males, 6 females)	CBD 600 mg x 1 dose, oral gelatin capsules (n = 12)	Acute	Placebo (n = 12; 6 males, 6 females)	VAMS
Crippa et al., 2011[26]	10	SAD diagnosis	RCT; crossover	Males with SAD diagnosis	CBD 400 mg oral x 1 dose, gelatin capsules (n = 10)	Acute	Placebo comparison with crossover (n = 10)	VAMS

Abbreviations used: CBD, cannabidiol; RCT, randomized controlled trial; VAMS, Visual Analogue Mood Scale; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; SCARED, Screen for Anxiety-Related Disorders; SAD, social anxiety disorder.

Table 2
Considerations for CBD

Potential benefit	Potential risks	
Efficacy	Product variability	Drug interactions
Studies have found CBD to be an effective alternative therapy in the acute treatment of anxiety disorders, specifically:	CBD is considered a dietary supplement, and thus lacks standardization in the following areas:	Potential CYP450 interactions: CBD has been found to be a potent inhibitor of CYP3A4 and CYP2D6, increasing the serum level of the following medications:
• GAD	• Dose-effect response	• Warfarin
• SAD	• Dosage strength	• Macrolides
• Anxiety related to PTSD	• Route of administration	• Calcium channel blockers
	• Purity	• Antiretrovirals
	• Regulation	• Antidepressants
	• Product manufacturing	• Antipsychotics
CBD has shown minimal adverse effects compared with existing pharmacotherapy for acute anxiety.	• Labeling	• Opioids
	• Patient access	It is important to consider patients with potential genetic polymorphisms of CYP450 enzymes:
	• Legal status	• Decreased CYP2C19 or CYP3A4 have potential risk of CBD accumulation.

Abbreviations used: CBD, cannabidiol; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder.

supported the a priori hypothesis that the limbic and paralimbic areas in the brain are likely mediators of CBD's anxiolytic effect. The study results support findings of another study, which found the role of CBD in GAD to occur owing to effects on the limbic and paralimbic regions of the brain.[18] Crippa et al.[17] noted sedation as an observed adverse effect of CBD in the study but did not expound on the magnitude or frequency of this reported effect.

GAD: CBD in anxiety and sleep

Shannon et al.[19] evaluated the use of open-label CBD therapy on anxiety and sleep levels in a case series of 72 adults seen at a psychiatric outpatient clinic over a 3-month timeframe. Patients were included in the study if they had either a diagnosis of anxiety or a sleep disorder and had at least 1 follow-up visit in the clinic after CBD was prescribed. Patients were excluded if they had a sole or primary diagnosis of schizophrenia, PTSD, or agitated depression. Use of other psychoactive medications and adjunctive counseling services did not preclude participation in this study. Patients' anxiety was assessed through the use of validated HAM-A. On HAM-A, anxiety scores range from 0 to 56, with a score below 17 being indicative of mild anxiety and a score above 25 indicating severe anxiety. Safety was assessed through spontaneous self-report in this study. Patients received CBD in fixed doses, ranging from 25 mg/d to 175 mg/d, with the majority of patients receiving the 25-mg daily dose. All patients completed the 1-month follow-up assessment of HAM-A, whereas 56.9% and 37.5% followed up at the 2- and 3-month timeframes for HAM-A, respectively. At the 1-month assessment, the majority of patients (79.2%) experienced an improvement in anxiety based on HAM-A scores. Of those who followed up at the 2-month assessment, 78.1% demonstrated an improvement in anxiety compared with the prior 1-month visit. There was no appreciable difference in mean HAM-A scores between the 2-month and 3-month follow-up assessments (mean HAM-A scores of 16.35 and 16.36, respectively). A few adverse effects were reported in this study: dry eyes, mild sedation, fatigue, and an increase in sexually inappropriate behaviors. The patients who experienced mild sedation reported resolution within the first weeks of treatment. Furthermore, a small percentage of patients who experienced fatigue or an increase in sexually inappropriate behavior discontinued therapy. The authors concluded that anxiety scores decreased over the course of the study, and the clinical effect on anxiety was maintained throughout the study duration. CBD was well-tolerated and associated with very few instances of treatment discontinuation.

Anxiety response in PTSD: Effectiveness of CBD oil for pediatric anxiety and insomnia as PTSD

A case report by Shannon et al.[20] evaluated the effectiveness of CBD oil in anxiety and sleep disorder secondary to PTSD in a 10-year-old girl. The girl had previously been treated with ineffective pharmacotherapy and had experienced adverse effects from the medication. CBD, administered initially as a capsule and subsequently as a sublingual spray for as-needed dosing, was used for the patient's anxiety and insomnia. The patient was also receiving eicosapentaenoic acid fish oil and diphenhydramine with CBD therapy. The patient was originally initiated on a CBD 25-mg capsule dosed daily, which she took for a duration of 4 months as monotherapy. After 4 months, the patient was prescribed adjunct CBD, administered as an as-needed sublingual spray and dosed at 6-12 mg per spray for breakthrough anxiety symptoms. The patient's anxiety was evaluated using SCARED, with a score above 25 indicating a childhood anxiety disorder. A SCARED score was evaluated before initiation of CBD and then monthly for an additional 5 months, for a total of 6 measurements. From baseline to sixth evaluation, the patient's SCARED score decreased from 34 to 18, a 47.06% reduction. No adverse effects of CBD were reported in this case report. The authors concluded that CBD oil may be an effective option to consider when attempting to reduce anxiety secondary to PTSD.

Healthy volunteer models of SAD: Anxiolytic effect of CBD during public speaking in real life

In this double-blinded study, Zuardi et al.[21] tested the hypothesis that increasing CBD doses would produce anxiolytic

effects in patients with anxiety. Fifty-nine healthy men and women within the age range of 18-35 years were selected for the study. These patients had no diagnosed anxiety disorder, and no disorders involving alcohol or other substance abuse. However, the study was set up to test anxiety levels in public speaking scenarios as a manifestation of SAD. The volunteers were randomly assigned to 5 groups of 12 participants. Each volunteer received either 1 of 3 doses of CBD capsules (100 mg, 300 mg, or 900 mg), clonazepam 1-mg tablet, or placebo in a double-blinded randomized design. VAMS was used in this study to evaluate anxiety levels as well as the sedative effects of CBD. To assess physiological measurements, systolic blood pressure (BP), diastolic BP, and heart rate were recorded. In the procedure, 1 participant was instructed to speak in front of their group. The other participants who were not speaking at the time were instructed to remain silent with a neutral expression. Each member in the group would take their turn to speak. Each participant's VAMS anxiety and sedation score, BP, and heart rate were recorded at baseline, before the speech, during the middle of the speech, and after the speech. Data were compared at the varying time phases. VAMS scores of subjective anxiety were noted to be significantly decreased when the CBD 300-mg group was compared with the placebo and CBD 100-mg groups during the postspeech phase ($P < 0.05$). Similarly, a significantly greater decrease in VAMS was noted in the comparison of the CBD 300-mg group with the CBD 900-mg group in the speech phase ($P < 0.05$). Higher sedative effects were noted with clonazepam in comparison with the CBD and placebo groups among the phases ($P < 0.05$). The authors concluded that the CBD 300-mg dose had a greater therapeutic effect on anxiety when compared with the 100-mg and 900-mg doses. These results confirmed prior study findings and suggested that CBD induces acute anxiolytic effects with an inverted U-shaped dose-response curve in humans—an effect that, at this time, is not fully understood and should not be considered as an absolute pharmacodynamics principle.[21,22]

Effects of ipsapirone and CBD on human experimental anxiety

In a double-blinded study, Zuardi et al.[23] used 40 healthy subjects separated into 4 groups of 10 who received either oral CBD 300 mg, diazepam 10 mg, ipsapirone 5 mg, or placebo. The volunteers were subjected to a simulated public speaking test (SPST) to compare the anxiolytic properties of the assigned drug. The effects of these drugs were measured using VAMS, STAI, and BSS, which evaluates somatic symptoms (fatigue, weakness) that would indirectly affect anxiety. After a 15-minute adaptation period, baseline measures were collected before the intervention (drug or placebo) was given. One hour and 20 minutes after the drug was taken, prestress measures were collected. After collection, the subjects watched a video with instructions about the task they would be performing. Each subject had 2 minutes to prepare a 4-minute speech about a topic covered previously in a university course and was told the speech would be recorded and analyzed by a psychologist. Anticipatory anxiety measurements were taken before the subject began speaking. During the middle of the speech, researchers interrupted the subject and subjective anxiety measurements were collected. Fifteen minutes after the speech ended, poststress measurements were collected. The VAMS results of the study demonstrated that there was a significant increase in subjective anxiety in all groups ($P < 0.001$) during the SPST procedure. Diazepam significantly decreased subjective anxiety throughout the study when compared with placebo ($P = 0.016$). Specifically, diazepam decreased prestress ($P = 0.042$) and poststress ($P = 0.002$) measurements. However, diazepam also significantly increased feelings of physical sedation at the prestress ($P = 0.036$) and anticipatory anxiety ($P = 0.003$) measurements. Ipsapirone significantly decreased performance anxiety ($P = 0.037$) measurements when compared with placebo, while CBD significantly decreased poststress anxiety ($P = 0.017$) measurements. Only diazepam showed significant physical and mental sedative effects, which may limit its therapeutic application in some patients. The authors concluded that acute administration of CBD or ipsapirone may have beneficial alternative anxiolytic effects when used in healthy subjects and may be appropriate alternatives for those experiencing sedative effects from other anxiolytic medications.

CBD presents an inverted U-shaped dose-response curve in a SPST

Linares et al.[24] conducted a double-blind, placebo-controlled trial of 57 healthy adult males who were randomized to receive either placebo or CBD dosed at 150 mg, 300 mg, or 600 mg daily before SPST. The SPST was administered according to the Bergamaschi procedures.[25] VAMS was used to assess subjective anxiety. In the analysis of variance test of group comparisons, there were no significant findings among groups and phases of the SPST ($P = 0.1$). A post hoc analysis among groups during the phases of SPST indicated that patients in the CBD 300-mg group demonstrated lower anxiety levels in the speech phase than the placebo group ($P = 0.042$). The study investigators inferred an inverted U-shaped dose-response curve based on VAMS results with sequential CBD doses, with the 150-mg and 600-mg doses associated with minimal anxiolytic effects and the intermediate 300-mg dose producing the most clinically significant outcome on anxiety. This result supports findings from previous studies.[21-23] No safety outcomes were reported in this study.

SAD: CBD reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients

In a double-blind, randomized, controlled clinical trial, Bergamaschi et al.[25] compared the effects of taking oral CBD 600 mg with those of taking placebo in SPST. A total of 36 patients were included in the study; 24 were treatment-naive patients with SAD and 12 served as healthy controls (HCs) who did not receive medications. Of the 24 treatment-naive patients with SAD, 2 separate groups of 12 were formed randomly. One group received CBD while the other received placebo, both packed in identical gelatin capsules. Subjective ratings using VAMS, SSPS-N, and physiological measures such as BP, heart rate, and skin conductance were all measured at 6 different time points during SPST. The time points of evaluation were selected for full evaluation of anxiolytic effects seen with CBD compared with those seen with placebo. In the first stage of the procedure, a single dose of CBD or placebo was administered in a double-blind fashion along with administration of baseline measurements. In the second phase, participants were given instructions to prepare a 2- to 4-minute speech that would be videotaped and analyzed by a

psychologist. Researchers collected anticipatory speech measurements before the public speaking occurred. Interruptions in the speech were made in the middle and speech measurements were again taken. The speech was allowed to continue for another 2 minutes and then concluded, and 2 postspeech measurements were made 15 minutes and 35 minutes after the speech. After analyzing the results from the study, the VAMS scale showed that the placebo group presented with significantly higher anxiety levels with greater cognitive impairment, discomfort, and alertness as compared with the HCs. The pretreated CBD SAD group had significantly reduced anxiety, cognitive impairment, and discomfort during the speech performance compared with the placebo group ($P = 0.009$). An important observation made by the authors was that negative self-evaluation was almost abolished by CBD. There were no significant differences found in vital signs. Overall, the effects of single dose CBD in patients experiencing SAD show a promising impact with a rapid-onset therapeutic effect.

Neural basis of anxiolytic effects of CBD in generalized SAD

In a double-blinded preliminary report, whose purpose was to confirm the hypothesis that CBD may be effective in treating SAD, Crippa et al.[26] assessed 10 men with generalized SAD, which was confirmed by the structured clinical interview (SCID) for *DSM-IV*. All the subjects in the study were determined to have a severe social phobia. To analyze the effects of CBD in these patients, researchers evaluated each subject using the VAMS assessment. During the test, subjective ratings on VAMS were made 30 minutes before the ingestion of the drug (prestress), at the time of drug ingestion (adaptation), and at 75 minutes after ingestion (poststress). Functional neuroimaging was used to determine the neurophysiologic effect of CBD in patients with SAD. SPECT imaging was used to compare the effects of CBD and placebo on rCBF. This process was completed in a double-blind, randomized, repeated measures, within-subject crossover design using a dose of 400 mg of CBD given in oral gelatin capsules. In the first session, the men were given CBD 400 mg or placebo. In the second session, this exercise was performed again, but this time the men who had received CBD earlier were administered the placebo and vice versa.

Upon analysis of the VAMS score, the study showed that acute administration of CBD reduced subjective anxiety in patients clinically diagnosed with an anxiety disorder, in this case SAD. Specifically, CBD showed a significantly faster time onset of decreasing anxiety ($P < 0.001$) in the patient compared with placebo. Based on the VAMS score numbers, those taking CBD began with a mean assessment at prestress anxiety of 48.3 and ended poststress anxiety with 30.8, a decrease of 36.23%. Patients in the placebo group began prestress at an anxiety level of 46.9 and ended with a poststress anxiety level of 42.1, a decrease of only 10.23%. The SPECT imaging was able to show that CBD was active in the paralimbic and limbic areas. Overall, the authors concluded that CBD has important advantages in treatment of SAD, such as a minimal adverse-effect profile and early onset of action. However, the authors also concluded that more double-blind, placebo-controlled studies are needed to evaluate the long-term effects of CBD for treatment of anxiety disorders. Last, investigators suggested the need for further research and definitive conclusions on whether a relationship exists between rCBF and CBD plasma levels, which would potentially provide a less invasive strategy for monitoring CBD's clinical effects.

Discussion

CBD has been studied for use in treating anxiety-like responses for more than a decade.[27] Several early studies evaluated the use of CBD in preventing neural responses to fearful faces.[28,29] Initial studies evaluating the difference in response between CBD and THC showed that while THC use often results in negative behavioral and psychological effects, CBD is safe and well-tolerated with no difference from placebo in regard to increasing unwanted anxiety, sedation, positive psychotic symptoms, and intoxication.[28,30,31] In addition, CBD may even have utility in minimizing the negative effects of THC.[32]

On the basis of the results of currently available published human studies, it is seen that CBD has demonstrated a developing role as an alternative therapy in the indications of anxiety disorders, specifically GAD, SAD, and anxiety related to PTSD. Because the majority of the reviewed studies had small sample sizes, low statistical power posed a notable limitation. Primarily adult, male patients were enrolled in the studies, with only 1 pediatric case report meeting criteria for review. In addition, several studies enrolled healthy volunteers modeling varying anxiety disorders. Very few studies that enrolled patients with an anxiety diagnosis and compared the outcomes of taking CBD with those of taking placebo were identified. Taken together, these overall study characteristics may limit the generalizability of results. Similarly, because wide ranges of CBD doses were implemented among the studies, future evaluations of more intermediate range CBD doses may be warranted to determine optimal dosing definitively. Last, many studies made conclusions related to the dose-response curve of CBD on the basis of the results of neuroimaging findings and subjective scores on anxiety assessments without assessing plasma levels; therefore, these findings should be interpreted with caution.

In the studies reviewed, CBD regularly showed improved clinical outcomes in GAD, SAD, and anxiety related to PTSD, with minimal adverse effects, which differs from other therapeutic agents that are currently used for these indications. These results indicate that CBD could provide a unique therapeutic opportunity to augment or replace existing pharmacotherapy in patients with inadequate relief while causing fewer adverse effects. While CBD did show positive benefits in these patient populations, it can be challenging to translate results across studies owing to the lack of a standardized assessment tool and the variety of dosing schedules and routes of administration that were used. The most regularly used screening tool in CBD studies is VAMS, but its use has not been universal. Further standardized approaches in dosing and outcome measurement will be useful to best determine an effective therapeutic dose of CBD for broader patient populations.

Of note, the increasing amount of human studies evaluating the role of CBD in the treatment of anxiety and anxiety-related disorders are showing potential therapeutic success, specifically when CBD is administered with acute dosing. Fewer studies exist that evaluate the safety and efficacy of long-term

use of CBD in human populations. While clinical evidence supporting the use of CBD in these patient populations now exists, there continue to be considerable challenges in terms of a lack of standardized dosage and route of administration. These challenges also persist in terms of lack of standardization in product manufacturing. Typically, CBD products are labeled not by strength per dose, but by strength of product contained in the entire package. The labeling of these products can lead to confusion for patients attempting to follow a specific dosage schedule based on their clinical indication, suggesting a need for focused patient education and follow-up with patients initiating CBD therapy for a chronic indication.

While CBD has a generally mild adverse-effect profile as demonstrated through human studies, some clinical considerations do exist. Clinical data have demonstrated the potential for CBD to increase plasma levels of warfarin, and suggest that CBD products may potentiate some drug interactions via CYP450 pathways.[33] CBD has the potential to function as a potent inhibitor of CYP3A4 and CYP2D6, which may result in increased serum concentrations of medications such as macrolides, calcium channel blockers, antiretrovirals, antidepressants, antipsychotics, and opioids.[34,35] In addition, patients with decreased CYP2C19 or CYP3A4 function may be at risk for increased CBD accumulation and exposure, while patients taking a CYP3A4 inducer may see a decrease in CBD exposure.[33,35] Patients taking anticoagulants or other interacting medications should be counseled about the effects of initiating and discontinuing CBD products. See Table 2 for a list of other CBD considerations.

Another potential challenge surrounding the use of CBD in the general population concerns the persistent issues regarding product purity. Generally, CBD products sold to the public for medical use contain high levels of CBD and low levels of THC, although these levels of THC may range between 0.3% and 5% based on state law.[36] Even with the level of THC provided on product labeling, actual content of THC may be higher than what is listed on the label as found in FDA test results of products in 2015 and 2016.[37,38] For patients where the presence of THC could be problematic because of workplace drug screenings or because the legal status of cannabis products in their state is in question, these factors should be considered before recommendation of CBD products. In addition, because of the lack of product regulation for safety and purity given its status as a dietary supplement, products may also have a variable level of CBD present in them, further increasing difficulty in ensuring that patients receive a desired dose to obtain a specific therapeutic effect. One study in 2015 demonstrated a wide range of product content of CBD, with products sold as medical cannabis products being both over- and underlabeled in regard to CBD content.[39] Both regulation and increased quality assurance are needed for CBD products to be routinely recommended for use as a medical product.

Last, patient access to CBD products can vary. While all 50 states have legislation that legalizes CBD products, restrictions vary widely, and CBD products are still considered by the federal government to be in the same restricted access class as marijuana. In similar fashion to their approach to medical marijuana, the federal government generally declines to enforce restrictions on CBD use. The legal status of CBD is evolving, and clinicians should pay careful attention to the laws surrounding CBD sales and usage in their states.

Conclusion

CBD has consistently demonstrated acute reduction in anxiety-related symptoms in patients, specifically within GAD and SAD. Additionally, the use of CBD for these disorders has shown increasingly minimal adverse effects compared with existing pharmacotherapy. Further studies are needed to determine long-term safety and efficacy of CBD products and a more standardized dose-effect response. Clinicians should be mindful of challenges related to product purity, legal status of CBD based on geographic area, and the potential for drug interactions when recommending the use of CBD for anxiety.

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Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users

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ABSTRACT

Cannabis is commonly used recreationally for its euphoric and relaxing effects, while its medical use is permitted in several jurisdictions. With only low-quality evidence suggesting anxiolytic effects of cannabis and strong public sentiment surrounding such purported effects, the purpose of this study was to examine the prevalence of cannabis for medicinal purposes (CMP) use for anxiety symptoms. An online survey was disseminated to CMP users registered with a Canadian licensed producer. Respondents completed demographic and validated self-report questionnaires (GAD-7, PHQ-9, MINI-SPIN, and panic disorder/agoraphobia DSM-5 criteria). Cannabis use behaviors were also discussed. Overall, 2032 completed responses with a verified user number were collected. Of the total sample, 888 (43.7%) reported CMP authorization to treat anxiety symptoms and completed all psychometric screening instruments. Rates of probable disorders were high (Generalized Anxiety Disorder: 45.6%, Social Anxiety Disorder: 42.4%, Major Depressive Disorder: 25.7%, Panic Disorder/Agoraphobia: 25.7%); 63.4% met screening criteria for ≥1 disorder. Most (92%) reported that cannabis improved their symptoms, despite continuing to endorse moderate-level severity. Nearly half (49%) reported replacing a non-psychiatric (53.7%) or psychiatric medication (46.3%) prescribed to them by their physician with CMP. Respondents endorsed daily CMP use and severity of anxiety (GAD-7, $p < 0.001$) and depressive (PHQ-9, $p < 0.001$) symptoms were positively associated with the amount of cannabis used/day. The vast majority perceived symptom improvement with CMP use and did not believe CMP use was associated with impairment or an inability to control use. Nevertheless, the possibility of cannabis use disorder cannot be ruled out as well as the possibility that improvements in non-psychiatric conditions were attributed to improvements in anxiety. These results highlight the need to systematically evaluate CMP use for mental illness.

1. Introduction

Cannabis is commonly used recreationally for its euphoric and relaxing effects. The dried plant is typically smoked or vaporized and also consumed in foods or used as a concentrated oil. Although considered an illicit substance in many parts of the world, regulatory bodies in the Netherlands, and several US states have legalized medicinal and/or recreational use, with Canada having legalized recreational use on October 17, 2018. Prior to this, only cannabis for medicinal purposes (CMP) could be legally obtained from licensed producers for a myriad of medical conditions, with appropriate physician authorization. A recent meta-analysis revealed moderate-quality evidence to support cannabinoid treatment of chronic pain and spasticity, with very low-quality evidence suggesting improvement in anxiety and no effect in depression (Whiting et al., 2015). Only small studies of synthetic cannabinoids (Fabre and McLendon, 1981; Glass et al., 1981; Ilaria et al., 1981; Lee, 2009) or cannabidiol (CBD) (Bergamaschi et al., 2011; Crippa et al., 2011) have been examined in clinically anxious populations. Yet, many Canadians report using cannabis to alleviate self-reported anxiety (Walsh et al., 2013).

Anxiety disorders are chronic conditions with a lifetime prevalence of 31.6% (Kessler et al., 2012). They include social anxiety disorder

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(SAD), generalized anxiety disorder (GAD), panic disorder (PD) and specific phobias. These disorders are associated with significant burden for afflicted individuals, their families and society (Katzman et al., 2014). While many established efficacious first-line treatments exist, including antidepressants and cognitive-behavioral therapy, 40–60% of patients continue to have residual, impairing symptoms while others are non-compliant or have difficulty accessing treatments (Katzman et al., 2014). Given such limitations, individuals may seek alternative treatments and public sentiment surrounding cannabis' purported anxiolytic effects suggest cannabis may fulfil this role.

The primary active components in cannabis are Δ9-tetrahydrocannabinol (THC) and CBD. While THC is thought to have anxiolytic, antidepressant and hypnotic effects, CBD has demonstrated anti-inflammatory, analgesic, anticonvulsant, and anxiolytic properties, (Walsh et al., 2017). Of the two primary cannabinoids, THC is the psychoactive constituent and at higher doses has been documented to induce panic, paranoia and anxiety, (D'Souza et al., 2004; Fusar-Poli et al., 2009). The ratio of these cannabinoids varies greatly between strains of cannabis and consequently may induce a wide variety of effects. For instance, when CBD is administered with THC, it has demonstrated an ability to "undo" the unwanted and anxiogenic effects of THC by acting as a pharmacological antagonist (Karniol et al., 1974; Zuardi et al., 1982). Given the various cannabinoids and other active compounds in the cannabis plant, it is difficult to discern the specific behavioral effects of cannabis. As such, the existing cannabis literature comprised of studies of pure or synthetic cannabinoids may not be a sufficient proxy to illustrate cannabis' potential anxiolytic effects. Canadians are currently using cannabis for anxiety symptoms (Sexton et al., 2016; Walsh et al., 2013) but whether these individuals are treating state anxiety or symptoms of a clinical disorder remains unclear. With the scientific literature indicating cannabis as a non-evidence-based treatment for anxiety, mood and related disorders (Turna et al., 2017), this study examines the prevalence of CMP use for anxiety, psychiatric symptom severity and CMP use behaviors in a sample of authorized Canadian medicinal cannabis users.

2. Methods

2.1. Study population and design

An online survey was disseminated to all authorized CMP users registered with Tilray (British Columbia, Canada, n = 16,675) on January 9, 2017, and was closed 48 h later. Respondents received a $10 account credit towards future Tilray purchases. Following acknowledgement of a disclosure statement, information regarding demographics and CMP use was collected. Questions were structured in multiple choice, checklist and rating scale format. Individuals were not able to skip question(s) they did not wish to answer, therefore, all completed questionnaires did not contain missing data. Many questions contained "skip logic", so that if the respondent answered "no", they did not complete further questions concerning this topic. Study data was collected and managed using Research Electronic Data Capture (REDCap) (Harris et al., 2009), a Health Insurance Portability and Accountability (HIPAA) and Personal Information Protection and Electronic Documents Act (PIPEDA) compliant online survey tool allowing participants to directly enter responses.

2.2. Outcome measures

All respondents answered questions regarding primary illness and symptoms treated with CMP. Those who identified anxiety as one of their primary symptoms treated with CMP in the second question then completed validated self-report symptom severity scales to characterize psychiatric morbidity including: 1) the GAD-7: a 7-item questionnaire used to screen for GAD and anxiety symptom severity, a score ≥10 was used to suggest moderate anxiety (Spitzer et al., 2006); 2) The Patient Health Questionnaire (PHQ-9) is a multipurpose instrument for screening, monitoring and measuring depressive symptom severity with a total score ≥15 suggesting moderately severe depression (Kroenke et al., 2001); 3) The MINI Social Phobia Inventory (Mini-SPIN) is a validated 3-item scale in which a total score ≥6 indicates significant SAD symptoms (Connor et al., 2001). Given that no brief measure for panic disorder was found in the literature, four screening questions from the Panic Agoraphobia Scale (PAS) (Bandelow, 1995) were included, and a positive screen for potential panic disorder symptoms was coded if respondents identified the presence of panic attacks and reported > 1 panic attack in the past 2 weeks. Respondents were instructed to answer questions based on the past two weeks. Additional questions regarding CMP use and its effect on symptoms were also incorporated. The survey included 25 anxiety-related questions.

2.3. Statistical analysis

Descriptive statistics, including means, standard deviations and percentages were used to describe demographics, perceived efficacy, conditions, etc. Data analysis was performed using R (version 3.3.1, R Core Team). Frequencies were compared using a chi-square test. A one-way ANOVA or *t*-test was used to examine mean differences between groups, where applicable.

2.4. Ethics approval

This study was approved by the Institutional Review Board Services.

3. Results

In total, 3405 responses were received and 2032 responses were paired with a verified user number. Of the total sample, 888 (43.7%, ANX group) identified anxiety as one of the primary symptoms for CMP use from a list of 14 prepopulated medical symptoms. These respondents were asked to complete all symptom severity screening questionnaires.

3.1. Sample demographics

The mean age of the ANX group was 36.3 ± 10.8 years (range: 16–84 years). The sample was primarily male (58.2%), married (36.1%), employed full-time (50.3%), living in an urban area (43.6%) and with a college education (32.2%); additional demographic characteristics can be found in Table 1. This sample was prescribed CMP by 607 different physicians.

3.2. Psychiatric comorbidity

Based on the cut-off for each respective screening tool, rates of probable anxiety and depressive disorders within the ANX were high (Table 2). In this sample 63.4% met screening criteria for ≥1 disorder.

The severity of anxiety (GAD-7) and depressive (PHQ-9) scores were positively associated with the amount of cannabis used per day. This was examined using a one-way ANOVA with GAD-7 score as the dependent variable and low (< 1 g/day), moderate (1–2g/day) or high (≥3 g/day) CMP use as the independent variables. Post-hoc comparisons revealed that high users had significantly higher GAD-7 (11.5 ± 5.8) and PHQ-9 (11.8 ± 6.9) scores than moderate (GAD-7: 9.1 ± 5.3; PHQ-9: 9.5 ± 6.6) or low users (GAD-7: 9.3 ± 5.3; PHQ-9:9.8 ± 6.1) (GAD-7: $F(2,771) = 14.0$, $p < 0.001$; PHQ-9: $F(2,771) = 9.3$, $p < 0.001$). No differences were observed between low and moderate users.

3.3. Psychiatric effects of CMP use

To better understand perceived efficacy of CMP for symptomatic

Table 1
Demographic characteristics of ANX sample.

Characteristic (n = 888)		%	Characteristic (n = 888)		%
Sex	Male	58.2	Employment	Full-time	50.3
	Female	41.5		Part-time	13.0
	Other	0.3		Unemployed (looking for work)	11.1
Marital Status	Married/Common-law	61.1		Unemployed (not looking for work)	5.4
	Single	31.1		Retired	2.5
	Divorced/Separated	7.1		Disabled	17.7
	Widowed	0.7			
Education	High School or less	25.0	Annual Household Income	≤$39,000	34.5
	Some college/university	23.5		$40,000 - $69,999	26.8
	Technical/non-university degree	32.2		$70,000 - $99,999	16.3
	University degree	14.8		≥$100,000	16.4
	Graduate degree	4.5	Ethnicity	Caucasian	85.1
Province	Alberta	64.2		More than one race	5.4
	Ontario	19.7		Metis	1.9
	British Columbia	6.0		Asian	1.7
	Other Provinces	10.1		Other[a]	5.9

[a] Other: Aboriginal, South Asian, Black, Hispanic and 'Other'.

Table 2
Prevalence of anxiety and depressive disorders in ANX as per self-report screening measures (n = 888).

Disorder	Diagnostic cut-off score	Prevalence (%)	Mean Score
GAD	GAD-7 ≥10	45.6%	9.8 ± 5.5
SAD	Mini-SPIN ≥6	42.4%	4.9 ± 3.5
MDD	PHQ-9 ≥15	25.7%	10.4 ± 6.4
PD/agoraphobia	Modified PAS criteria	25.7%	NA

relief, the ANX group was asked to identify the anxiety and depressive symptoms CMP use improved, using 21 prepopulated choices (allowed to check all that applied). The majority of the ANX group reported that CMP improved their "anxiety, worry, fears" (92.0%), "irritability" (75.5%), "difficulty falling to sleep" (72.4%), "anxiety attacks" (58.8%) and "low mood" (56.9%) (Fig. 1). When asked how effective CMP was at relieving these symptoms on a scale of 1 (not at all effective) to 5 (very effective), 64.9% reported a rating of 4 or more; only 1% responded "not at all effective". Respondents using > 3 g cannabis/day reported significantly greater perceived benefit related to cannabis use as compared to individuals using < 3 g/day ($p < 0.0001$).

Many in the ANX group reported using cannabis to feel relaxed (84.4%). Respondents were also asked which cannabis strains were thought to best improve their anxiety and which strains they found to worsen their anxiety. They could select as many of the 6 prepopulated options available. *Cannabis indica* was more often reported to have a subjective anxiolytic effect (51.5%), while *Cannabis sativa* was the most frequently reported anxiogenic strain (32.3%) (Fig. 2).

3.4. Cannabis use behaviors

A majority of the ANX group used cannabis recreationally (99.5%) prior to medicinal use. However, 85.5% reported trying at least 1 traditional mental health treatment before CMP ($\bar{x} = 2.6 \pm 2.0$ treatments), with 55.5% reporting medication and 20.5% reported cognitive-behavioral therapy. Use of other cannabinoid drugs was relatively

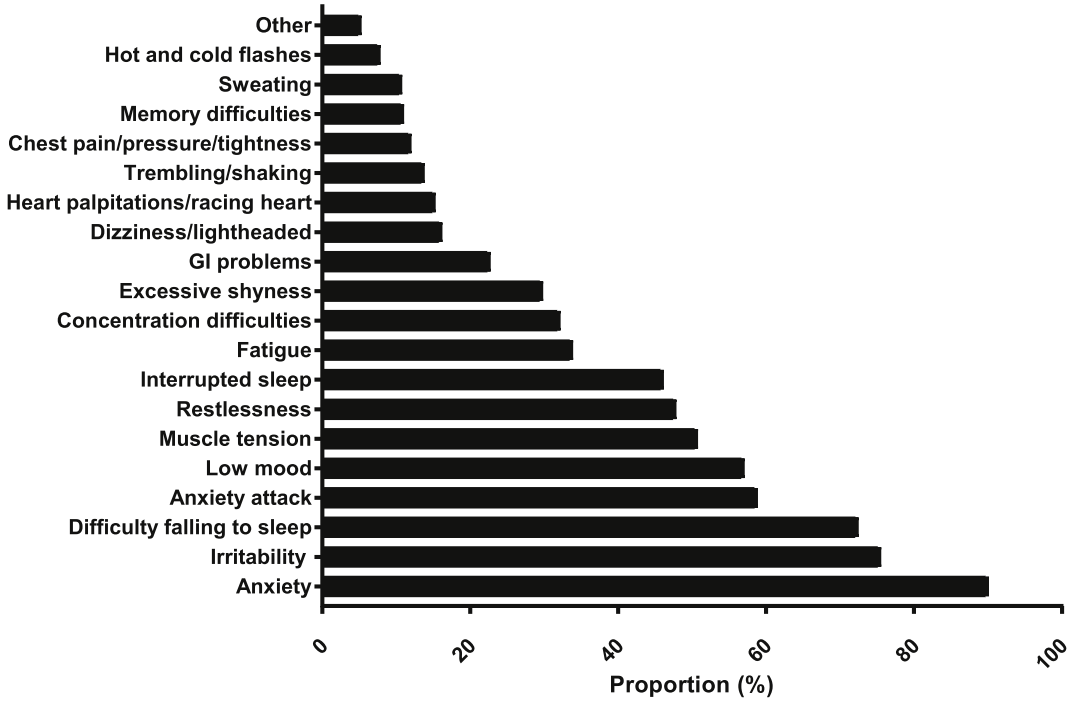

Fig. 1. Symptoms of anxiety and depressive disorders reported to be relieved by CMP use in ANX group (n = 888).

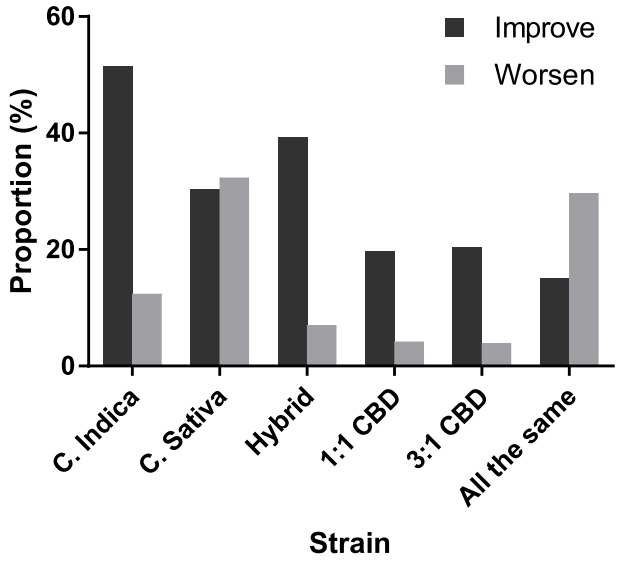

Fig. 2. Subjective reports of anxiogenic versus anxiolytic effects of varying cannabis strains (n = 888).

low (Dronabinol:1.0%, Nabilone:5.9%, Sativex:1.6%, Other Cannabinoids:0.6%). Fifty respondents (6%) endorsed having a primary mental health condition and had no previous treatment prior to their CMP. Although not significant, these individuals tended to be male, have lower levels of education and endorsed that cannabis is safer than prescription medication compared with respondents who had tried at least one traditional treatment. They also reported significantly younger mean age of recreational cannabis use (15.96 vs. 17.48, t (99.97) = −2.5571, p = 0.01).

In total, 22.1% of respondents stated that their use of cannabis had increased "a lot" since obtaining access to CMP, with 42% of individuals using 1–2 g of cannabis per day. Thirty-five percent reported using < 1 g/day while 23% of the sample used ≥3 g/day. Respondents did not believe they had difficulty controlling CMP use (79.7%) or that their social and leisure activities were impaired by it (84.4%). Most respondents also reported vaporizing (47.6%) as the preferred mode of delivery, followed by oral ingestion (21.4%, includes edibles, oils, etc.), joints (18.5%), etc.

Respondents were also asked which prescription drugs they had replaced with cannabis (up to 3 answers permitted) and at what rate they were substituting the prescription medication with CMP. Nearly half of the ANX sample (49%) reported substituting a prescribed medication with CMP to some degree, of whom 61% indicated that cannabis had completely (100%) replaced a drug prescribed to them by their physician for a given medical condition (Table 3). We also compared the rates of substitution between individuals with and without anxiety. No significant differences in medication substitutions or CMP usage patterns were found between those with anxiety and those without.

Table 3
Proportion of the ANX sample replacing a prescribed medication with medicinal cannabis (n = 888).

Drug Class	%
Antidepressants	23.8
Opioid	19.2
Benzodiazepine	15.8
NSAIDs	6.1
Antiepileptic	5.0
Sedative-Hypnotic	4.2
General Analgesic	3.9
Psychostimulant	3.7
Antipsychotic	3.0
All others	15.3

Table 4
Frequencies of primary condition for which CMP has been authorized by a medical doctor.

Indication	ANX group (n = 888)	All respondents (n = 2032)
Mental Health (Stress, Anxiety, Depression, PTSD, eating disorders)	52.9%	30.6%
Chronic Pain	17.2%	26.7%
Insomnia	8.0%	9.4%
Other	5.0%	8.9%
Arthritis	3.5%	7.7%
All others	13.4%	16.7%

3.5. Primary condition for CMP

Among all respondents (n = 2032), mental health (30.6%) was most frequently identified as the primary medical condition currently being treated with CMP. Mental health (52.9%) was also the most frequent indication in the ANX group (n = 888) (Table 4). Demographic characteristics and cannabis use behaviours were compared among individuals in the ANX group who were prescribed CMP to treat a mental health condition (52.9%) versus those taking CMP for a non-psychiatric condition (47.1%). Respondents who were prescribed CMP for a non-psychiatric condition appeared to use slightly more cannabis ($\chi2(6) = 19.339$, p = 0.004) and were more likely to be on disability ($\chi2(5) = 33.15$, p < 0.001; 24.1% vs. 11.9%) than respondents prescribed CMP to treat a mental health condition. Although not significant, most respondents using CMP for a non-psychiatric condition were male, married, living in a suburban area and have a technical or non-university degree. No significant differences were found between groups in terms of level of income, province of residence, scores on the PHQ-9 or GAD-7 nor in the perceived benefit of cannabis use.

4. Discussion

The primary finding of this study is the high frequency of CMP use for the treatment of self-reported anxiety symptoms (43.7%, ANX). Almost 2/3 of the ANX group met screening criteria for ≥1 disorder (63.4%), with GAD and SAD being the most common (Table 2). Similarly, anxiety and depressive scores were also higher in those using more cannabis (using ≥3 g/day). Although the majority of participants reported that CMP use improved their anxiety symptoms (Fig. 1), severity measures indicated at least ongoing moderate symptoms (Table 2). This suggests that even if cannabis has been helpful for these individuals, it may not be effectively decreasing symptoms to a clinically significant level. For instance, their symptoms may have previously been more severe and have, with CMP use, decreased to a moderate level. An alternative explanation may be that the improvement noted by CMP users in anxiety may be related to the relief of cannabis-withdrawal associated anxiety symptoms. Or that this improvement may have been confounded by improvements in the non-psychiatric conditions also treated with CMP. Mental health conditions were the leading indication for CMP authorization in both the ANX group and the overall sample (Table 4). Many were also replacing prescribed medications with CMP. The most frequently replaced drugs included psychotropics (antidepressants and benzodiazepines) and pain relievers (Table 3). While most denied social impairment and difficulty controlling use, many would be considered heavy users due to daily use. Cannabis indica, followed by hybrids, were most often rated as anxiolytic (Fig. 2). Interestingly, both strains contain high THC (above

18%) and relatively low CBD (1%). Although THC has been purported to have anxiolytic properties, it has also been associated with the development of panic, paranoia and anxiety, D'Souza et al., 2004; Fusar-Poli et al. (2009). Furthermore, while pre-clinical research suggests that CBD may be anxiolytic (Bergamaschi et al., 2011; Crippa et al., 2011), it is critical to note that the vast biochemical variability of these plants makes it difficult to discern which effects are attributable to which compound. Rather, the notion of an "entourage effect" or synergistic effect between the many cannabinoids, terpenoids and flavonoids (Elzinga et al., 2015) may provide one possible explanation of the reported anxiolytic properties of *Cannabis indica* and hybrids in this sample.

The prevalence of CMP use for anxiety in our sample exceeded what has been previously reported. An older study reported less than 10% of authorized Health Canada CMP users were prescribed cannabis for anxiety, while non-authorized use was significantly higher (Walsh et al., 2013). Canadian regulations surrounding CMP authorization have become more inclusive since this study in 2013, now requiring physician authorization for any condition the physician feels warrants cannabis treatment. This process involves acquiring a medical document which includes the name of the healthcare practitioner and patient, daily CMP quantity prescribed and duration of use; this document is then submitted to the licensed producer (Health Canada, 2017). This change is likely reflected in the considerable increase of authorized users in our sample using cannabis for anxiety. Despite these changes in CMP legislation, the scientific evidence examining cannabis treatment in anxiety disordered clinical populations is still in its infancy. When using the four levels of evidence as defined by the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Kennedy et al., 2016), the existing cannabis literature would be considered Level Three evidence for certain mental health conditions including social anxiety disorder, posttraumatic stress disorder and Tourette's Syndrome (Turna et al., 2017). The increasing number of CMP authorization for mental health issues, reveal that Canadian physicians are being approached for CMP prescriptions to treat these conditions and/or may be willing to prescribe for these symptoms despite a dearth of supporting evidence examining the efficacy and safety of CMP in anxiety.

There is strong public sentiment regarding CMP efficacy for a wide range of medical conditions, including subjective anxiolytic effects (Sexton et al., 2016). However, this is the first study to characterize symptom severity beyond subjective reports of anxiety noted in previous studies (Sexton et al., 2016; Walsh et al., 2013). Validated clinical self-report measures revealed clinically significant psychiatric symptoms in our sample, with 63.4% meeting criteria for at least 1 disorder. Yet, respondents perceived CMP treatment as efficacious for their anxiety symptoms. Given that the symptom severity measures used in this survey have demonstrated sensitivity to change with treatment in clinical trials, these results elude to a possible disconnect between respondent belief regarding CMP efficacy and quantifiable symptom improvement. Furthermore, respondents using > 3 g/day also reported greater perceived benefit, yet endorsed higher anxiety and depression symptoms. This finding can be interpreted in several ways: these individuals may be using more cannabis because they are more symptomatic; perhaps cannabis used in this group is not reducing anxiety/depressive symptoms but is providing an improved sense of well-being; or perhaps this a group of patients who have problematic use, as there is some evidence to suggest that higher daily use of cannabis is associated with cannabis use disorder (CUD) (van der Pol et al., 2015). However, we have no way of evaluating CUD within this sample, and the cross-sectional nature of the study limits our ability to derive any conclusions regarding symptomatic change with CMP use. Even though respondents endorsed moderate symptoms we cannot preclude the possibility of improvement in that their symptoms may have been more severe prior to beginning treatment with CMP. Despite many respondents reporting increased cannabis use since receiving CMP authorization and many endorsing daily use, symptoms indicating problematic cannabis use (social impairment and difficulty controlling use) were minimal. However, data from the National Survey of Drug Use and Health (NSDUH) has suggested that up to 11% of individuals using CMP meet criteria for DSM-IV cannabis abuse/dependence (Lin et al., 2016). Further, daily use is more frequent in medical cannabis users (33%) compared to recreational users (11%) (Lin et al., 2016). We cannot preclude cannabis use disorder (CUD) in our sample as it was not directly examined, however many respondents reported increased use of cannabis since obtaining a prescription. This may suggest the development of tolerance, a hallmark symptom of CUD. The recently published Lower-Risk Cannabis Use Guidelines (LRCUG) (Fischer et al., 2017) suggest frequency or intensity of use to be the strongest and most consistent predictors of severe and/or long-term cannabis-related health problems. However, these guidelines are not specific to medicinal use as there is no existing data to suggest that daily medicinal cannabis use increases risk of CUD. These data highlight the need for additional research to appropriately characterize patients that may benefit from CMP use while protecting those that may be at-risk to possible negative effects.

Of note, many respondents to our survey reported replacing a prescription medication with CMP, primarily antidepressants. A recent US study revealed that 71.8% of their sample of chronic pain medicinal cannabis users decreased use of anti-anxiety medications (benzodiazepines), and to lesser extent antidepressants (37.6%) while using medical cannabis (Piper et al., 2017). Given the high rates of CMP prescription seen for mental health conditions and lack of literature examining the efficacy of CMP in these conditions (NASEM, 2017; Turna et al., 2017), there is an imminent need to begin developing a systematic body of research examining CMP in these conditions. Future studies should examine both the efficacy of cannabis for mental health conditions, as well as its equivalence to current, evidence-based pharmacological treatments. These studies will be critical to inform the development of treatment guidelines so that physicians may prescribe cannabis treatments to patients in an evidence-based and informed manner.

As with any cross-sectional online survey, there are several limitations inherent to the study design. All responses were self-report and retrospective in nature. Although we utilized validated and reliable symptom severity scales to examine prevalence and severity of a given disorder, these do not replace physician confirmation of anxiety and mood disorders. Nevertheless, given that these individuals are physician-authorized CMP users for primarily mental health conditions, it is likely that a medical diagnosis was made by their prescribing physician. We may have a potentially unrepresentative sample as the study was open to self-selection and non-response biases; although the submission of multiple surveys from one participant was prevented, as a verified user number was required. Further participation was incentivized which may have produced additional biases and the number of survey respondents capped. In addition, due to limitations inherent in the cross-sectional design, we were unable to answer several important questions including the impact of potential confounders such as non-psychiatric comorbidity or how many respondents developed anxiety or depression after beginning use of recreational cannabis or CMP. Further, only 25 of 888 respondents in the ANX group endorsed only anxiety and depression and no non-psychiatric condition, limiting the generalizability of these findings. In light of these limitations, the presented findings should be interpreted cautiously and highlight the importance of additional studies to replicate findings in samples of CMP users.

Nevertheless, the results of this study show that patients and physicians are pursuing CMP for a variety of medical conditions including anxiety and a need to inform the significant gaps currently plaguing the existing literature is evident. This research highlights the importance of future studies to clarify the role of cannabis in the treatment landscape. For instance, cannabis is thought to be safe, but it is unclear whether regular use as an anxiolytic treatment poses additional risks. Further, the abuse liability of cannabis is an issue warranting further

consideration, as symptoms of tolerance and withdrawal are not well understood, and psychiatric populations may be particularly vulnerable to this potential consequence. CMP use for mental health conditions requires systematic evaluation to examine efficacy and equivalence using rigorously designed studies including, but not limited to double-blind randomized controlled trials. Research informing CMP prescribers will also be critical given that there is limited information to guide physicians on strains, frequency and dose. This raises a time-sensitive public health concern as legalization of recreational cannabis is forthcoming in Canada which may increase the rate of self-medication with cannabis for mental health purposes. With no information to guide CMP use, it is critical that the scientific literature catch up to policy to better inform patients and physicians respectively.

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ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

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DESCRIPTORS
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Anxiety disorders.

Abstract
Objectives: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa,* cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action. *Method:* The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints. *Results:* Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder. *Conclusion:* Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

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Introduction

Cannabis sativa is the most used drug of abuse worldwide and around 20% of youth use it heavily and regularly around the globe.[1] The main psychoactive component of the plant is Δ9-tetrahydrocannabinol (Δ9-THC), one of the substances responsible for the psychoactive effects of Cannabis.[2-4]

Cannabidiol (CBD) is another abundant compound in *Cannabis sativa*, constituting around 40% of the plant's active substances.[5] The pharmacological effects of CBD are different and often opposite to those of Δ9-THC.[6] The number of publications on CBD has increased remarkably over the last years and support the view that CBD has a vast array of possible therapeutic effects. Among these possibilities, the anxiolytic and antipsychotic properties of CBD stand out.[7-10] CBD's anxiolytic effects are apparently similar to those of approved drugs to treat anxiety,[11] although its effective doses have not been clearly established and the mechanisms underlying these effects are not fully understood. The low affinity of CBD for cannabinoid neuroreceptors[12,13] and its agonist properties at 5-HT1A receptors[14,15] have been repeatedly demonstrated.

Most studies on CBD have been conducted with rodents, but studies with human samples have also provided promising results.[16,17] Therefore, the aim of this paper is to review the scientific literature on the anxiolytic properties of CBD in animal and in humans.

Method

The articles selected for this review were identified by searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". In addition, the reference lists of the selected articles and relevant literature reviews and book chapters were handsearched for additional references. We included experimental studies with human and animal samples with no time limits. We sought to exclude studies that used smoked Cannabis, as it is not possible to establish the dose, composition, and proportion of the different cannabinoids in this case, besides the great individual variations in the samples enrolled. Finally, we did not include studies using extracts containing both THC and CBD in oral (Cannador®) or oromucosal spray (Sativex®) forms due to the difficulty to establish the effects of CBD alone (Table 1).

Animal studies

The two first articles about the effects of CBD on experimental anxiety were published in journals that were not indexed in the databases used for this review but were located through handsearch in the reference lists of relevant literature. These two investigations showed contradictory results. In one study, no significant effects of high doses of CBD (100 mg/kg) were seen in rats in the Geller-Seifter conflict test.[18] In the other, a low dose of CBD (10 mg/kg) had anxiolytic effects in rats submitted to the conditioned emotional response test.[19]

Later studies using the elevated plus maze (EPM) helped to elucidate this contradiction.[9] The EPM consists of two opposing open arms (50 x 10 cm) and two closed arms (50 x 10 x 40 cm) that intersect in their central portion. The arms are made of wood and stand 50 cm above the ground. In this study, mice injected with CBD, diazepam or vehicle (no active substances) were placed in the center of the maze facing the closed arms. The time spent and the numbers of entries in the open and closed arms were measured for 10 minutes. The frequency of entries in the open arms of animals receiving CBD presented an inverted U-shaped curve, with significantly higher rates than those observed in animals treated with vehicle, at the doses of 2.5, 5, and 10 mg/kg. The measures of mice treated with CBD 20 mg/kg did not differ from those of controls, suggesting that anxiolytic effects are only present at low doses, which explains the absence of effects with CBD 100 mg/kg reported in 1981.[18] The same inverted U-shaped dose-response curve was obtained with a wider range of doses of CBD in the EPM (Onaivi et al.).[20] Furthermore, the same pattern was observed with the direct infusion of CBD in the periaqueductal gray (PAG) of rats tested in the EPM,[15,21] confirming that anxiolytic effects should only be expected with low doses of CBD.

The mechanisms through which CBD acts to diminish anxiety have been studied in a number of animal models of anxiety using rodents. One of these studies used Vogel's conflict test,[22] in which the animal is water-deprived from and placed in a cage with an electrified grid at the bottom through which the animal receives a shock after licking water for a predetermined number of times. Three substances were tested in rats using the following procedure: CBD (2.5, 5 and 10 mg/kg), diazepam, and flumazenil (an antagonist of benzodiazepine receptors), in addition to vehicle (placebo). The tests showed that CBD produced effects consistent with those of diazepam by increasing the number of licks, even if they resulted in punishment. Flumazenil antagonized the anxiolytic effect of diazepam, but not that of CBD, suggesting that the effects of CBD are not mediated by the activation of benzodiazepine receptors.

There is strong evidence showing that the serotonergic system is involved in the anxiolytic action of CBD. The injection of the 5-HT1A receptor antagonist WAY-100635 (WAY) directly into the dorsolateral portion of the PAG (dlPAG) in rats antagonized the anxiolytic effects of CBD in the EPM and in Vogel's conflict test.[15] The participation of 5-HT1A receptors in the anxiolytic action of CBD was also derived from behavioral and cardiovascular responses to restraint stress in rats.[11] In this study, animals were intraperitoneally injected with vehicle or CBD (1, 10 and 20 mg/kg) and, after 30 minutes, they were restrained for 60 minutes. Immobilization increased blood pressure, heart rate, and anxiety responses in the EPM 24 hours later, and these effects were attenuated by CBD. Pretreatment with WAY blocked the anxiolytic action of CBD. The injection of CBD into the intra-dorsal PAG also blocked panic-like responses in the elevated T-maze (ETM) and flight responses to the electrical stimulation of this area.[23] The ETM has three arms with the same dimensions, two open and one closed, and allows the measure of entrance avoidance in the open arms when the animal is placed in the closed arm, as well as of escape when the animal is placed in the open arm. The panic-like response seen with CBD in the two procedures was antagonized by the previous intra-dlPAG administration of WAY.[22] Chronic oral administration of CBD also had anti-panic effects in the ETM that were neutralized

Table 1 Studies of the anxiolytic effect of cannabidiol in humans and animals

Study	Model	Route	Dose	Anxiolytic effect
Animals				
Silveira Filho et al.[18]	Conflict test	Intraperitoneal	100 mg/kg	–
Zuardi et al.[19]	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi et al.[20]	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0 and 100.0 mg/kg	+
Guimarães et al.[9]	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0 and 20.0 mg/kg	+
Moreira et al.[22]	Vogel's conflict test	Intraperitoneal	2.5, 5.0 and 10.0 mg/kg	+
Resstel et al.[10]	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos et al.[15]	Elevated plus maze test and Vogel's conflict test	Intra-dorsal periaqueductal gray		+
Bitencourt et al.[28]	Contextual fear conditioning	i.c.v.	2.0 microg/microl	+
Campos et al.[21]	Elevated plus maze test	Intra-dorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al.[19]	Restraint stress	Intraperitoneal	1, 10 and 20 mg/kg	+
Soares et al.[23]	Elevated T maze	Intra-dorsal periaqueductal gray	15, 30 or 60 nmol	+
Lemos et al.[29]	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL prefrontal cortex	10 mg/kg (i.p.) and 30 nmol (microinjection into the PL prefrontal cortex)	+
Casarotto et al.[26]	Marble-burying test	Intraperitoneal	15, 30 and 60 mg/kg	+
Gomes et al.[30]	Vogel's conflict test	Intra bed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al.[27]	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al.[31]	Prey-predator paradigm	Intraperitoneal	0.3, 3.0 and 30 mg/kg	+
Campos et al.[24]	Elevated T maze	Oral		+
Humans				
Zuardi et al.[7]	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi et al.[32]	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al.[34]	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al.[35]	Decreased skin conductance fluctuation in task with fearful faces during a fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al.[17]	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al.[33]	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

by intra-dlPAG injection of WAY. However, chronic administration of CBD did not change the extracellular concentration of serotonin in the dlPAG or the expression of 5-HT1A or 5-HT2C, indicating that CBD directly activates 5-HT1A receptors.[24] CBD was also found to activate the vanilloid receptor type 1 (TRPV1)[25] and there is evidence that this activation could explain the inverted U-shaped dose-response curve of CBD's anxiolytic effect seen in the EPM. TRPV1 receptors regulate the release of glutamate in the dlPAG and the increased activation of this system would result in increased anxiety. Thus, it has been suggested that elevated doses of CBD in the dlPAG could activate local TRPV1 receptors facilitating the glutamatergic neurotransmission and increasing anxiety.

To test this hypothesis, rats pre-treated with the TRPV1 antagonist capsazepine in the dlPAG were injected with CBD (30 and 60 mg/kg) in the same region and tested in the EPM. The dose of 60 mg/kg CBD, which had no anxiolytic action before, was able to reduce anxiety after pre-treatment with capsazepine, suggesting that the activation of TRPV1 receptors by the higher dose of CBD would counterbalance the anxiolytic effect of CBD produced by the activation of 5-HT1A receptors.[21]

Because serotonin has also been implicated in obsessive-compulsive disorder (OCD), the effects of CBD were tested in mice submitted to the marble-burying test (MBT), an animal model of compulsive behavior. CBD induced a significant reduction in the number of buried marbles at different doses (15, 30, and 60 mg/kg) compared to controls in a dose-dependent pattern. The same was found with the administration of the ISRS paroxetine (10 mg/kg) and diazepam (2.5 mg/kg). However, the effects of CBD 30 mg/kg persisted even after seven days of repeated daily administration, whereas the effects of diazepam disappeared. Pre-treatment with WAY (3 mg/kg) counteracted the effects of paroxetine, but did not affect the action of CBD, which was prevented by pre-treatment with the CB1 receptor antagonist AM251 (1 mg/kg).[26] This action of CBD in the MBT was recently replicated by another group using a higher dose (120 mg/kg).[27]

The participation of specific cannabinoid receptors (CB1) in the anxiolytic action of CBD has also been investigated using animal models. In the study with the EPM that reported the antagonism of the anxiolytic effect of intra-dlPAG CBD by WAY, the CB1 receptor antagonist AM251 was unable to avoid this effect.[15] However, this receptor system seems to be involved in another anxiolytic-like action of CBD, according to tests using a procedure known as contextual fear conditioning. In this procedure, animals are pre-conditioned to a hostile environment (foot shocks) and later exposed to the same environment, when they normally present freezing, the duration of which can be monitored as a measure of anxiety. Both CBD and diazepam are successful in attenuating freezing in rats, as well as the increased heart rate and blood pressure induced by re-exposure to the contextually feared environment.[10] This effect of CBD on contextual memory is also produced by the endocannabinoid reuptake inhibitor AM404, which increases the availability of cannabinoids in the synaptic cleft.[28] In this study, the two drugs were injected into the ventricles and their effects were counteracted by the CB1 receptor antagonist SR141716A, suggesting the involvement of the endocannabinoid system in the anxiolytic action of CBD in this model. The pre-limbic region of the prefrontal cortex appears to underlie this effect of CBD, as the reduction in contextual fear produced by systemic administration of CBD (10 mg/kg) is associated with reduced c-Fos expression in this area. In addition, the microinjection of CBD (30 nmol) in the pre-limbic region of the frontal cortex reduced freezing induced by re-exposure to the aversive context.[29] The effects of CBD on contextual fear indicate a possible therapeutic action of this cannabinoid in post-traumatic stress disorder.

Another area that is apparently involved in the anxiolytic-like effects of CBD is the bed nucleus of the stria terminalis (BNST). The intra-BNST injection of CBD (15, 30, and 60 nmol) increased the number of punished licks in Vogel's conflict test and the number of open arm entries in the EPM. These effects were blocked in rats pre-treated with WAY.[30]

CBD was also effective in an ethologic model that investigates behaviors induced by innate fear, the predator-prey paradigm.[31] This procedure was performed using a semi-transparent plexiglass box in the shape of a quadrangular arena (154x72x64 cm) with walls covered with a light-reflecting film and floor in transparent plexiglass over a board of stainless steel divided in 20 equal rectangles. One of the corners of the arena has a shelter box with black walls and a complex maze inside. Three days prior to the experiment, the mice were placed and kept in this arena, with free access to food and water until the day of the trial. The "no threat" group had its behaviors recorded for five minutes. Animals exposed to the predator (snake) were divided into four groups (n = 12/11 per group) and pre-treated with intraperitoneal injections of CBD (0.3, 3 and 30 mg/kg) or vehicle (control group). The group of animals that were not confronted with the predator presented no defensive behaviors. Animals pre-treated with CBD had significant reductions in explosive flight and defensive immobility, responses related to panic models. Risk assessment and defensive attention were unaltered in animals treated with CBD. These results suggest that CBD can be effective in the control of panic attacks.

Human studies

The first evidence of CBD's anxiolytic effects in humans, documented with assessment scales, was published in 1982 in a study on the interaction between CBD and THC.[7] The study sample consisted of eight volunteers with a mean age of 27 years, no health problems and who had not used *Cannabis sativa* in the previous 15 days. In a double-blind procedure, the volunteers received CBD, THC, THC + CBD, diazepam, and placebo in different sequences and days. The results showed that the increased anxiety following the administration of THC was significantly attenuated with the simultaneous administration of CBD (THC + CBD).

Based on this preliminary evidence, researchers decided to investigate a possible anxiolytic action of CBD in experimentally induced anxiety in healthy volunteers using the simulated public speaking (SPS) model.[32] The procedure consists of asking a subject to speak in front of a video camera for a few minutes, while subjective anxiety is measured with self-rated scales and physiological correlates of anxiety are recorded (heart rate, blood pressure, skin conductance). CBD (300 mg), as well as the anxiolytic drugs diazepam (10 mg) and ipsapirone (5 mg), administered in a double-blind design, significantly attenuated SPS-induced anxiety.

The SPS test may be regarded as a good model of anxiety and has apparent validity for social anxiety disorder (SAD), as the fear of speaking in public is considered a central feature in this condition. Therefore, the anxiolytic effect of CBD in healthy volunteers observed in this test led to the hypothesis that this cannabinoid could be effective to treat SAD. This hypothesis was recently tested in 24 patients with SAD who had their performance in the SPS test compared to that of a group of 12 healthy controls.[33] The patients with SAD were divided into two groups of 12, one of which received CBD 600 mg and the other placebo, in a double-blind procedure. The results showed that the levels of anxiety, somatic symptoms, and negative self-assessment were higher in patients who took placebo than in those of the CBD group who performed similarly to healthy controls in some measures.

In another study that investigated the effects of CBD on regional cerebral blood flow (rCBF) in healthy volunteers using single photon emission computed tomography (SPECT), SPS-induced anxiety was reduced in patients receiving CBD.[34] In that study, patients received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions with an interval of one week. CBD significantly reduced subjective anxiety as measured by rating scales, while brain activity was increased in the left parahippocampal gyrus and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus. This pattern of SPECT results is compatible with an anxiolytic action.

SPECT was also used later to investigate the neural correlates of CBD's anxiolytic effects in a sample of patients with SAD.[17] A single dose of CBD 400 mg was able to reduce subjective anxiety measures and SPECT showed changes in the same regions previously identified in healthy volunteers.

Functional magnetic resonance imaging (fMRI), which allows the acquisition of larger series of images with better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers.[35] This experiment showed that CBD (600 mg) attenuated fMRI responses during the recognition of fearful facial expressions in the amygdala and the anterior cingulate, and that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group also reported that the anxiolytic action of CBD occurs by altering the subcortical prefrontal connectivity via amygdala and anterior cingulated.[16]

Conclusion

Together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the proposition of CBD as a new drug with anxiolytic properties. Because it has no psychoactive effects and does not affect cognition; has an adequate safety profile, good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions,[36] CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice.[37] Future studies should test this possibility in clinical trials involving patients with different anxiety disorders, especially panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. In addition, because the actions of CBD are biphasic, the adequate therapeutic window for each anxiety disorder remains to be determined.

Regarding the mechanism underlying the anxiolytic effects of CBD, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT1A receptors, although other systems, as the endocannabinoid system itself, may also be implicated. Further investigation is warranted to clarify these issues, especially if we consider that CBD is a drug with a variety of effects in the nervous system.[38-40]

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The Endocannabinoid System and the Brain

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Abstract

The psychoactive constituent in cannabis, Δ^9-tetrahydrocannabinol (THC), was isolated in the mid-1960s, but the cannabinoid receptors, CB1 and CB2, and the major endogenous cannabinoids (anandamide and 2-arachidonoyl glycerol) were identified only 20 to 25 years later. The cannabinoid system affects both central nervous system (CNS) and peripheral processes. In this review, we have tried to summarize research—with an emphasis on recent publications—on the actions of the endocannabinoid system on anxiety, depression, neurogenesis, reward, cognition, learning, and memory. The effects are at times biphasic—lower doses causing effects opposite to those seen at high doses. Recently, numerous endocannabinoid-like compounds have been identified in the brain. Only a few have been investigated for their CNS activity, and future investigations on their action may throw light on a wide spectrum of brain functions.

Contents

INTRODUCTION: CANNABIS AND THE BRAIN

Cannabis Use Over Millennia: A Bird's-Eye View

The Assyrians (about second millennium BC to sixth century BC) used cannabis for its psychoactive, mind-altering effects as well as for its medical properties. It was named either *ganzi-gun-nu* ("the drug that takes away the mind") or *azzalu*, which was apparently a drug for "depression of spirits," for a female ailment (possibly amenorrhea), or even for annulment of witchcraft (Campbell Thomson 1949). The importance of cannabis intoxication seems to have been central in early Zoroastrian shamanic ecstasy (Mechoulam 1986). Its wide use in the Middle East has continued ever since. Indeed, it was a central theme in Arab poetry of the Middle Ages (Rosenthal 1971). In China and India it was known for the dual nature of its effects. In the Chinese classic medical pharmacopeia Ben Ts'ao, originally compiled around the first century AD, cannabis was recommended for numerous maladies, "but when taken in excess it could cause seeing devils" (Mechoulam 1986, p. 9).

In Europe, cannabis was introduced by the Napoleonic soldiers returning from Egypt and by British physicians returning from India. Industrial hemp, which contains negligible amounts of psychoactive material, was of course grown previously, but the psychoactive variety was unknown. The psychological effects caused by cannabis preparations—presumably North African hashish—became known in Europe mostly through the writings of members of the Parisian *Le Club des Hachichins* in the mid-nineteenth century, particularly Baudelaire, Gautier, and Moreau (Mechoulam 1986). Baudelaire, a major literary figure at the time, emphasized the "groundless gaiety" and "the distortion of sounds and colours" following cannabis use. Moreau, a psychiatrist, in his 1845 book, *Hashish and Mental Illness* (Moreau 1973), described in detail numerous psychological phenomenon noted in experimental subjects: feeling of happiness, excitement and dissociation of ideas, errors of time and space, enhancement of the sense of hearing, delusions, fluctuations of emotions, irresistible impulses, and illusions and hallucinations. This diversity of actions—some of them opposite to each other—has confounded cannabis research ever since. Indeed, Moreau reported that some of

his volunteers experienced "...occurrences of delirium or of actual madness". He concluded, "There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish..." (Moreau 1973, p. 18). But today few marijuana users will reach a state of "delirium or of actual madness." In most cases, they will report an increase in relaxation and euphoria and possibly enhancement of their senses, but an impairment of memory. These striking differences are probably due to the well-known biphasic activity of Δ^9-tetrahydrocannabinol (THC)—the psychoactive constituent—whose effects at low doses may be opposite to those produced by high doses. Moreau's volunteers presumably orally consumed large amounts of hashish, whereas today North Americans and Europeans usually smoke cannabis, and most users adjust their dose to achieve the desired effects.

Surprisingly, research on cannabis advanced slowly. A major reason for the neglect was the lack of knowledge of its basic chemistry. Modern research—namely research over the past 150 years—is based on quantitative data. Unlike morphine and cocaine, which had been isolated and made available in the nineteenth century and thus could be quantitatively investigated in vitro, in animals, and in humans, the psychoactive constituent(s) of cannabis were not isolated and their structures were not elucidated until the 1960s; hence quantitative research was not possible before then.

It is conceivable that the material reaching Europe in the past varied widely in its contents; thus its medical use also was not reliable, and research with it was of little value. Indeed, around the beginning of the twentieth century cannabis almost disappeared, both as a medicinal agent and for recreational purposes in Europe and in North America. In addition, the anti-cannabis laws made research on it, particularly in academic institutions, very difficult. Indeed, from the early 1940s until the mid-1960s, research on cannabis was limited to a few scattered groups. This paucity of early research has now been more than compensated for by the avalanche of papers on the plant cannabinoids and on the endogenous cannabinoids. Not surprisingly, the burst of recreational marijuana use, in the mid-1960s in the United States and later in Europe, coincided with the new wave of research on cannabis.

Δ^9-Tetrahydrocannabinol and Cannabidiol

Over nearly a century, numerous attempts were made to isolate in pure form the active marijuana constituent(s) and to elucidate its (or their) structure(s), but these attempts were unsuccessful (Mechoulam & Hanus 2000). Now we can understand the reason for this lack of success. There are more than 60 cannabis constituents, with closely related structures and physical properties, making their separation difficult. With the advance of modern separation techniques, the isolation and the structure elucidation of the active principle, THC, was finally achieved in 1964 (Gaoni & Mechoulam 1964). Shortly thereafter, THC was synthesized (Mechoulam et al. 1967). Thus, THC became widely available for research, and several thousand papers have been published on it. Surprisingly, although most of the plant cannabinoids have now been identified—and their structures are related chemically—the only major mood-altering constituent is THC.

Another major plant cannabinoid is cannabidiol (CBD), which was isolated during the late 1930s, but its structure was elucidated only in 1963 (Mechoulam & Shvo 1963). As it does not parallel THC in its central nervous system (CNS) effects, initially only a limited amount of research was focused on it. However, over the past two decades CBD was found to be a potent anti-inflammatory agent, to attenuate the memory-impairing effects produced by THC, and to cause a plethora of other effects. Hundreds of publications have addressed its various actions (for a review, see Mechoulam et al. 2009). Both THC and CBD are present in the plant mainly as their nonpsychoactive carboxylic precursors (THC-acid and CBD-acid), which slowly lose their acidic function (decarboxylate) in the

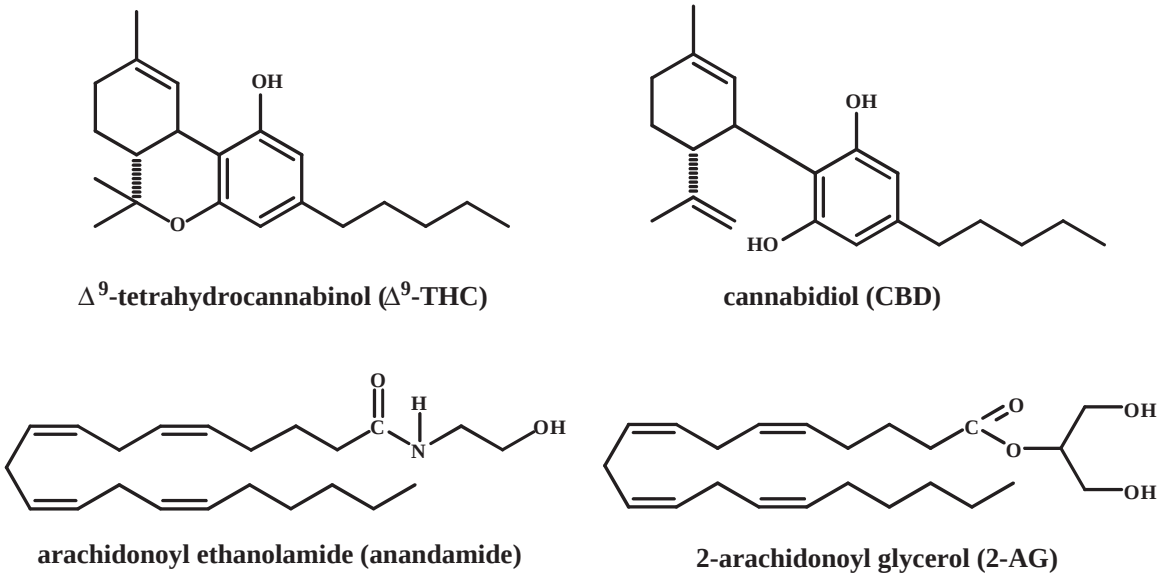

Figure 1

Structures of the plant cannabinoids Δ^9-tetrahydrocannabinol and cannabidiol and of the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol.

plant on heating. The structures of THC and CBD are presented in **Figure 1**.

The cannabis plant varieties differ tremendously in their contents. In industrial hemp the concentration of THC is less than 0.3%, in hashish in the 1960s it was about 5%, whereas in marijuana it was about 2% to 3%, but nowadays strains have been developed—mostly for illegal use—that contain up to 25%.

The Endocannabinoid Receptors

Originally it was assumed that cannabinoids act through a nonspecific membrane-associated mechanism; however, the very high stereospecificity of the action of some synthetic cannabinoids pointed to a more specific mechanism (Mechoulam et al. 1988). The first data indicating that cannabinoids may act through receptors were published by Howlett, who showed that cannabinoids inhibit adenylate cyclase formation, and the potency of the cannabinoids examined paralleled the level of their pharmacological action (Howlett et al. 1986). The same group shortly thereafter indeed reported the existence of binding sites in the brain (Devane et al. 1988). Their distribution was found to be consistent with the pharmacological properties of psychotropic cannabinoids (Herkenham et al. 1990), and the receptor was cloned (Matsuda et al. 1990). A second, peripheral receptor, CB2, was later identified in the spleen (Munro et al. 1993). Both CB1 and CB2 receptors belong to the superfamily of G protein–coupled receptors (GPCRs). The two cannabinoid receptors exhibit 48% amino acid sequence identity. Both receptor types are coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase (for a detailed review on the pharmacology of cannabinoids, see Howlett et al. 2002).

The CB1 Receptor

It was originally believed that the CB1 receptor was expressed mainly in the CNS, and hence it was considered a brain cannabinoid receptor. We are now aware that it is present in numerous peripheral organs, although in some of them the receptor levels are low. CB1 receptors are

among the most abundant GPCRs in the brain. The highest densities of CB1 receptors, in the rodent brain, are noted in the basal ganglia, substantia nigra, globus pallidus, cerebellum, and hippocampus, but not in the brainstem. The high CB1 levels in the sensory and motor regions are consistent with the important role of CB1 receptors in motivation and cognition. CB1 receptors appear to be involved in γ-aminobutyric acid (GABA) and glutamate neurotransmission, as they are found on GABAergic and glutamatergic neurons (Howlett et al. 2002). The CB1 receptor is present and active from the earliest phases of ontogenetic development, including during the embryonal stages, which indicates that it is of importance in neuronal development and newborn suckling (Fride et al. 2009). Surprisingly the CB1 receptor levels in rats are increased on transition from adolescence [postnatal days (PND) 35–37] to adulthood (PND 70–72), a pattern that is opposite to that of other neuroreceptor systems (Verdurand et al. 2012). Also, unexpectedly, ligands that interact similarly with CB1 receptors may have significantly different pharmacological profiles. This may be due to the ability of CB1 receptors to form heteromeric complexes with other GPCRs (Pertwee et al. 2010).

The distribution of CB1 receptors differs in neonatal brain and adult brain. It is abundant in white matter areas at the early age but is much less abundant later (Romero et al. 1997). It is of interest to determine whether this difference has anything to do with the behavioral landmarks associated with different ages.

The CB1 receptors are found primarily on central and peripheral neurons in the presynapse. These locations facilitate their inhibition of neurotransmitter release, which is one of the major functions of the endocannabinoid system. Activation of CB1 receptors leads to a decrease in cyclic adenosine monophosphate (cAMP) accumulation and hence to inhibition of cAMP-dependent protein kinase (PKA). CB1 receptor activation leads to stimulation of mitogen-activated protein (MAP) kinase activity, which is a mechanism by which cannabinoids affect synaptic plasticity, cell migration, and possibly neuronal growth (Howlett et al. 2002). CB1 receptors are also coupled, again through G proteins, to several types of calcium and potassium channels.

Several types of CB1 receptor gene knockout mice are available and are widely used (Zimmer et al. 1999). CB1 receptor gene polymorphisms have been observed, and their importance is yet unknown, although susceptibility to addiction and neuropsychiatric conditions has been suggested (Zhang et al. 2004).

The CB2 Receptor

It was originally assumed that CB2 receptors were present only in cells of the immune system; however, they have now been identified throughout the CNS (Ashton et al. 2006, Onaivi et al. 2008a, van Sickle et al. 2005), particularly in microglial cells (Nunez et al. 2004, Stella 2004), though at lower levels than those of the CB1 receptors. Under some pathological conditions, CB2 receptor expression is enhanced in the CNS as well as in other tissues. It seems possible that the CB2 receptor is part of a general protective system (for a review, see Pacher & Mechoulam 2011). In that review, we speculated that "The mammalian body has a highly developed immune system which guards against continuous invading protein attacks and aims at preventing, attenuating or repairing the inflicted damage. It is conceivable that through evolution analogous biological protective systems have evolved against nonprotein attacks. There is emerging evidence that lipid endocannabinoid signaling through CB2 receptors may represent an example/part of such a protective system" (Pacher & Mechoulam 2011, p. 194). In view of the various protective effects associated with the CB2 receptor, several synthetic CB2-specific receptor agonists, which do not bind to the CB1 receptor, have been synthesized. HU-308 was one of the first such compounds reported (Hanus et al. 1999); however, numerous additional ones are now known, and since they do not cause the psychoactive effects associated with CB1 agonists, several pharmaceutical firms are presently active in the field.

CB2 receptor agonists might be expected to become drugs in various fields, including neuropsychiatric, cardiovascular, and liver disease.

Endogenous Cannabinoid Agonists

The discovery of the cannabinoid receptors suggested that endogenous molecules, which may stimulate (or inhibit) the receptors, are presumably present in the mammalian body. The plant constituent THC, which, apparently by a quirk of nature, binds to these receptors, is a lipid compound; hence it was assumed that any possible endogenous cannabinoid molecules (endocannabinoids) would also be lipids. Indeed, we were able to isolate and identify two compounds, one from brain—which we named anandamide, based on the Sanskrit word *ananda* ("supreme joy")—and a second one [2-arachidonoyl glycerol (2-AG)] from peripheral tissues (Devane et al. 1992, Mechoulam et al. 1995). Their structures are presented in **Figure 1**. These two endogenous cannabinoids have been investigated in great detail (for a review, see Howlett et al. 2002). Additional endogenous molecules that bind to the cannabinoid receptors have been identified, but some of them may be artifacts, and interest in them is negligible.

Unlike most neurotransmitters (e.g., acetylcholine, dopamine, and serotonin), anandamide and 2-AG are not stored in vesicles but rather are synthesized when and where they are needed. Again, unlike most neurotransmitters, their action is not postsynaptic but rather mostly presynaptic, i.e., they serve as fast retrograde synaptic messengers (Howlett et al. 2002). However, whether both endocannabinoids, or only 2-AG, serve as fast retrograde synaptic messengers remains to be established. Thus 2-AG, after its postsynaptic synthesis, crosses the synapse and activates the cannabinoid presynaptic receptor, which makes possible the inhibition of various neurotransmitter systems that are present there. This is a primary activity of the endocannabinoids.

Contrary to THC, which is metabolized over several hours and excreted (or stored as one of its metabolites), endocannabinoids are rapidly removed by a membrane transport process yet to be fully characterized (Fu et al. 2011). In the cell, anandamide is hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH). 2-AG is also hydrolyzed enzymatically, both by FAAH and by monoacyl hydrolases. Suppression of these enzymes prolongs the activity of the endocannabinoids (Gaetani et al. 2009).

Although there is solid evidence that the activation of presynaptic CB1 receptors can lead to inhibition of the release of a number of different excitatory or inhibitory neurotransmitters both in the brain and in the peripheral nervous system, there is also in vivo evidence that CB1 receptor agonists can stimulate dopamine (DA) release in the nucleus accumbens (Gardner 2005). This effect apparently stems from a cannabinoid receptor-mediated inhibition of glutamate release. Indeed, many of the actions of cannabinoid receptor agonists (including endocannabinoids) are dose-dependently biphasic (Sulcova et al. 1998). Endocannabinoids also exhibit an "entourage effect"—namely enhancement of their activity by structurally related, biologically inactive, endogenous constituents (Ben-Shabat et al. 1988). The multiple functions of endocannabinoid signaling in the brain have recently been very well reviewed (Katona & Freund 2012).

In the following review of the effects of brain endocannabinoids and related fatty acid amides of amino acids (FAAAs) and closely related compounds on emotions and cognition, we summarize the large number of published observations. It seems that many of the FAAAs in the CNS that have been investigated—and most have not been investigated yet—have significant effects. If we assume that the dozens of compounds of this type present in the brain are not biosynthesized by mistake but rather play some physiological role, it is tempting to speculate that their levels and their interactions may be of importance in the profile of emotions and possibly of individual personalities. This topic is further discussed in the Conclusions section of this review.

THE CANNABINOID SYSTEM IN ANXIETY AND DEPRESSION

Freud considered the problem of anxiety a "nodal point, linking up all kinds of most important questions; a riddle, of which the solution must cast a flood of light upon our whole mental life" (Freud 1920). We have made some progress since Freud's time, but according to the National Institute of Mental Health, anxiety disorders still affect about 40 million people in the United States alone, and antianxiety drugs are among the top prescription drugs.

Cannabis has been used for millennia as a medicinal agent (Mechoulam 1986). In India, bangue (the local name for cannabis at the time) was believed to help the user to be "delivered from all worries and care" (Da Orta 1563), and its extensive present-day use throughout the world is presumably due, in part at least, to the same effects. For recent reviews on cannabis and anxiety, see Gaetani et al. (2009), Moreira & Wotjak (2010), Parolaro et al. (2010), and Zanettini et al. (2012). For general reviews on the endocannabinoid system, including detailed data on anxiety and depression and emerging pharmacotherapy, see Pacher et al. (2006) and Pertwee (2009).

A few years ago the major pharmaceutical firm Sanofi-Aventis developed and initiated marketing for an antagonist (or more precisely an inverse agonist) of the CB1 receptor. Because CB1 agonists enhance appetite, such a drug could become a major weapon against obesity. Many other companies had related compounds in various stages of development. The Sanofi compound, named rimonabant, indeed affected obesity and even blocked the psychoactive effects of THC, including short-term memory and lowered cocaine-seeking responses to suitable cues (in animals). However, although psychiatric disorders were indicated as exclusion criteria, rimonabant-treated patients had enhanced anxiety problems and suicidal tendencies (Christensen et al. 2007), and the drug had to be withdrawn from the market. This rather expensive proof is a further addition to previous evidence, indicating the importance of the CB1 cannabinoid system in anxiety. Interestingly, Lazary et al. (2011) have recently suggested that as some variants of the CB1 receptor gene contribute more significantly than others to the development of anxiety and depression, by genomic screening—possibly in combination with the gene of the serotonin transporter—high-risk individuals could be identified and excluded from the treatment population and thus CB1 antagonists could still be useful. Such screening and treatment would represent a model for modern personalized medicine.

As mentioned previously, many of the psychological effects of cannabis, as well as of THC, are biphasic, depending principally on the dose level and to a certain extent upon the personality of the user. In normal subjects, THC may cause either euphoria and relaxation or dysphoria and anxiety (D'Souza et al. 2004, Wade et al. 2003). Pure THC may not entirely mimic the effects of cannabis, which contains additional cannabinoid constituents, such as CBD, that modulate the effect of THC. Besides, CB1 receptors rapidly desensitize following the administration of agonists, further diminishing the effect of agonists.

Cannabidiol, which does not bind to either CB1 or CB2, possesses anxiolytic and antipsychotic properties (Mechoulam et al. 2002) both in animals and in humans. It shows anxiolytic-like effects with mice in the elevated plus maze and in the Vogel conflict test (Guimarães et al. 1990, Moreira et al. 2006). In humans it was found to lower anxiety in stressful situations (Bergamaschi et al. 2011). The mode of action of CBD as an anxiolytic molecule is not well understood. Most probably it involves action as a serotonin receptor 1A (5-HT_{1A}) agonist (Campos & Guimaraes 2008), enhancement of adenosine signaling through inhibition of uptake (Carrier et al. 2006), or inhibition of the GPR55 receptor (Sharir & Abood 2010).

Endocannabinoids and Anxiety

There are no direct experimental data on the role of endocannabinoids on anxiety in

humans. To our knowledge neither anandamide nor 2-AG has ever been administered to human subjects. This is an absurd situation, presumably a result of regulatory limitations. By contrast, when insulin was discovered in the 1920s, it became an available drug within a year. We can only assume that, because many of the physiological systems are regulated through checks and balances by a variety of endogenous molecules, the endocannabinoids, which affect neurotransmitter release, apparently exert such an action on anxiety, which is a normal human reaction to a variety of stressful conditions.

Considerable data exist on the direct effects of endocannabinoids on anxiety in animals. Rubino et al. (2008) have shown that methanandamide (a stable analog of anandamide) injected into the prefrontal cortex of rats leads to an anxiolytic response. However, large increases of the dose administered led to an anxiogenic response due to TRPV1 stimulation.

An indirect pathway for enhancement of endocannabinoid levels is by blocking their enzymatic hydrolysis. The Piomelli group (Kathuria et al. 2003) reported a novel class of potent, selective, and systemically active carbamate-based inhibitors of FAAH, the enzyme responsible for the degradation of anandamide. The best inhibitors in this series (URB532 and URB597) had anxiolytic properties in rats in the elevated zero-maze test and suppressed isolation-induced vocalizations due to augmented brain levels of anandamide. These effects could be prevented by blockage of the CB1 receptor. These results indirectly confirmed that anandamide has antianxiety properties. The rationale behind this approach is based on the mechanism of anandamide formation and release, which is known to take place when and where needed. As mentioned above, contrary to the classical neurotransmitters, anandamide is not stored in synaptic vesicles but rather is synthesized and released in the synaptic cleft following neuronal activation. Presumably its levels and those of FAAH in anxiety and depression will be highest in the brain areas involved in the regulation of mood and emotions. Therefore, inhibition of anandamide metabolism would enhance CB1 activation mainly where anandamide levels are highest. Following the same experimental rationale, Moise et al. (2008) confirmed that URB597 inhibited FAAH activity and led to elevated levels of additional fatty acid amides (N-palmitoyl ethanolamine and N-oleoyl ethanolamine), but not of anandamide itself, in hamster brain. However, Cippitelli et al. (2008) have reported an elevation of anandamide levels in rats with URB597, which was found to reduce anxiety associated with alcohol withdrawal. Blockade of the CB1 receptor with rimonabant induced anxiogenic-like behavior in the elevated plus maze; URB597 induced anxiolytic-like effects in this assay. URB597 did not alter unconditioned or conditioned social defeat or rotarod performance.

Enhancement of 2-AG levels produces similar effects. Sciolino et al. (2011) have shown that enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-AG-hydrolyzing enzyme monoacylglycerol lipase (MGL), produces anxiolytic effects under conditions of high environmental aversiveness in rats.

Recently, two parallel publications indicated that the CB2 receptor is also involved in endogenous antianxiolytic activity. García-Gutiérrez & Manzanares (2011) reported that mice overexpressing the CB2 receptor showed lower anxiety-like behaviors in the open field, the light-dark box, and the elevated plus maze tests, indicating that increased expression of the CB2 receptor significantly modifies the response to stress in these tests. Busquets-Garcia et al. (2011), using doses of URB597 and JZL184 that selectively modulated the concentrations of anandamide and 2-AG, respectively, recorded similar anxiolytic-like effects in two behavioral paradigms. However, whereas the anxiolytic-like effects of URB597 were mediated through a CB1-dependent mechanism, the anxiolytic-like effects of JZL184 were CB1 independent. The anxiolytic-like effects of JZL184 were absent in CB2 knockout mice and were prevented by pretreatment with selective CB2 antagonists. These two

publications indicate the crucial role of the CB2 receptor on the modulation of anxiety. As activation of the CB2 receptor does not lead to undesirable psychoactivity, these observations may be of significant clinical importance, and therefore the CB2 receptor represents a novel target to modulate anxiety-like responses. The protective effect of the CB2 receptor is in line with our previous suggestion that this receptor is part of a general protective mechanism (Pacher & Mechoulam 2011).

The molecular mechanism of the effect of endocannabinoids on anxiety is still to be fully clarified. Andó et al. (2012) have confirmed considerable involvement of CB1 receptors in the effect of exo- and endocannabinoids on GABA efflux. However, they also found that CB2-like receptors are likely involved. Hofmann et al. (2011) have described a new form of cannabinoid-mediated modulation of synaptic transmission, so far in the dentate gyrus only. They report that anandamide action under certain conditions is not mediated by CB1 receptors, CB2 receptors, or vanilloid type I receptors, and is still present in $CB1^{-/-}$ animals. It would be of interest to determine whether this new pathway (through a receptor?) is involved in anxiety and depression.

The endocannabinoid system plays a gatekeeper role with regard to activation of the hormonal hypothalamic-pituitary-adrenal (HPA) axis. Tonic endocannabinoid signaling constrains HPA axis activity, ultimately habituating the stress response and restoring homeostasis. Specifically, glucocorticoids produced in response to stress recruit endocannabinoids to increase the excitability of principal neurons in the prelimbic region of the medial prefrontal cortex; the principal neurons initiate inhibitory relays terminating HPA axis activation (Hill et al. 2011). However, following chronic stress, endocannabinoid signaling downregulation is implicated in the overload of hormonal signaling that can result in anxiety and depression in humans. For an excellent review of this literature, see Riebe & Wotjak (2011).

The Endocannabinoid System, Neurogenesis, and Depression

Hill et al. (2008) have summarized the results of the experimental work done on the endocannabinoid system and depression and have concluded that research so far supports the assumption that hypofunctional endocannabinoid signaling contributes to depressive illness and that enhanced endocannabinoid signaling is associated with antidepressant efficacy. However, a hyperfunctional endocannabinoid system contributes to depression. This discrepancy was explained by showing that in the animal model of depression that was used, endocannabinoid signaling was differentially altered in various brain areas. The antidepressive drug imipramine affected some, though not all, of these changes.

In view of the excellent existing summary by Hill et al. (2008), in the present review we discuss mainly the relation between cannabinoids, their two known receptors, and neurogenesis. A leading current hypothesis of depression is that is it is linked with neurogenesis. This hypothesis is based on the downregulation of neurogenesis in depressive-like behaviors in animals and on its upregulation by antidepressant treatments.

Over the past few years, considerable data have indicated that the endocannabinoid system plays a central role in neurogenesis (for reviews, see Galve-Roperh et al. 2009, Oudin et al. 2011). It is established that CB1 mRNA is expressed in many regions of the developing brain (Buckley et al. 1998), activation of CB1 is required for the axonal growth response (Williams et al. 2003), the endocannabinoid system drives neural progenitor cell proliferation (Aguado et al. 2006), and cannabinoids actually promote neurogenesis (Berghuis et al. 2007). Reductions in adult neurogenesis were noted in CB1- and CB2-knockout mice (Aguado et al. 2006, Palazuelos et al. 2006). Jin et al. (2004) have reported that both CB1 and VR1 receptors are involved in adult neurogenesis.

Endocannabinoids, particularly 2-AG and diacylglycerol lipases (DAGLs), which are

involved in 2-AG synthesis, play a major role in axonal growth and guidance during development (Oudin et al. 2011). Harkany and colleagues (Keimpema et al. 2010) have shown that the synthesizing enzymes (the DAGLs) alone are not sufficient to account for the growth effect of 2-AG, but both the DAGLs and the degradation enzyme, MGL, play a role. However, MGL is temporally and spatially restricted from the neurite tip, thus enhancing 2-AG activity during axonal growth. The CB2 receptor has recently been shown to promote neural progenitor cell proliferation via mTORC1 signaling (Palazuelos et al. 2012).

Because depression decreases neurogenesis, the findings summarized above are particularly exciting, as they not only help us understand the role of endocannabinoids as endogenous antidepressants but also suggest that synthetic endocannabinoid-like compounds may be developed as a novel type of antidepressive drug.

Onaivi et al. (2008a) and van Sickle et al. (2005) have reported that, contrary to previous reports, CB2 receptors are present in the brain. This unexpected discovery led several groups to investigate the relevance of this receptor in various brain pathological states. Thus, transgenic mice overexpressing the CB2 receptor showed decreased depressive-like behaviors in several relevant assays. Also, contrary to wild-type mice, these transgenic mice showed no changes in BDNF gene and protein expression under stress (García-Gutiérrez et al. 2010). The Onaivi group reported that in Japanese depressed subjects there is high incidence of a certain polymorphism in the CB2 gene (Onaivi et al. 2008b). Hu et al. (2009) compared the antidepressant action of the CB2 agonist GW405833 with the action of desipramine in two antidepressive rodent assays—the time of immobility and a swimming assay. Although both desipramine and GW405833 significantly reduced immobility, contrary to desipramine, GW405833 had no effect in the swimming test. These results indicate that desipramine and cannabinoid drugs have different mechanisms in their antidepressive action.

These results together indicate that as increased CB2 receptor expression reduces depressive-related behaviors, apparently via a mechanism that differs from the mode of action of most antidepressants used at present, the CB2 receptor could be a novel therapeutic target for depression. It will be of interest to establish whether the activity of the CB2 receptor in depression is related to neurogenesis.

CANNABINOIDS AND REWARD SYSTEMS

Although the conditions under which cannabinoid drugs have rewarding effects are more restricted than with other drugs of abuse (such as cocaine and heroin), when they produce reward-related behavior, similar brain structures are involved (for an excellent recent review, see Serrano & Parsons 2011).

Rewarding/Aversive Effects of Cannabinoids

In humans, marijuana produces euphoria, but dysphoria, dizziness, and anxiety are also reported, probably the result of the previously mentioned biphasic effects of THC. Following administration of THC to humans, some studies have shown increased dopamine transmission (Bossong et al. 2009) but others have shown no change in dopamine transmission (Barkus et al. 2011) as measured by positron emission tomography. The endocannabinoid system may play a specific role in appreciation of rewards, as THC pretreatment attenuated the brain response to feedback of monetary rewards as measured by functional magnetic resonance imaging (fMRI) (van Hell et al. 2012).

In animal models, early research suggested that THC was not rewarding to monkeys (Harris et al. 1974) when assessed in the drug self-administration paradigm. In rodents, some investigators have reported that THC (as well as other abused drugs such as cocaine) reduces the threshold for electrical brain stimulation reward (Gardner et al. 1988), but other investigators report that it increases the

threshold (Vlachou et al. 2007). Unlike the self-administration paradigm, the conditioned place preference (CPP) paradigm can be used to assess both the rewarding and the aversive effects of drugs. Conflicting findings were reported in studies using the CPP paradigm with rodents. Early reports revealed that THC produced CPPs (Lepore et al. 1995), but other reports showed conditioned place aversions (e.g., Mallet & Beninger 1998a, Parker & Gillies 1995) due to differing CPP procedures. Indeed, unlike other rewarding drugs, such as cocaine or heroin, low-dose pre-exposure to the effects of THC is necessary to establish a CPP in rodents (Valjent & Maldonado 2000).

More recently, Tanda et al. (2000) have developed a very sensitive and reliable method of establishing self-administration in monkeys, which relies on the use of very low doses of THC but does not require pre-exposure to the drug. In addition, both anandamide (Justinova et al. 2005) and 2-AG (Justinova et al. 2011) are self-administered by monkeys with or without a cannabinoid self-administration history, and both effects are prevented by pretreatment with rimonabant, indicating that the rewarding effect is CB1 receptor mediated. Treatment with the FAAH inhibitor, URB597, shifts the anandamide self-administration dose-response curve to the left, such that anandamide has rewarding effects at lower doses (Justinova et al. 2008). However, URB597 is not self-administered by monkeys (Justinova et al. 2008) and does not produce a CPP in rats (Gobbi et al. 2005), possibly because it neither causes THC-like effects nor increases extracellular mesolimbic DA levels in rats (Justinova et al. 2008, Solinas et al. 2007). In contrast, DA is known to be released in the striatum by THC (Bossong et al. 2009). Cues associated with marijuana use also activate the reward neurocircuitry associated with addiction in humans (Filbey et al. 2009). Indeed, microinjections of THC into the posterior ventral tegmental area (VTA) and into the posterior shell of the nucleus accumbens (NAcc) serve as rewards for both self-administration and CPP in rats (Zangen et al. 2006).

Cannabinoids and Relapse

Treatment of addiction is often hindered by the high rate of relapse following abstinence from the addicting drug. Multiple factors such as exposure to drug-associated stimuli, drug priming, and stress can precipitate drug craving and relapse in humans. In humans, alterations in the CB1 receptor gene and in the FAAH gene have been shown to enhance fMRI activity in reward-related areas of the brain during exposure to marijuana cues (Filbey et al. 2010).

Considerable recent research suggests that CB1 receptor antagonism (or inverse agonism) interferes with drug- and cue-induced relapse in animal models. Relapse is characterized by drug-seeking behavior in extinction triggered by renewed exposure to drug-associated cues or a priming dose of a drug itself (Everitt & Robbins 2005). Such drug-seeking behavior contrasts with actual drug-taking behavior during the self-administration session. Rimonabant prevents drug-associated cues from producing relapse following extinction training in rats and mice (De Vries & Schoffelmeer 2005). Recent evidence suggests that rimonabant is relatively more effective in interfering with drug-seeking behavior than drug-taking behavior (De Vries & Schoffelmeer 2005). In an early report, the CB1 receptor agonist, HU-210, was shown to reinstate cocaine seeking following long-term extinction of cocaine self-administration (De Vries et al. 2001), an effect that was prevented by rimonabant. Of most therapeutic importance, however, was that rimonabant alone blocked drug seeking evoked by the cocaine-paired cues and by a priming injection of cocaine, as well as seeking of heroin (De Vries et al. 2005, Fattore et al. 2003), methamphetamine (Anggadiredja et al. 2004), and nicotine (De Vries et al. 2005) evoked by drug-associated cues and by a priming injection of the drug itself. Therefore, blockade (or inverse agonism) of the CB1 receptor interferes generally with drug-seeking behavior.

Drug-seeking behavior represents the incentive motivational effects of addictive drugs under control of the mesolimbic DA system.

The regulation of the primary rewarding effects of drugs of abuse may be in part controlled by endocannabinoid release in the VTA, which produces inhibition of the release of GABA, thus removing the inhibitory effect of GABA on dopaminergic neurons (Maldonado et al. 2006). In the NAcc, released endocannabinoids act on CB1 receptors on axon terminals of glutamatergic neurons. The resulting reduction in the release of glutamate on GABA neurons that project to the VTA results in disinhibition of the VTA dopamine neurons. Blockade of CB1 receptors attenuates the release of DA in the NAcc in response to rewarding medial forebrain bundle electrical stimulation (Trujillo-Pisanty et al. 2011). The prefrontal cortex and NAcc appear to play a primary role in the prevention of cue-induced reinstatement of heroin (Alvarez-Jaimes et al. 2008) and cocaine (Xi et al. 2006) seeking by CB1 antagonism.

Although blockade of CB1 receptors affects cue- and drug-induced relapse, it does not appear to affect cocaine seeking that is reinstated by exposure to mild footshock stress (De Vries et al. 2001). Indeed, stress-induced relapse to heroin or cocaine seeking is much more sensitive to manipulations of the corticotrophin-releasing factor and noradrenaline systems than the DA system (Shaham et al. 2000). For instance, infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala prevents footshock-induced but not cocaine-induced reinstatement of cocaine seeking (Leri et al. 2002).

Rimonabant showed great promise as an antirelapse treatment; however, as mentioned above, it was removed from the European market as a treatment for obesity because of the undesirable side effects of anxiety. The generality of the effects of cannabinoids on motivational processes may explain these undesirable side effects. Given that rimonabant not only acts as a CB1 antagonist but is also a CB1 inverse agonist, the relapse-preventing properties, and potentially the adverse side effects, may also be mediated by its inverse cannabimimetic effects that are opposite in direction from those produced by cannabinoid receptor agonists (Pertwee 2005). Recent evidence suggests that at least some adverse side effects of CB1 receptor antagonists/inverse agonists seen in clinical trials (e.g., nausea) may reflect their inverse agonist properties (Bergman et al. 2008). It will be of interest to evaluate the potential of more newly developed CB1 receptor neutral antagonists, such as AM4113 (Sink et al. 2008), to prevent drug-seeking behavior.

Recently, selective CB2 receptor agonists were shown to inhibit intravenous cocaine self-administration, cocaine-enhanced locomotion, and cocaine-enhanced accumbens extracellular dopamine in wild-type and CB1 receptor knockout mice but not in CB2 knockout mice. This effect was blocked by a selective CB2 receptor antagonist. These findings suggest that brain CB2 receptors also modulate cocaine's effects (Xi et al. 2011). Again, as mentioned above, the CB2 receptor seems to have general protective properties (Pacher & Mechoulam 2011).

Although considerable evidence indicates that antagonism of the CB1 receptor interferes with cue- and drug-induced relapse, there is a growing literature suggesting that FAAH inhibition and cannabidiol also prevent relapse to drug seeking. FAAH inhibition has been selectively evaluated for prevention of nicotine seeking (Forget et al. 2009, Scherma et al. 2008). However, it is not clear if these effects are mediated by the action of anandamide or other fatty acids [oleoylethanalamide (OEA) and palmitoylethanalamide (PEA)], which act on peroxisome proliferator-activated receptor-α (PPAR-α) receptors, because Mascia and colleagues (2011) recently showed that selective PPAR-α agonists also counteract the reinstatement of nicotine seeking in rats and monkeys. Thus, elevations in fatty acids produced by blockade of FAAH may have potential in treating relapse. Most recently, Cippitelli et al. (2011) found that FAAH inhibition reduced anxiety produced by nicotine withdrawal. Cannabidiol, the nonpsychoactive compound in marijuana, also attenuated cue-induced reinstatement of heroin seeking as well as restored disturbances of glutamatergic and endocannabinoid systems

in the accumbens produced by heroin seeking (Ren et al. 2009). Apparently, in addition to the many other ailments that cannabidiol improves (Mechoulam et al. 2002), it may also be a potential treatment for heroin craving and relapse.

CANNABINOIDS AND COGNITION

Cognition involves the ability to acquire, store, and later retrieve new information. Several recent reviews are available on the effects of cannabis on cognition in humans and other animals (Akirav 2011, Marsicano & Lafenetre 2009, Ranganathan & D'Souza 2006, Riedel & Davies 2005). Clearly, the chief psychoactive component in cannabis, THC, produces acute cognitive disturbances in humans and animals, more profoundly affecting short-term than long-term memory.

Effects of Cannabis on Cognition in Humans

When under the influence of THC, humans demonstrate transient impairment in short-term episodic and working memory and consolidation of these short-term memories into long-term memory, but no impairment in retrieval of information once it has been previously encoded into long-term storage (Ranganathan & D'Souza 2006). However, a recent naturalistic study revealed that cannabidiol prevented the memory-impairing effects of acute THC in humans (Morgan et al. 2010). Therefore, the relative THC/cannabidiol ratio in cannabis will profoundly modify the effects of cannabis on memory in human marijuana smokers.

The effect of chronic cannabis exposure on cognitive abilities of abstinent individuals is, however, controversial and fraught with contradictions in the literature. Polydrug abuse and pre-existing cognitive and emotional differences between cannabis users and nonusers make interpretation of the human literature problematical. In a review of the literature, Solowij & Battisti (2008) conclude that chronic exposure to marijuana is associated with dose-related cognitive impairments, most consistently in attention and working memory functions—not dissimilar to those observed under acute intoxication. On the other hand, several reports indicate that few, if any, cognitive impairments are produced by heavy cannabis use over several years (e.g., Dregan & Gulliford 2012, Lyketsos et al. 1999). More recently, a thorough review of the specific versus generalized effects of drugs of abuse on cognition (Fernandez-Serrano et al. 2011) reported that there has been only one study (Fried et al. 2005) of "pure" cannabis users. Fried et al. (2005) conducted a longitudinal examination of young adults using neurocognitive tests that had been administered prior to the first experience with marijuana smoke. Individuals were defined (by urination samples and self-reports) as light (fewer than five times a week) or heavy (greater than five times a week) current or former (abstinent for at least three months) users. Current heavy users performed worse than nonusers in overall IQ, processing speed, and immediate and delayed memory tests. In contrast, former heavy marijuana smokers did not show any cognitive impairment. Fernandez-Serrano et al. (2011) conclude that the acute effects of cannabis on prospective memory are attenuated in long-term abstinence (at least three months).

Drawing conclusions from the human literature is challenging (Ranganathan & D'Souza 2006) because of widely differing methodologies, including different tasks, lack of sufficient controls, participant selection strategies (only experienced cannabis users included in samples), different routes of administration, different doses administered, often small sample sizes, tolerance of and dependence on cannabinoids, and the timing of the test (given the long half-life of THC). In addition, factors such as a predisposition to substance use in general may confer greater vulnerability to cannabis-related cognitive effects. Therefore, experimental investigation of the effects of cannabinoids on various processes involved in learning and memory rely heavily upon animal models. These models provide insights into the critical role of the

endocannabinoid system in the physiology of learning and memory.

Effects of CB1 Agonists on Learning and Memory in Nonhumans

Consistent with the human literature, most reports using animal models suggest that acute administration of CB1 agonists selectively disrupts aspects of short-term or working memory while leaving retrieval of previously learned memory (long-term or reference memory) largely intact. A common behavioral paradigm designed to evaluate these different aspects of memory is the delayed matching (or nonmatching) to sample (DMS) task. Once the animal has learned to perform this operant task (reference memory), it must then indicate (usually by pressing a bar) which test sample matches (or does not match) the original sample stimulus presented several seconds earlier (working memory). CB1 agonists (THC and WIN-55,212) disrupt accuracy of such performance in a delay-dependent manner, consistent with a selective disruption of working memory (Heyser et al. 1993). These effects are blocked by the CB_1 antagonist rimonabant. It is important to note that these effects occur at doses that do not interfere with the acquisition of the original reference memory of the task. A simpler variant of the DMS procedure used in rodents, the spontaneous object recognition task, does not rely upon prior operant training, but instead relies upon a rodent's natural preference to explore novel objects. In this task, a rat or mouse is allowed to spontaneously explore two identical objects, then after a delay is given a choice to explore a novel object or the previously presented sample object. In this measure of short-term memory, CB1 agonists (WIN-55,212 and CP55,940) produced a delay-dependent deficit in discrimination between the novel and familiar objects in the choice task (O'Shea et al. 2004, Schneider & Koch 2002), with the disruptive effect enhanced 21 days after chronic pretreatment in adolescents but not adults (O'Shea et al. 2004).

Spatial memory tasks also rely upon accurate working memory. A demanding spatial memory task is the 8-arm radial maze, which requires rats to first learn which arms contain food rewards (reference memory) and then to remember which arms have already been visited in a test session (working memory) after an imposed delay. THC increases the number of working memory errors (re-entries) at low doses, and these effects are blocked by rimonabant (Lichtman & Martin 1996). The impairment of working memory by THC (5 mg/kg) in adult rats is enhanced following chronic exposure (once a day for 90 days), but disappears following 30 days of abstinence from the drug (Nakamura et al. 1991). On the other hand, adolescent rats treated with very high escalating doses of THC (2.5–10 mg/kg) chronically for 10 days and left undisturbed for 30 days until their adulthood exhibited greater impairment in spatial working memory on the radial arm maze than did vehicle controls. The working memory deficit was also accompanied by a decrease in hippocampal dendritic spine density and length (Rubino et al. 2009).

The commonly employed spatial memory task, the Morris water maze, requires animals to navigate in a pool of water to locate a hidden platform by learning its location relative to salient visual cues. The water maze task can be used to evaluate the effect of cannabinoid agonists on reference memory (location of the platform remaining fixed across days and on trials within a day) and working memory (location of platform is changed each day, but remains constant across trials within a day). In the water maze task, THC disrupts working memory at much lower doses than those that disrupt reference memory; in fact, doses sufficient to disrupt working memory are below those that produce other effects characteristic of CB1 agonism, including antinociception, hypothermia, catalepsy, or hypomotility (Varvel et al. 2001). Vaporized marijuana smoke produces a similar effect (Niyuhire et al. 2007a).

Although exogenous CB1 agonists consistently suppress working memory in these models, manipulations that elevate endogenous cannabinoids do not consistently produce such an impairment. On the one hand, elevation

of anandamide (by FAAH inhibition), but not 2-AG (by MGL inhibition), interfered with the consolidation of contextual conditioned fear and object recognition memory (Busquets-Garcia et al. 2001); on the other hand, several other studies have reported facilitation of working memory by FAAH inhibition (Campolongo et al. 2009a, Mazzola et al. 2009, Varvel et al. 2007). Likewise, FAAH-deficient mice (with tenfold increases in brain levels of anandamide) also showed improved rather than impaired performance in this task. Therefore, the effects of exogenously administered CB1 agonists are not always consistent with the effects of manipulations that elevate the natural ligands for the receptors. However, FAAH inhibition also elevates several other fatty acids, including OEA and PEA, which are ligands for PPAR-α. Mazzola et al. (2009) recently found that the enhanced acquisition of a passive avoidance task by the FAAH inhibitor, URB597, was not only reversed by a CB1 antagonist, but also by a PPAR-α antagonist (MK 886). The PPAR-α agonist (WAY1463) also enhanced passive avoidance performance, and this effect was blocked by a PPAR-α antagonist (Campolongo et al. 2009a). Therefore, FAAH inhibition may enhance memory not only by increasing anandamide, but also by elevating OEA and PEA. Most recently, Pan et al. (2011) reported that MGL knockout mice, with elevated levels of 2-AG, show improved learning in an object recognition and water maze task. Thus, there is evidence that both anandamide and 2-AG enhance learning and memory under some conditions.

Effects of CB1 Antagonists on Learning and Memory in Nonhumans

The findings that CB1 agonists produce working memory deficits suggest that inhibition of these receptors may lead to enhancement of short-term memory. However, the literature is replete with mixed findings. CB1 antagonist administration produces memory enhancement in mice in an olfactory recognition task (Terranova et al. 1996) and a spatial memory task in an 8-arm radial maze (Lichtman 2000). In addition, CB_1-/- mice are able to retain memory in an object recognition test for at least 48 hours after the first trial, whereas wild-type controls lose their capacity to retain memory after 24 hours (Reibaud et al. 1999). In contrast, studies using other paradigms, such as the DMS, have shown no benefits of rimonabant on learning or memory (e.g., Hampson & Deadwyler 2000, Mallet & Beninger 1998b). One explanation (Varvel et al. 2009) for the mixed findings is that the temporal requirements of the task predict the potential of CB1 antagonism to facilitate or not facilitate performance. Studies showing enhancement of memory generally require memory processes lasting minutes or hours, whereas studies showing that rimonabant is ineffective generally require retention of information lasting for only seconds, suggesting that blockade of CB1 receptors may prolong the duration of a memory rather than facilitate learning. If this is the case, then rimonabant may facilitate retention of memories tested after long intervals but may have no benefits in tasks such as DMS and repeated acquisition that require rapid relearning of new information (for review, see Varvel et al. 2009).

Role of Endocannabinoids in the Hippocampus in Learning and Memory

The decrement in working memory by cannabinoids appears to involve their action at the hippocampus. The hippocampus is one of the areas of the brain with the highest density of CB1 receptors, and large amounts of anandamide are found in the rodent hippocampus. Interestingly, the selective detrimental effect of CB1 agonists on working memory (but not reference memory) resembles the effects of hippocampal lesions on these two forms of memory (Hampson & Deadwyler 2000, Heyser et al. 1993). Furthermore, THC-induced deficits in the DMS paradigm are associated with specific decreases in firing of individual hippocampal neurons during the sample but not the match part of the experiment (Heyser et al. 1993). Intracranial administration of the CB1 agonists

directly into the hippocampus also disrupts working memory performance in an 8-arm radial maze (Lichtman et al. 1995, Wegener et al. 2008), water maze spatial learning (Abush & Akirav 2010), and object recognition memory (Clarke et al. 2008). In contrast, intrahippocampal AM251 also has been shown to disrupt memory consolidation of an inhibitory avoidance task (de Oliveira et al. 2005). Recent work suggests that the cannabinoid and the cholinergic systems in the hippocampus interact during performance of a short-term memory task in the rat (Goonawardena et al. 2010). These effects may be mediated by cannabinoid-induced decreases in acetylcholine release in the hippocampus. Acetylcholine is also implicated in the pathophysiology of Alzheimer's disease and other disorders associated with declined cognitive function.

Overall, the literature implicates changes in hippocampal functioning as the source of working memory deficits produced by THC, although other brain regions are currently being investigated as well (Marsicano & Lafenetre 2009). Cannabinoid receptors localized to different brain regions modulate distinct learning and memory processes, such that the role of endocannabinoids in other regions may be different than their role in the hippocampus. In fact, Campolongo et al. (2009b) showed that infusion of CB1 agonist WIN 55,212,2 into the basolateral amygdala actually enhanced consolidation of inhibitory avoidance learning by enhancing the action of glucocorticoids in this region. Consistently, Tan et al. (2011) found that delivery of a CB1 antagonist to this region interferes with olfactory fear conditioning. The differential effects of CB1 agonists on different brain regions may account for different findings reported between systemic and localized administration of cannabinoid agonists.

Long-term changes in synaptic strength are believed to underlie associative memory formation in the hippocampus and amygdala. The impairments in working memory produced by CB1 agonists may be the result of the suppression of glutamate release in the hippocampus, which is responsible for the establishment of long-term potentiation, a putative mechanism for synaptic plasticity (Abush & Akirav 2010, Shen et al. 1996). Retrograde signaling by endocannabinoids results in suppression of neurotransmitter release at both excitatory (glutamatergic) and inhibitory (GABAergic) synapses in the hippocampus in a short- and a long-term manner. Endocannabinoid-induced long-term depression (LTD) is one of the best examples of presynaptic forms of long-term plasticity. Recent evidence indicates that presynaptic activity coincident with CB1 receptor activation and NMDA receptor activation is required for some forms of endocannabinoid LTD. The long-lasting effects of LTD appear to be mediated by a CB1 receptor–induced reduction of cAMP/PKA activity in the hippocampus (Heifets & Castillo 2009).

Endocannabinoid Modulation of Extinction of Aversive Memory

Avoidance of aversive stimuli is crucial for survival of all animals and is highly resistant to extinction. Considerable evidence indicates that the endogenous cannabinoid system is specifically involved in extinction learning of aversively motivated learned behaviors (Marsicano et al. 2002, Varvel & Lichtman 2002). A seminal paper by Marsicano et al. (2002) reported that CB1 knockout mice and wild-type mice administered the CB1 antagonist rimonabant showed impaired extinction in classical auditory fear-conditioning tests, with unaffected memory acquisition and consolidation. This effect appeared to be mediated by blockade of elevated anandamide in the basolateral amygdala during extinction (Marsicano et al. 2002). Using the Morris water maze task, Varvel & Lichtman (2002) reported that CB1 knockout mice and wild-type mice exhibited identical acquisition rates in learning to swim to a fixed platform; however, the CB1-deficient mice demonstrated impaired extinction of the originally learned task when the location of the hidden platform was moved to the opposite side of the tank. Because animals deficient in CB1 receptor activity show impairments

in suppressing previously learned behaviors, CB1 agonists would be expected to facilitate extinction of learned behaviors in nondeficient animals. Indeed, WIN-55,212 facilitated extinction of contextual fear memory and spatial memory in rats (Pamplona et al. 2006).

The effect of enhancing the endogenous levels of anandamide by blocking its reuptake or by inhibiting FAAH during extinction learning has also recently been investigated. Chhatwal et al. (2005) reported that the reuptake blocker (and FAAH inhibitor) AM404 selectively facilitated extinction of fear-potentiated startle in rats, an effect that was reversed by rimonabant pretreatment. Varvel et al. (2007) reported that mice deficient in FAAH, either by genetic deletion ($FAAH^{-/-}$) or by pharmacological inhibition, displayed both faster acquisition and extinction of spatial memory tested in the Morris water maze; rimonabant reversed the effect of FAAH inhibition during both task phases. These effects appear to be specific to extinction of aversively motivated behavior, because neither CB1-deficient mice (Holter et al. 2005) nor wild-type mice treated with rimonabant (Niyuhire et al. 2007b) displayed a deficit in extinction of operant responding reinforced with food. Most recently, Manwell et al. (2009) found that the FAAH inhibitor URB597 promoted extinction of a conditioned place aversion produced by naloxone-precipitated morphine withdrawal but did not promote extinction of a morphine-induced or amphetamine-induced CPP.

It has been well established that extinction is not unlearning, but instead is new inhibitory learning that interferes with the originally learned response (Bouton 2002). The new learning responsible for extinction of aversive learning appears to be facilitated by activation of the endocannabinoid system and prevented by inhibition of the endocannabinoid system. More recent work has suggested that the apparent effects of manipulation of the endocannabinoids on extinction may actually reflect its effects on reconsolidation of the memory that requires reactivation (Lin et al. 2006, Suzuki et al. 2008). That is, every time a consolidated memory is recalled it switches to a labile state and is subject to being disrupted. Depending upon the conditions of retrieval and the strength of the original trace, these reactivated memories can undergo two opposing processes: reconsolidation, when the conditions favor the permanence of the trace, or extinction, when the conditions indicate that the memory has no reason to persist. Suzuki et al. (2008) have proposed that the endocannabinoid system is important for the destabilization of reactivated contextual fear memories; that is, reconsolidation or extinction relies on a molecular cascade (protein synthesis and cAMP response element-binding-dependent transcription) that is impeded by prior blockade of the CB1 receptors. Fear memory cannot be altered during restabilization if it was not previously destabilized via activation of the CB1 receptor. Whatever the actual mechanism for facilitated extinction of aversive memories with activation of the endocannabinoid system and inhibited extinction with inhibition of the endocannabinoid system, these results have considerable implications for the treatment of posttraumatic stress disorder. Progress in enhancing endocannabinoid signaling will be of great benefit in the treatment of this distressing disorder.

CONCLUSIONS

Cannabinoid research was originally initiated with the limited aim of understanding the action of an illicit drug. After the chemistry of the plant and the pharmacological and psychological actions of THC were elucidated—or actually only assumed to be elucidated—in the 1960s and early 1970s, research in the field waned. However, over a decade starting from the mid-1980s, two specific receptors and their ligands—the bases of the endocannabinoid system—were found to be involved in a wide spectrum of biological processes. This endocannabinoid system has opened new vistas in the life sciences, particularly in aspects associated with the CNS.

One of the main results of activation of the presynaptic CB1 receptor is inhibition of neurotransmitter release. By this mechanism the

endocannabinoids reduce excitability of presynaptic neurons. CB1 receptors are responsible for the well-known marijuana effects as well as for effects on cognition, reward, and anxiety. In contrast, a major consequence of CB2 receptor activation is immunosuppression, which limits inflammation and associated tissue injury. Enhancement of CB2 receptor expression and/or of endocannabinoid levels has been noted in numerous diseases, including CNS-related ones. Thus, a main result of CB2 receptor activation seems to be a protective effect in a large number of physiological systems.

In the present review we have summarized evidence that cannabinoids modulate anxiety, brain reward function, and cognition by acting at CB1 (and possibly CB2) receptors in distinct brain regions. The effects of cannabis on anxiety appear to relate to the dose of THC and are modulated by the anxiolytic action of cannabidiol (if present in the plant material). A major function of the endocannabinoid system is the homeostatic regulation of the HPA axis in response to stressors. Although THC does not appear to be as rewarding as other drugs of abuse (cocaine, heroin, amphetamine) in animal models of drug abuse, recent work suggests that under optimal conditions, animals do self-administer THC. The rewarding effects of THC are mediated by elevation of DA in the mesolimbic DA system. Blockade of CB1 receptors in this system interferes with the potential of drugs or drug-related cues (but not stress) to produce relapse in animal models.

Both the animal and human literatures suggest that CB1 agonists interfere with short-term working memory and may interfere with consolidation of these memories into long-term memories while leaving previously learned long-term reference memory intact. In cannabis, these effects of THC may be prevented by a sufficiently high dose of cannabidiol. In addition, the memory-impairing effects of THC are usually limited to the acute effects of the drug itself. Recent literature suggests that the endocannabinoid system may play an especially important role in the extinction of aversively motivated learning. Treatments that amplify the action of endocannabinoids may play a critical role in treating posttraumatic stress disorder in the future. Memory decline in aging may also be protected by the action of the endocannabinoid system. Mice lacking CB1 receptors showed accelerated age-dependent deficits in spatial learning as well as a loss of principal neurons in the hippocampus, which was accomplished by neuroinflammation (Albayram et al. 2011). These exciting findings suggest that CB1 receptors on hippocampal GABAergic neurons protect against age-dependent cognitive declines. In addition, interesting recent work suggests that cannabidiol reduces microglial activity after β-amyloid administration in mice and prevents the subsequent spatial learning impairment (Martin-Moreno et al. 2011), suggesting that this nonpsychoactive compound in marijuana may be useful in treating Alzheimer's disease. Cannabidiol has also been shown to recover memory loss in iron-deficient mice, a model of neurogenerative disorders (Fagherazzi et al. 2012).

A very large number of anandamide-like compounds, namely FAAAs or chemically related entities, have been found in the brain (Tan et al. 2010). The action of very few of them has been evaluated. However, those that have been investigated show a variety of effects. Arachidonoyl serine has vasodilator activity—an important protective property in some brain diseases—and lowers the damage caused by head injury (Cohen-Yeshurun et al. 2011). Surprisingly, this effect is blocked by CB2 antagonists, although this compound does not bind to the CB2 receptor. Apparently, its action is indirectly CB2 related. Oleoyl serine, which is antiosteoporotic, is also found in the brain (Smoum et al. 2010); oleoylethanolamide regulates feeding and body weight (Fu et al. 2005); stearoylethanolamide shows apoptotic activity (Maccarrone et al. 2002); the anti-inflammatory palmitoylethanolamide may also be protective in human stroke (Naccarato et al. 2010); arachidonoyl glycine is antinociceptive (Bradshaw et al. 2009); and arachidonoyl dopamine affects synaptic transmission in dopaminergic neurons

by activating both cannabinoid and vanilloid receptors (Marinelli et al. 2007). Presumably, the additional many dozens of related endogenous molecules found in the brain will also exhibit a wide spectrum of activities. Why does the brain invest so much synthetic endeavor (and energy) to prepare such a large cluster of related molecules rather than just a few of them?

If subtle chemical disparity is one of the causes for the variability in personality—an area in psychology that is yet to be fully understood—we may have to look for a large catalog of compounds in the brain with distinct CNS effects. Is it possible that the above-described large cluster of chemically related anandamide-type compounds in the brain is related to the chemistry of the human personality and the individual temperamental differences? It is tempting to assume that the huge possible variability of the levels and ratios of substances in such a cluster of compounds may allow an infinite number of individual differences, the raw substance which of course is sculpted by experience. The known variants of CB1 and FAAH genes (Filbey et al. 2010, Lazary et al. 2010) may also play a role in these differences. If this intellectual speculation is shown to have some factual basis, it may lead to major advances in molecular psychology.

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ORIGINAL INVESTIGATION

Anxiogenic-like effects of chronic cannabidiol administration in rats

Maha M. ElBatsh · N. Assareh · C. A. Marsden · D. A. Kendall

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Abstract
Rational Several pre-clinical and human-based studies have shown that acutely administered cannabidiol (CBD) can produce anxiolytic-like effects
Objectives The present study investigated the effects of chronic administration of CBD on rat behaviour and on the expression of brain proteins.
Methods Male Lister-hooded rats (150–200 g, n=8 per group) received daily injections of CBD (10 mg/kg, i.p.) for 14 days. The rats were subjected to two behavioural tests: locomotor activity and conditioned emotional response (CER). The expression of brain-derived neurotrophic factor (BDNF), its receptor tyrosine kinase B (Trk B), extracellular signal-regulated kinases (ERK1/2) and phospho-ERK1/2 and the transcription factor cyclic AMP response element binding protein activation (CREB) and phospho-CREB were determined in brain regions such as the frontal cortex and hippocampus using Western immunoblotting.
Results CBD significantly increased the time spent freezing in the CER test with no effect on locomotor activity. CBD significantly reduced BDNF expression in the hippocampus and frontal cortex with no change in the striatum. In addition, CBD significantly reduced TrkB expression in the hippocampus with a strong trend towards reduction in the striatum but had no effect in the frontal cortex. In the hippocampus, CBD had no effect on ERK1/2 or phospho-ERK2, but in the frontal cortex, CBD significantly reduced phospho-ERK1/2 expression without affecting total ERK.
Conclusion Chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported. In addition, CBD decreased the expression of proteins that have been shown to be enhanced by chronic treatment with antidepressant/anxiolytic drugs.

Keywords Cannabidiol · Anxiety · BDNF · ERK · CREB · Hippocampus · Cannabinoids

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Introduction

The *Cannabis sativa* plant contains at least 66 different cannabinoids, including the main psychoactive component, Δ^9-tetrahydrocannabinol (Δ^9-THC) and other non-psychoactive components such as cannabidiol (CBD) (Ashton 2001; Mechoulam and Hanus 2002). Although the relative amounts of phytocannabinoids in cannabis preparations are highly variable, the content of CBD can exceed that of THC, in cannabis resin for example (Potter et al. 2008). CBD represents one of the most promising candidates for clinical utilisation, in a variety of conditions, due to its lack of cognitive and psychoactive actions and its excellent tolerability in humans (Mechoulam and Hanus 2002). Retrospective studies in cannabis users and small clinical trials have shown that moderate recreational or medicinal use of cannabis in humans results in mood elevation with a reduction in stress, anxiety and depressive symptoms (Gruber et al. 1996; Williamson and Evans

2000), and some of these effects have been attributed to CBD. However, the molecular mechanisms underlying these effects are unclear, and several mechanisms of actions have been proposed for CBD, including diffuse targets within the endocannabinoid system (Bisogno et al. 2001), inhibition of serotonin reuptake and increased catecholaminergic activity (Russo and McPartland 2003), activation of serotonergic (5HT1A) receptors (Russo et al. 2005), transient receptor potential type V1 (TRPV1) (Bisogno et al. 2001) and V2 (TRPV2) (Qin et al. 2008) and enhancement of adenosinergic signalling (Carrier et al. 2006). CBD, unlike Δ^9-THC, has very low affinity for either cannabinoid CB1 or CB2 receptors (Petitet et al. 1998), but it has been shown to block the transport of anandamide, the archetypal endocannabinoid ligand (Bisogno et al. 2001) and to inhibit its enzymatic hydrolysis (Mechoulam and Hanus 2002). Thus, the action of CBD could involve other cannabinoid receptors such as the abnormal cannabidiol receptor, a non-CB1/non-CB2 receptor (Franklin and Stella 2003; Jarai et al. 1999). Actions of CBD at GPR55, an orphan G protein-coupled receptor, either as an agonist or antagonist have also been described (Oka et al. 2007; Ryberg et al. 2007).

Acute anxiolytic properties of CBD have been demonstrated in several preclinical studies that employed various paradigms such as the Vogel conflict test (Moreira et al. 2006), the elevated plus maze (Guimaraes et al. 1990) and fear conditioning (Lemos et al. 2010; Resstel et al. 2006). Recently, antidepressant-like effects have also been reported in mice following acute CBD administration (Zanelati et al. 2010). However, the effects of repeated CBD administration on affective behaviours in pre-clinical tests have not been reported.

The neurotrophin, brain-derived neurotrophic factor (BDNF), has been implicated in a variety of affective disorders including anxiety and depression (Bergami et al. 2009; Martinowich et al. 2007). Multiple classes of antidepressant drugs, as well as electroconvulsive shock treatment, can significantly increase BDNF messenger RNA (mRNA) expression in the hippocampus and prefrontal cortex (Duman and Monteggia 2006; Nibuya et al. 1995). This neurotrophin is thought to enhance neurogenesis (Li et al. 2008) via its receptor, tyrosine kinase B (TrkB), which activates a variety of downstream signalling pathways including extracellular signal-regulated kinases (ERKs) (Patapoutian and Reichardt 2001). Cyclic AMP response element binding protein activation (CREB) is one of the long-term transcriptional modulators that is thought to mediate the effects of antidepressants on BDNF expression (Malberg and Blendy 2005). The effects of repeated CBD administration on the expression and function of these signalling proteins are unknown.

Aim of the work

In order to assess the therapeutic potential of CBD for the treatment of affective disorders, it is necessary to understand the effects of repeated administration. Therefore, the aim of the present study was to test the hypothesis that repeated CBD administration would induce anxiolytic-like effects in aversive conditioned rats and modify the expression of proteins in the brain that have been associated with chronic antidepressant/anxiolytic drug treatments .

Material and methods

Animals

Male Lister-hooded rats (150–200 g, $n=16$) were obtained from the Biomedical Sciences Unit, University of Nottingham (a colony derived from Charles River UK stock). Animals were housed in groups of four and maintained on a 12/12-h light/dark cycle, temperature was maintained at 22±2°C and relative humidity 40–60%. Animals had free access to standard rat laboratory chow and water. All animal procedures were carried out in accordance with the UK Home Office Animals (Scientific Procedures) Act of 1986 and Local Ethical Committee Approval.

Drugs and treatment

Pure crystalline CBD (99.3% by HPLC with no other phytocannabinoids detectable) was a generous gift from GW Pharmaceuticals. It was dissolved in a vehicle of 3:1:16 solution of ethanol/Tween 80/0.9% saline. The rats received daily i.p. injections of either vehicle or CBD (10 mg/kg) for 14 days ($n=8$ per group). The dose of CBD was selected on the basis of other studies that reported effects of the drug in animal models of anxiety (Moreira et al. 2009; Moreira et al. 2006; Oviedo et al. 1993; Resstel et al. 2009; Resstel et al. 2006). Moreover, this dose of CBD (10 mg/kg) was reported to induce an anxiolytic-like effect after acute administration (Moreira et al. 2006; Resstel et al. 2006). CBD and vehicle solutions were prepared immediately before use and injected intraperitoneally (i.p.) in a volume of 1 ml/kg.

Procedures

Physiological measurements

Body weight and food consumption were measured daily throughout the experiment. Each cage housed four rats, and the average amounts of chow consumed per rat per day were determined.

Locomotor activity

Locomotor behaviour was recorded for 20 min on the third and ninth days of the experiment in a sound-isolated room (Fig. 1). The rats were habituated to the activity boxes (40×24×25 cm, clear acrylic) for 1 h on the second day. The activity boxes were cleaned with 20% (*v*/*v*) ethanol after removal of rats. Spontaneous locomotor activity, in terms of total distance moved (cm), mean velocity (cm/s) and rearing frequency, was recorded using Ethovision software [Ethovision (version 2.0), Noldus Information Technology, Costerweg, and The Netherlands]. The duration of periods of rearing and grooming was scored manually.

Conditioned emotional response testing

The conditioned emotional response (CER) has been used as a model of conditioned aversion in order to evaluate the anxiolytic effects of several classes of drugs such as selective serotonin reuptake inhibitors (Inoue et al. 1996) and benzodiazepines (Li et al. 2001). A conditioned fear response to a context is produced by exposing the animal to an environment (context) where an aversive or unpleasant stimulus (mild foot shock) is delivered (Rudy et al. 2004). Re-exposure to the same context induces conditioned fear responses, such as freezing behaviour.

The test consisted of two phases: conditioning on the 10th day and testing on the 11th day (Fig. 1). Rats were individually conditioned on the 10th day of the experiment by exposure to inescapable foot shock. Rats were subjected to 0.4 mA of footshock for 1 s every minute for 10 min in a shock chamber with a metal grid floor. This chamber had Perspex walls (26×23×39 cm) with 21 stainless steel rods spaced 1.5 cm apart as the floor, and this was and connected to a shock generator (Campden Instruments, Loughbrough, UK). Twenty-four hours after the last shock session, the rats were again placed in the shock chamber for 10 mins but without shocks, and freezing behaviour was measured. Freezing was defined as the complete absence of movement, except respiration, while the animal assumed a characteristic tense posture. The chamber was cleaned with 20% (*v*/*v*) ethanol before and after use (Finn et al. 2004a). The tests were all carried out between 0900 and 1300 hours.

Western immunoblotting

Rats were killed on day 15 of the experiment by a blow to the head followed by decapitation, and their brains were removed rapidly. The meninges were removed and brain regions dissected on ice and stored at −80°C. The expression of various proteins was measured in the hippocampus, frontal cortex and striatum.

Sample preparation A volume of lysis buffer [20 mM Tris, 1 mM EGTA, 320 mM sucrose, 0.1% Triton X100, 1 mM NaF and 10 mM beta-glycerophosphate dissolved in 500 ml distilled water (pH 7.6) containing protease inhibitor cocktail tablets (Sigma, UK)] was added based on the weights of frontal cortical samples to give a final concentration of 100 mg/ml. Samples were kept on ice through the assay all the time. The samples were homogenised by hand and mixed (rotating mixer) in a cold room for 10 min. The samples were centrifuged at 13,000×*g* for 10 min at 4°C. The supernatant was removed, and the Lowry test (Lowry et al. 1951) was performed to measure the protein concentrations in each sample. Laemmli solubilisation buffer (2×) was added to the samples to give a 1:2 dilution, then the protein concentration was adjusted using volumes of lysis buffer calculated from the protein assay. The samples were assayed immediately or stored at −20°C until needed. For CREB and phospho-CREB assays, the pellets were resuspended in lysis buffer to make a 3:5 dilution.

SDS gel electrophoresis Sodium dodecyl sulphate polyacrylamide electrophoresis gels (SDS-PAGE) were prepared in different concentrations suitable for running different proteins, e.g. 15% SDS-PAGE were used to run BDNF and TrkB immunoblots and 10% SDS-PAGE for CREB, phospho-CREB (p-CREB), ERK1/2 and phospho-ERK1/2 (p-ERK1/2). A layer of 4% gel (stacking gel) was added to the top of the running gel, and the comb was then placed into the gel to prepare ten wells.

Based on preliminary studies, 20–50 μg of protein was loaded onto each lane of the SDS gels. The gels were run in 1× running buffer [Tris (30.3 g), glycine (144 g) and SDS (10 g) dissolved in 1 L distilled water] at 200 V for 45 min using the Bio-Rad apparatus. A standard marker of known molecular weight (Bio-Rad laboratories Ltd, UK) was run alongside.

The proteins were transferred to nitrocellulose paper in the transfer buffer; Tris (30.3 g), glycine (144 g) and were dissolved in distilled water. Methanol (2 L) was added, then made up to 10 L with distilled water using the Bio-Rad apporatus at 100 V for 60 min at 4°C. Protein transfer was checked by adding a few drops of Ponceaus solution (Sigma, UK). The solution can be rapidly removed by washing with Milli-Q water then Tris-buffered saline-Tween (TBST) (25 mM Tris, 125 mM NaCl dissolved in distilled water, pH 7.6).The blots were blocked with 5% fat-free dried milk powder in TBST for 60 min using a platform shaker (Stuart Scientific, UK).

The specific primary antibodies for different proteins were prepared in 5% milk in TBST. The blots were kept in small plastic bags with the antibody overnight in the cold room (4°C) on a platform shaker (Stuart Scientific, UK).

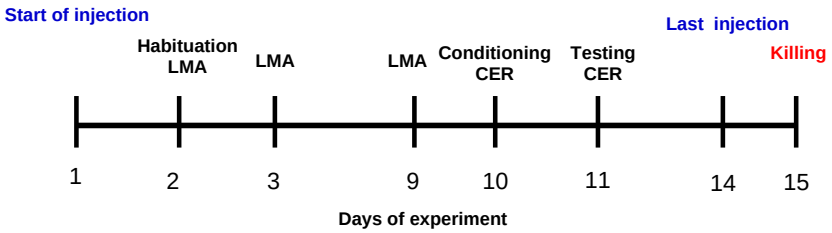

Fig. 1 Timeline showing the experimental protocol employed. Rats received daily intraperitoneal injection of vehicle or CBD (10 mg/kg). *LMA* Locomotor activity, *CER* conditioned emotional response. Note that the same groups of rats were used for all behavioural tests before killing for brain analysis on day 15

Next day, the blots were washed three times with TBST buffer, then washed three times for 5 min and three times for 15 min.

The secondary antibody was prepared as 1:2,000 dilutions in 5% milk in TBST and added to the blots for 60 min at room temperature with shaking (Pardon et al. 2005).

In the dark room, the blots were exposed to enhanced chemiluminescence (ECL) reagent (Amersham Biosciences, UK) for 1 min then blotted dry on filter paper and wrapped in Saran wrap cling film. The blots were placed in an X-ray cassette and exposed to Hyperfilm ECL autoradiography film (Amersham Biosciences, UK) for 5–30 min. The films were developed using Kodak GBX developer (Sigma, UK), then fixed using Ilford Hypam rapid fixer (Ilford Imaging Ltd, UK). The developed films were scanned using a GS-710 Imaging Densitometer (Bio-Rad) and analysed using the Quantity One software package for image analysis

Antibodies Anti-BDNF (1:500, Santa Cruz Biotechnology, Inc.), anti-TrkB (1:1,000, upstate cell signalling), anti-CREB (1:1000, Cell Signalling Technology), anti-p-CREB (1:500, Cell Signalling Technology), anti ERK1/2 (1:1,000, Cell Signalling Technology), anti-pERK (1:1,000, Cell Signalling Technology) and anti-ß-actin (1:400,000, Sigma) primary antibodies were used. The secondary antibodies [horse-radish-peroxidase (HRP), DakoCytomation, Denmark] goat anti-rabbit IgG for BDNF, TrkB, ERK1/2, p-ERK1/2, CREB and p-CREB goat anti-mouse IgG for ß-actin were prepared as 1:2,000 dilutions in 5% milk in TBST.

Statistical analysis

Data are presented as means±standard error of the mean (SEM). Data were analysed by Prism 4 software using unpaired *t* tests (for comparisons between treatment condition and the vehicle control) and the two-way repeated measures ANOVA for changes in body weight and food consumption over time followed by a Bonferroni post hoc test. Results were considered statistically significant if $P<0.05$.

Results

Effect of repeated CBD administration on body weight

Body weight was measured daily between 0900 and 1000 hours. Two-way repeated measures ANOVA revealed significant increases in body weight with time [$F_{(14,196)}$= 1041.0; $P<0.0001$], but there was no effect of treatment [$F_{(1,196)}=0.02$; $P=0.88$]. There were accompanying significant increases in food consumption with time [$F_{(13,26)}$= 21.09; $P<0.0001$], but there was no effect of CBD treatment on the weight of food consumed [$F_{(1,26)}=0.01$; $P=0.93$] (data not shown).

Behavioural effects of repeated administration of CBD

Locomotor activity

The locomotor activity test was performed twice to detect any changes in locomotor activity over the course of CBD treatment. The first test was on the third day of drug injection, and the second was on the ninth day of treatment. CBD had no effect on total distance moved [$t_{(14)}=1.4$; $P=0.18$] or velocity [$t_{(14)}=1.4$; $P=0.18$] on the third day. This lack of effect of CBD on total distance [$t_{(14)}=0.04$; $P=0.97$] and velocity [$t_{(14)}=0.04$; $P=0.97$] continued to the ninth day.

Rearing and grooming behaviour were examined as markers of anxiety-related behaviour. CBD had no effect on rearing frequency [$t_{(10)}=0.18$; $P=0.86$], rearing duration [$t_{(13)}=0.36$; $P=0.72$] or grooming duration [$t_{(14)}=0.30$; $P=0.77$] on the third day or on the ninth day; on rearing frequency [$t_{(14)}=0.11$; $P=0.92$], rearing duration [$t_{(14)}=0.38$; $P=0.71$] or grooming duration [$t_{(14)}=0.49$; $P=0.63$].

Conditioned emotional response

The freezing behaviour of the rats was scored on the CER testing day (day 11). Freezing was expressed as a percentage of the total cage exposure time (10 min). Repeated administration of CBD significantly increased the time spent in freezing behaviour on the testing day of the CER procedure [$t_{(14)}=2.76$; $P=0.02$] (Fig. 2).

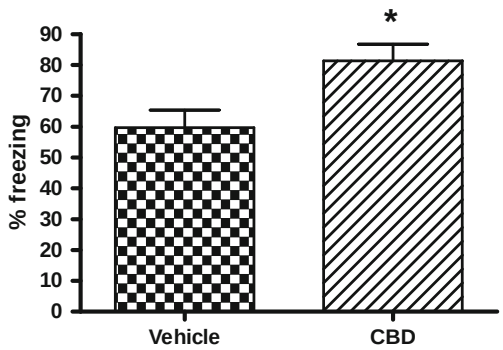

Fig. 2 Effects of chronic administration of CBD on percentage of time spent in freezing behaviour in the CER test on the test day (day 11 of the experiment). *Columns* represent the mean and bars represent the SEM. CBD significantly increased freezing compared to the vehicle-treated group; $n=8$ per group (*$P<0.05$)

Effect of chronic (14 days) CBD administration on protein expression

BDNF and TrkB

Western blots showed clear bands at the expected molecular weights for BDNF (13 kDa), TrkB (145 kDa) and ß-actin (45 kDa) were used as a reference protein for equal loading (Fig. 3), and there were no differences in ß-actin expression verifying equal gel loading of samples. The protein levels are presented as percentage changes compared with vehicle-treated control rats designated as 100%. CBD significantly reduced BDNF expression in the hippocampus [$t_{(14)}=3.31$; $P=0.005$] and frontal cortex [$t_{(14)}=2.47$; $P=0.027$], but there was no effect of CBD on BDNF expression in the striatum [$t_{(14)}=0.69$; $P=0.50$] (Fig. 4).

Moreover, CBD significantly reduced TrkB expression in the hippocampus [$t_{(14)}=3.36$; $P=0.005$] with a trend towards a reduction expression in the striatum [$t_{(14)}=1.84$; $P=0.087$]. There was no effect of CBD on TrkB expression in the frontal cortex [$t_{(14)}=1.20$; $P=0.22$] (Fig. 5).

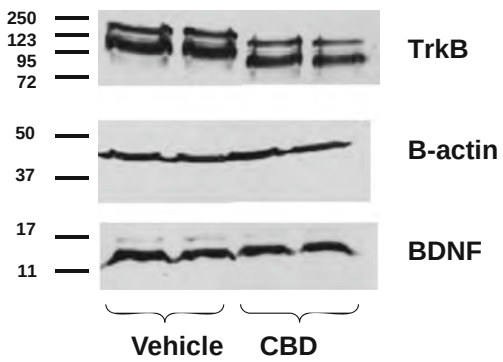

Fig. 3 Example of TrkB, ß-actin and BDNF Western blots in the hippocampus. Western blots showed clear bands at the expected molecular weights for BDNF (13 kDa), TrkB (145 kDa) and ß-actin (45 kDa). CBD reduced BDNF and Trk B expression in the hippocampus with equal loading

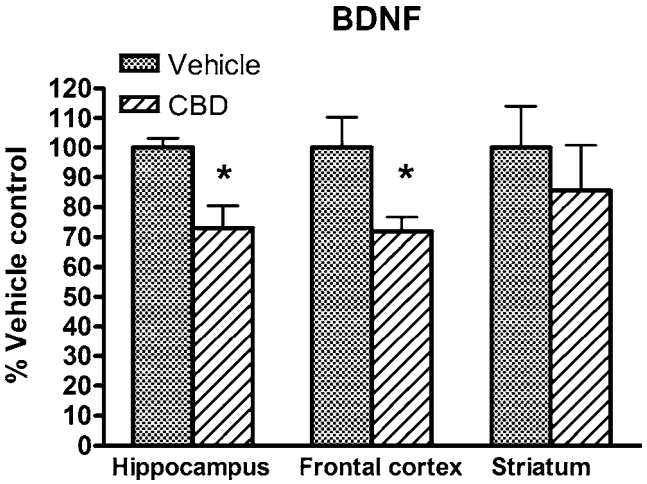

Fig. 4 Effect of chronic administration of CBD on BDNF expression. Data are expressed as percentage changes compared with the vehicle-treated group (designated as 100%) and presented as mean±SEM. Upaired *t* tests were performed with Prism 4.0 software. *$P<0.05$ compared with vehicle, $n=8$ per group. CBD (10 mg/kg for 14 days) significantly reduced BDNF expression in the hippocampus and frontal cortex

ERK1/2 and p-ERK 1/2 expression

Using Western immunoblotting, protein bands representing ERK 1/2 and p-ERK 1/2 were detected at 44 and 42 kDa in frontal cortex, although the p-ERK1

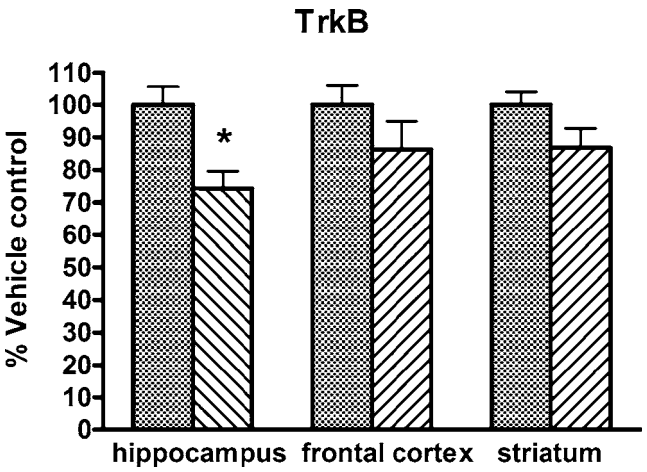

Fig. 5 Effect of chronic administration of CBD on TrkB expression. Data are expressed as percentage changes compared with the vehicle-treated group (designated as 100%) and presented as mean±SEM. Upaired *t* tests were performed with Prism 4.0 software. *$P<0.05$ compared with vehicle, $n=8$ per group. CBD (10 mg/kg for 14 days) significantly reduced Trk B expression in the hippocampus

expression in the hippocampus was too low to detect. It should be noted that, although ERK1 and ERK2 were found at similar levels in the different brain areas, the signal was always much stronger for p-ERK2 than for p-ERK1, which was below the detection thresholds in some experiments (Fig. 6).

In the hippocampus, CBD had no effect on ERK1 [$t_{(14)}$=0.89; P=0.39], ERK2 [$t_{(14)}$=0.67; P=0.51] or p-ERK2 [$t_{(14)}$=0.68; P=0.51]. In the frontal cortex, CBD had no effect on ERK1 [$t_{(14)}$=0.78; P=0.45] or ERK2 [$t_{(14)}$=0.77; P=0.45] but significantly reduced p-ERK1 [$t_{(14)}$=2.49; P=0.026] and p-ERK2 [$t_{(14)}$=2.46; P=0.028] (Fig. 7).

CREB and p-CREB

Protein bands representing CREB and p-CREB were detected at 43 kDa in the frontal cortex, but p-CREB was undetectable in the hippocampus. CBD had no effect on CREB [$t_{(14)}$=0.51; P=0.62] or p-CREB [$t_{(14)}$=0.33; P=0.75] expression in the frontal cortex or CREB expression in the hippocampus [$t_{(14)}$=1.20; P=0.25].

Discussion

The phytocannabinoid CBD, which is one of the most abundant bioactive components of the cannabis plant, has been reported to have an acute anxiolytic effect in both animals and humans (Crippa et al. 2004; Lemos et al. 2010; Moreira et al. 2006; Zuardi et al. 1982). More recently, CBD has also been shown to have an acute antidepressant-like effect, via the activation of 5-HT1A receptors, in a mouse forced-swimming test (Zanelati et al. 2010) without changing activity in the open field.

In the present study, no change in body weight was detected after administration of CBD for 14 days. On the contrary, Ignatowska-Jankowska et al. (2011) reported that repeated administration of CBD (2.5 and 5 mg kg^{-1} day^{-1}) for 14 days decreased the body weight gain of rats. This variance from the present study's findings may be related to the difference in species or dose of CBD used.

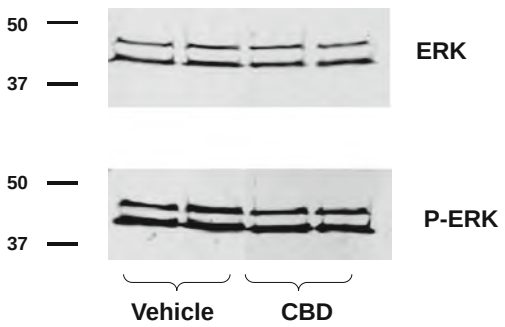

Fig. 6 Example Western blot of ERK and pERK expression in frontal cortex. Protein bands representing ERK 1/2 and p-ERK 1/2 were detected at 44 and 42 kDa in frontal cortex. CBD reduced both p-ERK1 and p-ERK2

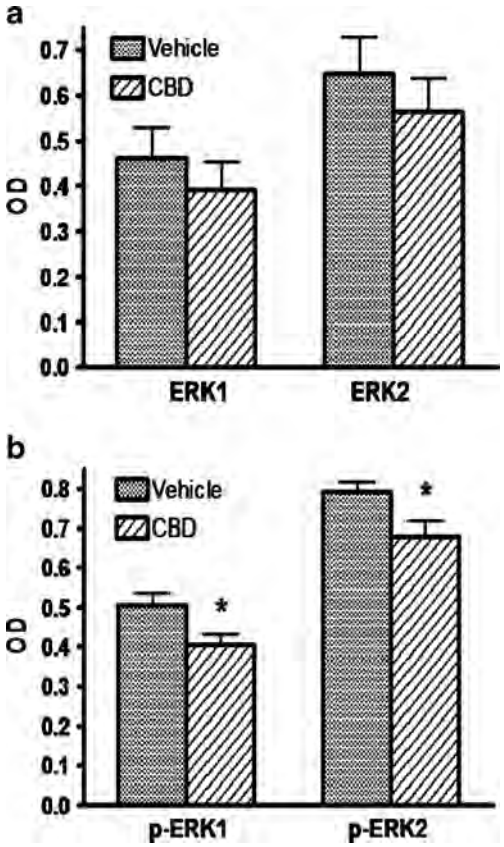

Fig. 7 Effect of chronic administration of CBD on protein expression of **a** ERK 1/2 and **b** p-ERK 1/2 in the frontal cortex. Unpaired t tests were performed with Prism 4.0 software. *P<0.05, n=8 per group. CBD (10 mg/kg for 14 days) significantly reduced p-ERK1/2 expression in the frontal cortex

In the present study, the locomotor activity of the rats in a neutral environment was measured to detect any hypoactivity or changes in rearing and grooming hyperactivity associated with CBD treatment that could interfere with the interpretation of behavioural changes in the CER test. The administration of CBD (10 mg/kg, i.p. for 14 days) failed to affect the rats' spontaneous locomotor activity. This result is in agreement with Wiley et al. (2005) and Finn et al. (2004b) who reported that acute administration of CBD had no effect on locomotor activity of mice or rats respectively.

Rearing and grooming were examined as markers of anxiety-related behaviour as increased self-grooming in rats is frequently observed after the application of mild stressors, such as novelty or handling of the animals (van Erp et al. 1994). Anxiolytic drugs attenuate the increase in grooming induced by a novel environment without significantly affecting general locomotor activity,

which dissociates grooming activity from sedation (Dunn et al. 1981; Moody et al. 1988).

In the present study, there were no differences in rearing and grooming between the treatment groups in agreement with Finn et al. (2004b), who found that rearing and grooming were unaltered by acute administration of a lower dose of CBD (5 mg/kg).

In the CER test, however, the rats were exposed to an environment paired previously with inescapable electric foot shock, which results in a well-characterised freezing response. The duration of freezing has been used as an index of induced fear and anxiety (Fanselow 1980), and a number of anxiolytic drugs decrease the duration of freezing (Hashimoto et al. 1996; Inoue et al. 1996).

Resstel et al. (2006) observed that acute injection of CBD (10 mg/kg, i.p.) reduced the freezing time in conditioned rats, and Bitencourt et al. (2008) reported that CBD facilitated conditioned fear extinction in rats, which might contribute to the anti-anxiogenic effect detected in the same study. In the present study, it was hypothesised that CBD would induce an anxiolytic-like effect in the CER test in the form of reduced conditioned freezing. However, on the contrary, repeated CBD administration significantly *increased* the time spent in freezing behaviour indicating an anxiogenic-like effect after chronic administration.

There were some differences in methodology between the present study and those previously reporting anxiolytic effects. For example, rats were individually housed in the study of Resstel et al. (2006), while they were group housed in the present study. There were also differences the conditioning protocols in that the rats received six 2.5 mA foot shocks in the study of Resstel et al. (2006) and ten 0.4 mA shocks in the present study. Nevertheless, it seems unlikely that the qualitative differences in behavioural outcomes between acute and chronic administration of CBD could be explained by relatively minor variations in methodology. It is noteworthy that the anxiolytic effect of CBD in humans has only been reported after acute administration (Zuardi et al. 2006).

Long et al. (2009), however, demonstrated that chronic daily administration of CBD to male adult C57BL/6JArc mice for 21 days produced moderate anxiolytic-like effects in the open-field test at 50 mg/kg and in the light–dark test at a low dose (1 mg/kg). This variance from the present study's findings may be related to the species used, the behavioural test employed or the dose and duration of CBD administration. For example, in the study of Magen et al. (2009) the optimal dose of CBD for cognitive enhancement in the bile duct ligation model was 5 mg/kg over a 4-week period, while 1 and 10 mg/kg were ineffective. This indicates a complex dose–response relationship for CBD, at least in this model, which complicates interpretation of inter-study differences. Although the dose of CBD used in the present study was reported to induce an anxiolytic-like effect after acute administration in previous studies (Moreira et al. 2006; Resstel et al. 2006), a biphasic effect of CBD was reported in other studies (Guimaraes et al. 1990; Kwiatkowska et al. 2004; Malfait et al. 2000; Rock et al. 2008), which emphasises the need for additional long-term multi-dose studies.

The neurotrophic hypothesis of depression (Nestler et al. 2002) suggests that BDNF is reduced in depression and increased by many antidepressant/anxiolytic treatments. We hypothesised that CBD might increase expression of BDNF protein, its receptor (TrkB) or the downstream mitogen-activated protein kinase (MAPK) signalling protein cascade (ERK). This is, of course, relevant to potential anxiolytic actions of CBD since antidepressant drugs are the first line therapy for long-term anxiety (Dell'Osso et al. 2010). We focused on the hippocampus, frontal cortex and striatum as these brain areas may be dysfunctional in affective disorder (Kennedy et al. 1997; Sheline 2000). However, in the present study, Western immunoblotting showed that chronic administration of CBD significantly *decreased* BDNF expression in the hippocampus and frontal cortex while having no effect on BDNF levels in the striatum. Moreover, CBD also significantly reduced TrkB expression in the hippocampus with a strong trend towards a decrease in the striatum but with no effect in the frontal cortex. Magen et al. (2009) reported that chronic administration of CBD (5 mg/kg) for 4 weeks to female Sabra mice had no effect on BDNF mRNA in the hippocampus but normalised the reduced BDNF after bile duct ligation, a model of hepatic encephalopathy. Zanelati et al. (2010) reported that acute administration of CBD (30 mg/kg) did not affect BDNF expression in the mouse hippocampus, although it showed an antidepressant-like effect in the forced swim test.

Previous studies have demonstrated that chronic antidepressant treatment increases the expression of CREB in limbic regions of rat brain (Nibuya et al. 1996). CREB in its phosphorylated form is a transcription factor that mediates the actions of intracellular messengers on gene expression. The function of CREB is regulated largely by phosphorylation at Ser^{133}, which results in activation of gene transcription (Thome et al. 2000). CREB activation could alter the expression of specific gene products involved in the modulation of anxiety, such as BDNF and could, thereby, underlie some of the effects of antidepressant treatment on long-term anxiety. Since the phosphorylation of CREB may be mediated by the MAPK pathway through the phosphorylation of ERK and TrkB signals, at least partly, through MAPK activation, we focused our attention on the effects of CBD on p-CREB and p-ERK induction.

In the present study, CBD had no effect on CREB expression in the frontal cortex and hippocampus or p-

CREB expression in the frontal cortex, while in the hippocampus, p-CREB was undetectable. With respect to ERK and p-ERK, CBD significantly reduced p-ERK1/2 in the frontal cortex without affecting total ERK1/2 expression, and there was no apparent change in ERK1/2 or p-ERK2 expression in the hippocampus.

Given the pleiotropic effects of cannabidiol, it is difficult to propose a straightforward molecular mechanism to explain the effects of the drug on the expression of these proteins, but, although no direct assessments of neurogenesis were made in these animals, the combined negative effects of cannabidiol on BDNF and BDNF-related signalling proteins would certainly not be consistent with the enhanced neurogenesis reported for clinically effective antidepressants/anxiolytics and would probably predict the opposite.

Conclusion

The data presented indicate an anxiogenic-like profile of behaviour in normal healthy rats following repeated CBD administration. This was accompanied by reductions in the expression of the neurotrophin BDNF and related signalling proteins, and, overall, the results are not consistent with the potential clinical anxiolytic properties suggested by acute experiments with CBD. This emphasises the need for additional long-term multi-dose studies of the drug in models of affective disease.

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Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow

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Animal and human studies have suggested that cannabidiol (CBD) may possess anxiolytic properties, but how these effects are mediated centrally is unknown. The aim of the present study was to investigate this using functional neuroimaging. Regional cerebral blood flow (rCBF) was measured at rest using ^{99m}Tc-ECD SPECT in 10 healthy male volunteers, randomly divided into two groups of five subjects. Each subject was studied on two occasions, 1 week apart. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. SPECT images were acquired 90 min after drug ingestion. The Visual Analogue Mood Scale was applied to assess subjective states. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping (SPM). CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolytic effects of CBD were predicted *a priori* revealed two voxel clusters of significantly decreased ECD uptake in the CBD relative to the placebo condition ($p < 0.001$, uncorrected for multiple comparisons). These included a medial temporal cluster encompassing the left amygdala–hippocampal complex, extending into the hypothalamus, and a second cluster in the left posterior cingulate gyrus. There was also a cluster of greater activity with CBD than placebo in the left parahippocampal gyrus ($p < 0.001$). These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

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Keywords: cannabidiol; anxiety; regional cerebral blood flow; SPECT; neuroimaging

INTRODUCTION

Cannabidiol (CBD) constitutes up to 40% of *Cannabis sativa* (Grlie, 1976) and has quite different psychological effects to the plant's best known constituent, Δ^9-tetrahydrocannabinol (Δ^9-THC) (Perez-Reyes *et al*, 1973; Zuardi *et al*, 1982). In particular, in animal studies CBD has effects similar to anxiolytic drugs in conditioned emotional paradigms (Zuardi and Karniol, 1983), the Vogel conflict test (Musty *et al*, 1984), and the elevated plus maze test (Guimaraes *et al*, 1990; Onaivi *et al*, 1990). Using the latter test, anxiolytic effects were also reported for three derivates of CBD, HU-219, HU-252, and HU-291 (Guimaraes *et al*, 1994). In humans, oral administration of CBD in healthy volunteers attenuates the anxiogenic effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) (Zuardi *et al*, 1982). This effect does not seem to involve any pharmacokinetic interactions (Agurell *et al*, 1981; Zuardi *et al*, 1982), and CBD does not bind to the central known cannabinoid receptor, CB_1, (Bisogno *et al*, 2001; Mechoulam *et al*, 2002) and hence cannot be a competitive antagonist (Howlett *et al*, 1992). CBD may thus possess inherent anxiolytic properties unrelated to THC-type activity. This is consistent with its anxiolytic effect on anxiety elicited by simulated public speaking (Zuardi *et al*, 1993a).

As the receptors that mediate the psychological effects of CBD are unknown, its mechanism of action on the brain is unclear. The aim of the present study was to use functional

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neuroimaging to investigate this. In view of its anxiolytic effect, we tested the hypothesis that CBD would affect neural activity in areas that normally mediate anxiety. We compared the effects of CBD and placebo on resting cerebral regional blood flow (rCBF) in healthy volunteers in a double-blind, cross-over design. Based on previous functional imaging studies of anxiety (Maddock and Buonocore, 1997; Fischer *et al*, 1996; Liotti *et al*, 2000; Ketter *et al*, 1996), we predicted that, relative to placebo, CBD would modulate rCBF in limbic and paralimbic areas: the orbitofrontal, cingulate and medial temporal cortex, and the insula.

MATERIALS AND METHODS

Subjects

A total of 10 healthy male postgraduate students were studied. None had undergone rCBF SPECT examinations or other nuclear medicine procedures before. All were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and were nonsmokers (of tobacco). Their mean age was 29.8 years (range 25–42 years, SD = 5.1), their mean weight was 74.1 kg (67–85 kg, SD = 6.05), and their body mass index ranged between 21 and 25 kg/m^2. The subjects had not taken any medicines for at least 3 months before the study (Mathew *et al*, 1992). No subject had a history of head trauma, neurological, or major medical illnesses, based on a semistandardized medical questionnaire and physical examination. Neither the subjects (based on the Structured Clinical Interview for DSM-IV, First *et al*, 1997) nor their first-degree relatives (based on subjects' report) had a history of psychiatric illness. No subject had used marijuana more than five times in their lives (nor in the last year), and none had used any other illegal drug. The experiment was conducted with the understanding and consent of each subject, following approval by the local ethical committee.

Cannabidiol

CBD in powder, approximately 99.9% pure (supplied by THC-Pharm, Frankfurt, Germany), was dissolved in corn oil (Zuardi *et al*, 1993a, 1995). The same amount of corn oil was used as a placebo. The drug and placebo were packed inside identical gelatin capsules.

Self-Rating Scale

Subjective states were evaluated by means of the Visual Analogue Mood Scale (VAMS) of Norris (1971), translated into Portuguese by Zuardi and Karniol (1981b). It consists of 16 analogue scales to measure drug effects, which were arbitrarily divided by Norris into four factors: anxiety, physical sedation, mental sedation, and other feelings and attitudes. A factor analysis with the Portuguese version of this scale (Zuardi *et al*, 1993a) extracted four factors that can be identified with those of the Norris proposal. Prior to the experiment, each volunteer had performed a training session completing this scale.

Procedure

Subjects were told not to consume any alcohol for 24 h and caffeine for at least 4 h before each visit to the laboratory (Mathew *et al*, 1999). Subjects who reported having less than 6 h of sleep the previous night were excluded. After at least 8 h of fasting, subjects were instructed to have a light, standardized breakfast 2 h before the experiment. They were randomly divided into two groups of five subjects. Each subject was evaluated on two different occasions, 1 week apart. In the first session, after a 30-min period of adaptation, subjects were given a single dose of oral CBD (400 mg) or placebo, in a double-blind procedure. The sessions were held in the morning (between 0800 and 1200) to minimize the effects of circadian variation. SPECT image acquisition was performed 110 min after drug ingestion. Subjective ratings on the VAMS were made 30 min before drug ingestion, at the time of drug ingestion, and at 60 min and at 75 min afterwards. In the second session, an identical procedure was followed except that the other drug was administered (ie those given CBD in the first session received placebo in the second; and *vice versa*). Subjects were informed that they would receive CBD and placebo, but they were not told in which order. The investigators were also blind to the content of the capsules.

SPECT

Subjects had a venous cannula inserted into their right arm, and rested supine with minimal environmental sensory stimulation. They were instructed to keep their eyes closed under eye pads and to relax for 15 min without falling asleep. Their ears were unplugged. VAMS ratings were made just before and 15 min after insertion of the venous cannula. At 30 min after insertion of the venous cannula, 740 MBq (20 mCi) of ethyl-cisteinate-dimer (ECD) labeled with technetium-99 m (^{99m}Tc-ECD) was injected. Subjects rested for an additional period of 5 min postinjection, after which the venous cannula was removed.

Image acquisition started 20 min after the ^{99m}Tc-ECD injection, using a double-detector SOPHA® DST system (Sophy Medical Vision, Twinsburg, USA). High-resolution low-energy collimators were used, with 128 views acquired on a 128 × 128 matrix (30 s per view), with a total acquisition time of 30 min, and approximately 75 000 counts/frame/head. Raw images were prefiltered with a Butterworth filter (order number 4, cutoff frequency 0.16), and reconstructed by filtered back-projection as transaxial slices parallel to the long axis of the temporal lobe. Attenuation correction was performed considering a pixel size of 2.55 mm and using the first-order algorithm of Chang (coefficient 0.12/cm).

Image Processing and Analysis

Images were analyzed using Statistical Parametric Mapping software (SPM99) (Friston *et al*, 1995). Reconstructed transaxial datasets were transferred to a PC (Pentium IV, 2.2 GHz, 512 Mb RAM), converted to Analyze format and reoriented to neurological convention (ie left = left).

Placebo images were realigned to CBD images using sinc interpolation. Linear (translations and rotations) and non-linear ($7 \times 8 \times 7$ nonlinear basis functions) deformations were used to register images to the SPM SPECT template, which is based on the Montreal Neurological Institute (MNI) template (Mazziotta *et al*, 1995). Finally, an isotropic Gaussian filter of 12 mm was applied to diminish inter-individual differences, and to conform data to the theory of Gaussian Random Fields (Friston *et al*, 1995), in order to allow the subsequent application of parametric statistical tests.

Between-condition (CBD *vs* placebo) comparisons of regional tracer uptake were performed on a voxel-by-voxel basis using paired *t*-tests. Before statistical testing, the regional ECD uptake of every voxel in each subject was standardized to the mean global uptake of the image in that subject, using proportional scaling. Only voxels with signal intensities above a threshold of 0.8 of the global mean (calculated using the standardized values) entered the statistical analysis. The resulting statistics at each voxel were transformed to *Z*-scores, thresholded at $Z = 2.33$ (corresponding to $p < 0.01$, one-tailed), and displayed as 3-D statistical parametric maps (SPM). These maps were first inspected for the presence of voxel clusters of significant difference in the regions where effects of CBD had been predicted *a priori* (medial temporal, cingulate, orbitofrontal, and insular cortices). Clusters in these regions were considered as significant if they included voxels with *Z*-scores of 3.09 or greater (corresponding to one-tailed $p < 0.001$), and contained more than 20 voxels. Levels of $p < 0.001$, uncorrected for multiple comparisons, have been frequently used in previous SPM analyses of positron emission tomography (PET) (Dougherty *et al*, 1999; Bremner *et al*, 1999b) and SPECT (Blackwood *et al*, 1999; Busatto *et al*, 2000) data, and are considered to provide good protection against false-positive results when there are clear hypotheses as to the location of findings. The SPMs were also inspected for differences in other, unpredicted regions. These areas were reported as significant if they survived a correction for multiple comparisons based on Gaussian random field theory ($p < 0.05$) (Friston *et al*, 1995).

For each voxel cluster showing significant between-condition differences, estimates were calculated for the mean, median, and maximal percentages of ECD count rate change (and their variances) (Table 1). These indices were obtained by partitioning the Student's *t*-test value of each voxel into its main components, with the numerator of the *t* statistic used as an approximation of the magnitude of the signal change for each contrast (placebo > CBD or CBD > placebo), and the denominator (the standard error) used to calculate the variances. The MNI coordinates for the voxels of maximal statistical significance for each anatomical brain region included in a given cluster were converted to the Talairach and Tournoux (1988) system using the method described by Brett *et al* (2002).

The four VAMS factors were submitted to an ANOVA for repeated measures in both CBD and placebo sessions. The differences between CBD and placebo in each phase of the experimental session (−30, 0, 1′00, 1′15) were analyzed by *t*-tests. Correlations between the regional tracer uptake and each of the VAMS factors scores were also investigated with SPM99, at the same statistical significance levels as described above for the between-condition rCBF comparisons. The last point in which the VAMS was applied (75′ after drug intake) was chosen for these correlations due to its proximity to the injection of the SPECT tracer. Moreover, this is the point where CBD is expected to have its maximum anxiolytic effect among all the time points chosen for assessment during the experimental session (Zuardi *et al*, 1993a). The choice for

Table 1 Limbic and Paralimbic Areas of Significant rCBF Differences in CBD Compared to Placebo Condition

Finding and cluster[a]	Cluster mean[b] and median[c] % signal change	Cluster mean[b] and median[c] variance	*P*-value (corrected)[d]	Regions included in cluster	Peak[e] % signal change (variance)	Peak[e] *Z*-score[f]	Coordinates[g]		
							x	y	z
Placebo > CBD									
Cluster 1 (102 voxels)	4.61	9.51	0.99	Left posterior cingulate cortex	4.81 (4.51)	3.40	−4	−27	47
	4.57	8.72		(BA 31)/paracentral lobule (BA5/6)					
Cluster 2 (203 voxels)	4.63	10.83	1.00	Left hypothalamus	5.61 (8.26)	3.12	−6	−6	−8
	4.56	10.53		Left amygdala–hippocampal complex /uncus	3.77 (4.53)	2.94	−16	−11	−21
CBD > Placebo									
Cluster 3 (114 voxels)	5.06 5.17	10.88 10.14	0.96	Left parahippocampal / fusiform gyri	4.53 (2.91)	3.69	−30	−15	−24

[a]Total number of voxels in each cluster that surpassed the initial threshold of $Z = 2.33$ are shown between parentheses.
[b]Average of all the voxel values in the cluster.
[c]Middle value in the distribution of frequencies of the cluster.
[d]Level of statistical significance after correction for multiple comparisons using Gaussian random field theory (Friston *et al*, 1995).
[e]Voxel of maximal statistical significance in the cluster.
[f]*Z*-score for the voxel of maximal statistical significance within each cluster.
[g]Talairach and Tornoux (1988) coordinates obtained through the conversion of SPM MNI (Mazziotta *et al*, 1995) coordinates according to Brett *et al* (2002).

this time point was also based on previous studies, which have shown that the plasma peak of an oral dose of CBD usually occurs between 1 and 2 h after ingestion (Agurell *et al*, 1981).

RESULTS

Visual Analogue Mood Scale

The administration of CBD was associated with significantly decreased subjective anxiety ($F(3,27) = 18.56$, $p < 0.001$) and increased mental sedation ($F(3,27) = 42.85$, $p < 0.001$), while placebo was not ($F(3,27) = 1.86$, $p = 0.16$ and $F(3,27) = 2.24$, $p = 0.11$, respectively) (Figure 1). In addition, an analysis at each time point indicated the following: (i) CBD was associated with significantly decreased anxiety at cannula insertion (60′ after drug intake, $t = 2.95$, $p = 0.009$) and resting phases (75′ after drug intake, $t = 5.50$, $p < 0.001$) as compared to placebo; (ii) CBD was associated with significantly increased feelings of mental sedation at cannula insertion (60′ after drug intake, $t = -3.91$, $p = 0.001$) and resting phases (75′ after drug intake, $t = -3.67$, $p = 0.002$) as compared to placebo.

Between-Condition rCBF Comparisons

The SPM showing increases in ECD uptake in the CBD relative to placebo condition revealed only one cluster (>20 voxels) that surpassed the initial $Z = 2.33$ statistical cutoff (Figure 2). This cluster, which achieved statistical significance at the $p < 0.001$ level (uncorrected for multiple comparisons), was located in the medial temporal cortex, where the effects of CBD had been predicted *a priori*, and involved the left parahippocampal gyrus, extending inferiorly to encompass the left fusiform gyrus (Table 1).

Significantly decreased ($p < 0.001$, uncorrected for multiple comparisons), ECD uptake in the CBD relative to the placebo condition was evident in two regions where effects of CBD had been predicted *a priori* (Table 1). One cluster included the medial portion of the left amygdala–hippocampal complex and uncus, as well as the hypothalamus. The other was located in the superior portion of the left posterior cingulate gyrus (Brodmann area—BA31),

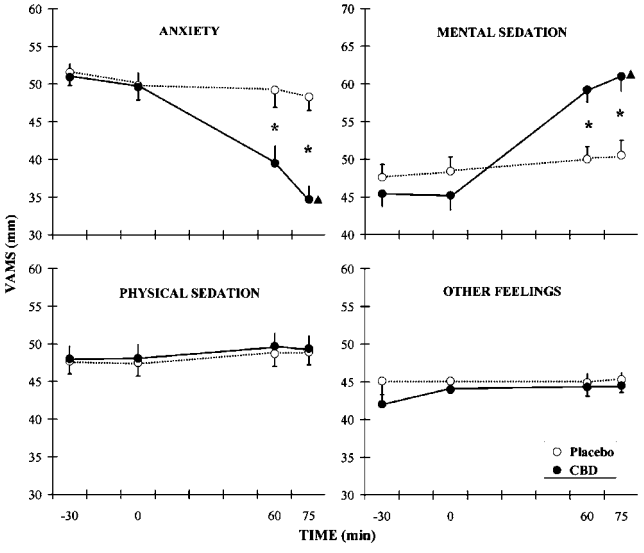

Figure 1 Effect of CBD and placebo (PLCB) on the four factors of the VAMS. Points are means (± SEM) of 10 healthy subjects in the following phases of the experiment: predrug (−30), drug intake (0), prestress (60), and adaptation (75). Asterisk (*) indicates significant difference from placebo in each phase. Triangle (▲) indicates ANOVA significant changes.

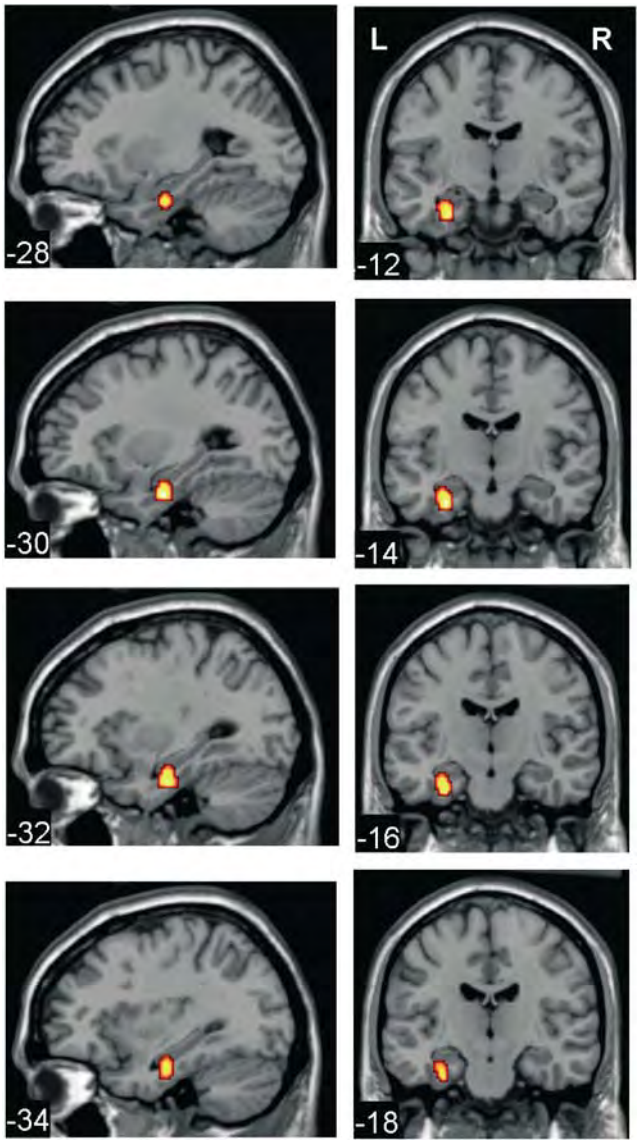

Figure 2 The brain region where there was significantly increased rCBF in healthy volunteers ($n = 10$) during CBD *vs* placebo has been overlaid on coronal sections (−18, −16, −14, −12) and sagittal sections (−28, −30, −32, −34) of a reference brain, imaged with structural MRI and spatially normalized into an approximation to the Tailarach and Tornoux (1988) stereotactic atlas. The results are displayed in neurological convention (ie left = left). The numbers associated with each frame represent the standard coordinate in the *y*- (for the coronal frames) and *x*-axis (for the sagittal frames). The voxel cluster shown was located in the left parahippocampal gyrus extending inferiorly to encompass the left fusiform gyrus (peak *Z*-score = 3.69, coordinates$_{x,y,z} = -30, -14, -30$; $p < 0.0001$ uncorrected for multiple comparisons; 114 voxels).

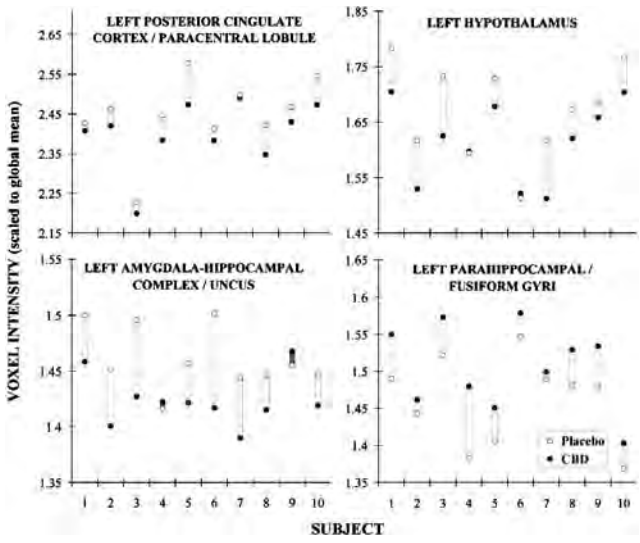

Figure 3 Tracer uptake values during the CBD (filled circle) and PLCB (hollowed circle) conditions are plotted for the 10 subjects, using the voxel of maximal significant difference of each of the four regions reported in Table 1. From left to right and top to bottom: −4, −27, 47 (left posterior cingulate cortex/paracentral lobule), −6, −6, −8 (left hypothalamus), −16, −11, −21 (left amygdala–hippocampal complex), and −30, −15, −24 (left parahippocampal/fusiform gyri). Individual values were normalized to the global ECD uptake for each subject and condition. The graphs show that the large majority of individual subjects showed lower ECD activity in the CBD condition relative to the placebo condition in the left amygdala–hippocampus complex, hypothalamus, and posterior cingulate cortex/paracentral lobule, while all subjects had greater ECD uptake in the CBD condition relative to the placebo condition in the left parahippocampal/fusiform gyri.

extending towards the paracentral lobule (BA5/6). At the $p<0.001$ uncorrected level of significance, this SPM showed additional, unpredicted foci of decreased rCBF in the ECD relative to the placebo condition (>20 voxels) in the right cerebellum, medial occipital cortex, left inferior temporal, and posterior lateral frontal cortex, but none of these retained significance after correction for multiple comparisons.

Figure 3 displays, for each subject, the magnitude of tracer uptake changes between the CBD and placebo conditions at the voxel of maximal statistical significance in the regions where ECD uptake differences were observed (as summarized in Table 1). All 10 subjects showed greater ECD uptake values in the CBD condition relative to the placebo condition in the left parahippocampal/fusiform gyri. Of the 10 subjects, eight showed lower ECD activity in the CBD condition relative to the placebo condition in the left amygdala–hippocampal complex; eight in the left hypothalamus; and nine in the left posterior cingulate cortex/paracentral lobule (Figure 2). Similar patterns across individual subjects were observed when we used the mean tracer uptake values of all voxels included in the clusters of significant difference between the CBD and placebo conditions (data not shown).

Correlations with Subjective Status Ratings

No correlations were observed between subjective anxiety ratings and ECD uptake in the brain areas where the effects of CBD had been predicted *a priori* ($p<0.001$, uncorrected), or in other unpredicted areas after correction for multiple comparisons.

DISCUSSION

When undergoing neuroimaging procedures, such as PET or SPECT, subjects often report increased anxiety before scanning, which is greater than that during or after image acquisition (Grey *et al*, 2000; Gur *et al*, 1987; Giordani *et al*, 1990; Malizia, 1999). The results of the present study showed that a single dose of CBD induced significant decreases in state anxiety before SPECT scanning. Our data thus suggest that this compound has anxiolytic properties, consistent with the results from previous studies in both laboratory animals (Zuardi and Karniol, 1983; Musty *et al*, 1984; Guimaraes *et al*, 1990; Onaivi *et al*, 1990) and humans (Zuardi *et al*, 1982, 1993a).

The anxiolytic effects found in the present study were detected before the anxiety-evoking situation (the tracer injection and scanning procedure), indicating that CBD can affect anticipatory anxiety. In a previous study (Zuardi *et al*, 1993a), the anxiolytic effect of CBD was evident after the stress of public speaking. These antianxiety effects are in contrast to the anxiogenic effects of high doses of Δ^9-THC (Malit *et al*, 1975; Zuardi *et al*, 1982; Mathew *et al*, 1999), and may help to reconcile apparently conflicting findings obtained with *Cannabis sativa* in relation to anxiety (Johns, 2001; Tournier *et al*, 2003).

Consistent with an anxiolytic effect, we found that CBD significantly modulated resting activity predominantly in limbic and paralimbic cortical areas, which are usually implicated in the pathophysiology of anxiety (Gray, 1982; Graeff, 1994). Thus, between-condition activity differences were detected in a left medial temporal cluster, which included portions of the amygdala and the hippocampus, as well as the hypothalamus, the left posterior cingulate gyrus, and the left parahippocampal gyrus.

The only brain region that showed significantly increased activity in the CBD relative to the placebo condition was the left parahippocampal gyrus. Deactivation of the parahippocampal region in healthy volunteers has been reported after panic attacks induced by lactate (Reiman *et al*, 1989) and CCK-4 (Javanmard *et al*, 1999), and with anxiety induced by presentation of combat-related images (Bremner *et al*, 1999b) and autobiographical memory scripts (Liotti *et al*, 2000). In addition, the abnormal asymmetry of resting activity in the parahippocampal gyri has been associated with panic disorder and with vulnerability to lactate-induced panic (Reiman *et al*, 1984, 1986; Nordahl *et al*, 1990, 1998; Bisaga *et al*, 1998; De Cristofaro *et al*, 1993). These studies suggest that anxiety can be associated with reduced parahippocampal activity, consistent with an anxiolytic effect of CBD and the increased activity in this region that we observed.

In contrast, activity in the left amygdala–hippocampal complex, hypothalamus, and posterior cingulate cortex decreased with CBD relative to placebo. The amygdala is thought to play a key role in mediating fear and anxiety (Deakin and Graeff, 1991; LeDoux, 1998; Gorman *et al*, 2000), being activated during fear conditioning (Furmark

et al, 1997; Morris *et al*, 1998; LaBar *et al*, 1998; Buchel *et al*, 1998), while processing anxious faces (Breiter *et al*, 1996; Morris *et al*, 1996; Whalen *et al*, 1998; Hariri *et al*, 2002) and during pharmacologically induced anxiety (Ketter *et al*, 1996; Benkelfat *et al*, 1995; Servan-Schreiber *et al*, 1998). Functional and structural changes in the amygdala have also been reported in PTSD (Pitman *et al*, 2001; Rauch *et al*, 1996; Shin *et al*, 1997; Rauch *et al*, 2000; Liberzon *et al*, 1999), panic disorder (Uchida *et al*, 2003; Bystritsky *et al*, 2001), generalized anxiety disorder (Thomas *et al*, 2001; De Bellis *et al*, 2000), and in social (Birbaumer *et al*, 1998; Tillfors *et al*, 2001; Furmark *et al*, 2002) and simple phobias (Wik *et al*, 1997). The reduction in amygdala activity that we observed with CBD is thus consistent with the anxiolytic effect that it had in our subjects. The hippocampus has also been implicated in the processing of anxiety. Functional neuroimaging studies have shown increased activity in the hippocampus in association with anxiety in OCD (McGuire *et al*, 1994), panic disorder (Bisaga *et al*, 1998; Bystritsky *et al*, 2001; Boshuisen *et al*, 2002), PTSD (Osuch *et al*, 2001), and in social phobia (Schneider *et al*, 1999). However, other studies have reported either decreased or no difference in activity in the hippocampus in association with normal anxiety or anxiety disorders (Schuff *et al*, 2001; Schneider *et al*, 1999; Bremner *et al*, 1997; Fredrikson *et al*, 1997; Fischer *et al*, 1996; Paradiso *et al*, 1997; Liotti *et al*, 2000).

The hypothalamus is a major component of the central autonomic nervous system, and is often involved in mediating the effects of stress and anxiety (Afifi and Bergman, 1998). Functional imaging studies during fear and anxiety induction in healthy subjects (Fredrikson *et al*, 1995b; Javanmard *et al*, 1999) and in panic disorder patients (Boshuisen *et al*, 2002) have reported increases in the activity of the hypothalamic region, and hypothalamic–pituitary–adrenal axis abnormalities have been commonly reported in anxiety disorders (Hageman *et al*, 2001). The reduced hypothalamic activity that we observed is thus consistent with the anxiolytic effect of CBD.

The posterior cingulate cortex is strongly linked to temporolimbic structures (Vogt *et al*, 1992; Maddock, 1999; Afifi and Bergman, 1998), and is thought to play a central role in emotion and anxiety (MacLean, 1993; Maddock, 1999). Increased activity in the posterior cingulate gyrus has been associated with watching anxiety-provoking videos (Fischer *et al*, 1996, Fredrikson *et al*, 1995a), and with experimentally provoked obsessions and anxiety in patients with obsessive–compulsive disorder (OCD) (McGuire *et al*, 1994). Untreated patients with OCD show increased metabolism in the posterior cingulate (Perani *et al*, 1995) that decreases with treatment, with the change in posterior cingulate rCBF correlated with symptomatic improvement (Rauch *et al*, 2001, 2002). There have also been reports of increased posterior cingulate activation during symptom provocation in post-traumatic stress disorder (Bremner *et al*, 1999a) and panic disorder (Bystritsky *et al*, 2001). However, anxiety induction in phobic patients has been associated with deactivation in the posterior cingulate region (Wik *et al*, 1993) and Busatto *et al* (2000) reported a negative correlation between rCBF in the left posterior cingulate cortex and severity of symptoms in OCD.

We did not observe a correlation between the severity of anxiety and rCBF in the areas where activity was modulated by CBD, but this may have been difficult to detect because there was a 15-min gap between the points when the ratings were made and the SPECT tracer was injected.

While the areas where we found modulatory effects of CBD are thus implicated in mediating anxiety, and have also been associated with the anxiolytic effects of diazepam (Di Piero *et al*, 2001), citalopram (Van der Linden *et al*, 2000; Furmark *et al*, 2002), sertraline, and desipramine (Hoehn-Saric *et al*, 2001), these effects of CBD could be related to an effect other than on anxiety. For instance, we also observed sedative effects of CBD, confirming former findings in animals (Pickens, 1981; Monti, 1977; Colasanti *et al*, 1984; Zuardi *et al*, 1981a, 1991) and humans (Carlini *et al*, 1979; Zuardi *et al*, 1982, 1993b). This effect has been reported to be dose-related (Pickens, 1981) and CBD has also been shown to decrease wakefulness (Monti, 1977) and to cause longer sleep duration in insomniacs (Carlini and Cunha, 1981). Thus, the reduced hypothalamic activity observed after CBD use in our study could equally be related to sedative effects of CBD, as suggested to occur with other sedative compounds (Tung *et al*, 2001).

Other pharmacological effects of CBD have been reported in studies in laboratory animals and humans, such as anti-inflammatory (Malfait *et al*, 2000), anticonvulsant (Carlini *et al*, 1973; Izquierdo *et al*, 1973; Cunha *et al*, 1980), neuroprotective (Hampson *et al*, 1998), and hormonal effects (Zuardi *et al*, 1984, 1993a). In addition, the pharmacological profile of CBD is similar to that of clozapine, an 'atypical' antipsychotic drug (Zuardi *et al*, 1991, 1995), and both CBD and clozapine induce *c-fos* expression in the prefrontal cortex and lateral septal nucleus in rats (Zuardi *et al*, 2001). The mechanism(s) of action whereby CBD produces all these effects remains obscure. This is largely in contrast with the effects of Δ^9-THC, which mimics the endogenous cannabinoids in many of its actions. CBD does not act through the known cannabinoid receptors, but the stereospecificity previously observed may indicate that CBD binds to another type of receptor in the brain (Mechoulam *et al*, 2002).

In conclusion, our results suggest that CBD has anxiolytic effects that are mediated through an action on limbic and paralimbic areas of the brain. However, the findings need to be seen as preliminary, given the limitations of the study. Firstly, it would have been desirable to measure plasma levels of CBD and relate them to the magnitude of change in rCBF. Without a dose–response curve, uncertainty about the regional cerebral effects of CBD remains. Nevertheless, it should be pointed out that it is not clear whether there is a relation between plasma levels of cannabinoids—especially CBD—and their clinical effects (Agurell *et al*, 1986). In addition, the subject sample was modest and the use of SPECT limited the study's statistical power. Finally, given the limited spatial resolution of the SPECT technique and the smoothing procedure, the interpretation of large foci of tracer uptake changes as involving different brain structures of small size (such as the amygdala, hippocampus, and hypothalamus) should be made with caution. These limitations could be overcome by examining a larger sample and using functional magnetic resonance imaging, which would permit the acquisition of

greater numbers of images with a better spatial and temporal resolution.

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Review

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

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Cannabidiol (CBD) is a major phytocannabinoid present in the *Cannabis sativa* plant. It lacks the psychotomimetic and other psychotropic effects that the main plant compound Δ^9-tetrahydrocannabinol (THC) being able, on the contrary, to antagonize these effects. This property, together with its safety profile, was an initial stimulus for the investigation of CBD pharmacological properties. It is now clear that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric disorders such as anxiety, depression and psychosis. Although the pharmacological effects of CBD in different biological systems have been extensively investigated by *in vitro* studies, the mechanisms responsible for its therapeutic potential are still not clear. Here, we review recent *in vivo* studies indicating that these mechanisms are not unitary but rather depend on the behavioural response being measured. Acute anxiolytic and antidepressant-like effects seem to rely mainly on facilitation of 5-HT1A-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex. Other effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. Considering its safety profile and wide range of therapeutic potential, however, further studies are needed to investigate the involvement of other possible mechanisms (e.g. inhibition of adenosine uptake, inverse agonism at CB2 receptor, CB1 receptor antagonism, GPR55 antagonism, PPARγ receptors agonism, intracellular (Ca^{2+}) increase, etc.), on CBD behavioural effects.

Keywords: cannabidiol; anxiety; depression; psychosis; serotonin; anandamide

1. HISTORY

Cannabidiol (CBD) is the main non-psychotropic phytocannabinoid present in the *Cannabis sativa* plant, constituting up to 40 per cent of its extract. The chemical characterization of the main cannabinoids present in this plant by Mechoulam's group in the 1960s [1] originated the first wave of scientific interest in this compound. With the discovery of the endocannabinoid (eCB) system in the early 1990s and the rise, in the words of Bill Devane [2], of the new dawn of cannabinoid pharmacology, there was a renewed interest in CBD, with the number of related published studies growing exponentially since then.

Recent comprehensive reviews suggest that this compound is one of the most promising candidates for a therapeutic tool in a wide range of disorders [3,4]. In the present paper, we will review the evidence that supports its use in psychiatric disorders and the proposal mechanisms that try to explain it.

2. CANNABIDIOL AND ANXIETY

Early reports describing the effects of CBD in animal models of anxiety were inconsistent. Silveira Filho &

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One contribution of 15 to a Theme Issue 'Endocannabinoids in nervous system health and disease'.

Table 1. Preclinical and clinical studies investigating the anxiolytic properties of CBD. ↓, anxiolytic effect; ↑, anxiogenic effect; CFC, contextual fear conditioning; EPM, elevated plus maze; ETM, elevated T maze; GAD, generalized anxiety patients; OF, open field; VCT, Vogel conflict test; i.p., intraperitoneal injection; i.c.v., intracerebroventricular injection; DPAG, dorsal periaqueductal grey; BNST, bed nucleus of the stria terminalis; PL, prelimbic cortex; IL, infralimbic cortex; CeA, central amygdala.

model	species	effective doses	CBD effect	references
studies with laboratory animals				
Geller-Seifter conflict model	rat	100 mg kg^{-1} i.p.	no effect	[5]
conditioned emotional responses	rat	10 mg kg^{-1} i.p.	↓	[6]
EPM	rat	2.5–10 mg kg^{-1} i.p	↓	[7]
EPM	mouse	1–10 mg kg^{-1} i.p.	↓	[8]
VCT	rat	10 mg kg^{-1}	↓	[9]
CFC	rat	10 mg kg^{-1} i.p.	↓; decreased autonomic responses	[10]
predator exposure (Cat)+ EPM	rat	5 mg kg^{-1}	↓	[11]
restraint stress + EPM	rat	30 nmol intra-cisterna magna	decreased autonomic and delayed anxiogenic effect	[12]
predator exposure (snake)	mouse	3–30 mg kg^{-1} i.p.	panicolytic	[13]
marble burying	mouse	30 mg kg^{-1} i.p	decreased compulsive behaviour	[14]
CFC/fear memory extinction	rat	6.35 nmol i.c.v.	↓; facilitated extinction	[15]
ETM/DPAG electric stimulation	rat	30–60 nmol intra-DPAG	↓, panicolytic	[16]
restraint stress + EPM	rat	10 mg kg^{-1} i.p.	decreased autonomic and delayed anxiogenic effect	[17]
EPM/VCT	rat	15–30 nmol intra-DPAG	↓	[18]
EPM/VCT	rat	30–60 nmol intra-BNST	↓	[19]
CFC	rat	30–60 nmol intra-BNST	↓, decreased autonomic responses	[20]
CFC	rat	30 nmol intra-PL	↓	[21]
CFC	rat	30 nmol intra-IL	↑	[21]
CFC	rat	10 mg kg^{-1} i.p./daily/14 days	↑	[22]
CFC/fear reconsolidation	rat	10 mg kg^{-1} i.p.	↓; memory reconsolidation impairment	[23]
model/measures	subjects	dose (mg, p.o.)	CBD effect	references
clinical studies				
simulated public-speaking	healthy volunteers	400 mg	↓	[24]
neuroimaging study	healthy volunteers	400 mg	↓	[25]
fearful facial stimuli	healthy volunteers	600 mg	↓	[26]
fearful facial stimuli	healthy volunteers	600 mg	↓	[27]
anxiety symptoms (visual analogue mood scale)	GAD	400 mg	↓	[28]
simulated public speaking	social phobics	400 mg	↓	[29]

Tufik [5] did not find any effect of CBD (100 mg kg^{-1}) in rats tested in the classical Geller-Seifter conflict model of anxiety, whereas Zuardi & Karniol [6] described that a much lower CBD dose (10 mg kg^{-1}) attenuated conditioned emotional responses. These apparent contradictory results were subsequently explained by Guimarães *et al.* [7]. Using an ethologically based model of anxiety, the elevated plus maze, they showed that CBD promotes anxiolytic-like effects with an inverted U-shaped dose-response curve, higher doses (more than 20 mg kg^{-1} in rats) being ineffective (table 1).

The anti-anxiety properties of CBD in rats were later confirmed in different species (mice) and animal models, including the Vogel conflict test and contextual fear conditioning [8–10]. More recently, CBD was shown to decrease defensive behaviours evoked by predator exposure, a proposed model of panic attacks and posttraumatic stress disorder (PTSD) [11,13]. CBD also reduces marble burying behaviour in mice, suggesting that this compound could be effective in obsessive-compulsive disorder (OCD) [14]. Moreover, CBD can interfere in learning and/or memory of aversive events, processes that have

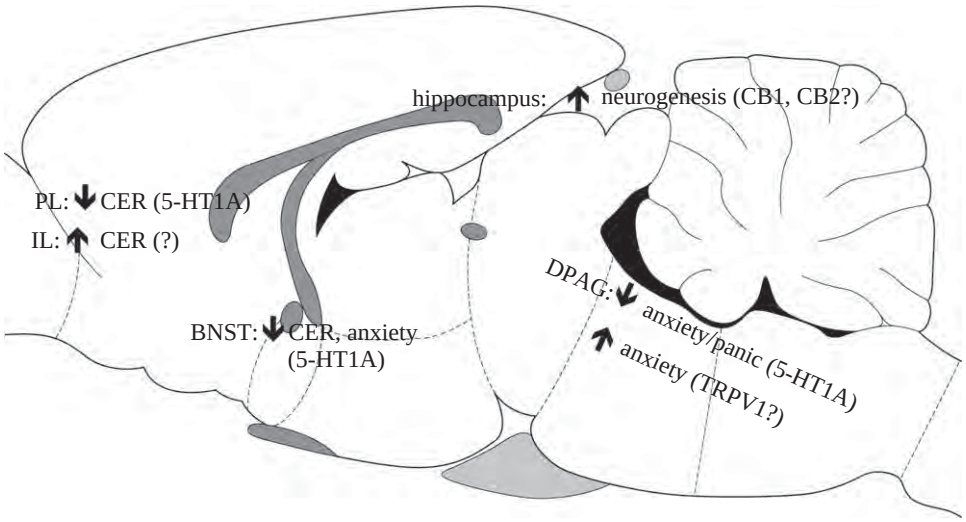

Figure 1. Possible brain sites and mechanisms of CBD effects on anxiety. BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CER, conditioned emotional response; DPAG, dorsal periaqueductal grey; IL, infralimbic prefrontal cortex; PL, prelimbic prefrontal cortex.

been associated with PTSD pathophysiology [30]. Intracerebroventricular administration of CBD facilitates extinction in a contextual aversive conditioning model [15]. In this same paradigm, it can also impair reconsolidation, resulting in the attenuation of the aversive memory trace. In this study, the impairment of contextual fear memory did not show reinstatement and was long-lasting (22 days) [23]. Contrasting with these results, Elbatsh *et al.* [22] have recently reported that repeated (14 days) administration of CBD increases freezing in a contextual fear conditioning test. The reasons for this difference is unknown, but may involve the distinct conditioning protocols and drug administration regime (chronic versus acute) used compared with other studies that investigated the effects of CBD in this model [15,21,23]. Moreover, in this study, it is also possible that CBD could have interfered in learning/memory mechanisms, because the animals were conditioned under the drug effect [22].

(a) *Clinical anxiolytic effects of cannabidiol*

In agreement with the results obtained in animal models, clinical studies confirmed that CBD has anxiolytic properties (table 1). Following the initial report that it blocks the anxiogenic effects of high doses of the main psychoactive compound present in the *Cannabis sativa* plant, Δ^9-tetrahydrocannabinol (THC) [31], it was demonstrated that CBD can also reduce anxiety in healthy volunteers during a neuroimaging study or after a simulated public-speaking procedure [24,25]. More recently, using the latter procedure, Bergamaschi *et al.* [29] showed that CBD (600 mg p.o.) decreases anxiety in treatment-naive social phobic patients.

(b) *Brain sites of cannabidiol anxiolytic effects*

Neuroimaging studies show that CBD changes the activity of brain regions related to the control of emotional process [25,27]. It attenuates blood oxygenation in the amygdala and the anterior and posterior cingulate cortex in subjects exposed to fearful faces [27], impairs the connectivity between the pre-frontal and subcortical regions [27] and decreases the activation of left-amygdala–hippocampal complex and left posterior cingulate gyrus [25].

These clinical findings were complemented by studies in rodents, using direct administration into brain sites related to anxiety- or panic-like responses (figure 1). Microinjection of CBD into the dorsal portions of the periaqueductal grey (DPAG) promoted anxiolytic-like effects in the elevated plus maze, elevated T maze and Vogel conflict tests. It also decreased escape latency in a model of panic attacks, electrical stimulation of the DPAG [16,18]. Anxiolytic effects were also found after CBD injection into the bed nucleus of the *stria terminalis* (BNST) in rats tested in the elevated plus maze, Vogel conflict test and contextual fear conditioning [19,20]. This latter effect corroborates results showing that the effects of CBD in a contextual fear conditioning model is associated with decreased neuronal activation (measure by cFos expression) in this area [21]. This same treatment attenuated the activation of the pre- and infra-limbic cortical regions. In these two brain areas, however, CBD produced opposite effects, decreasing and facilitating, respectively, conditioned emotional responses [10]. Recently, Hsiao *et al.* [26] showed anxiolytic effects of CBD injection into the central nucleus of the amygdala. Other possible brain sites of CBD anxiolytic effect have not yet been investigated (e.g. the hippocampus).

(c) *Mechanisms of the anxiolytic effects of cannabidiol*

CBD can produce multiple pharmacological actions over a wide range of drug concentrations (table 2) [3,4]. CBD is proposed to activate or modify the function of several receptors in the central nervous system (CNS), including CB1, CB2, GPR55, TRPV1 and 5-HT1A receptors (table 2) [32,33,35,42]. Moreover, it could inhibit the anandamide hydrolysing enzyme (fatty acid amide hydrolase, FAAH) and the adenosine

Table 2. Possible mechanisms of CBD behaviour effects. Evidence from *in vitro* studies. CHO, Chinese hamster ovary cells.

biological system	mechanism	biological system	concentration range	references
endocannabinoid/ endovanilloid related mechanisms	CB1 receptor antagonist	mouse brain membranes	4.9 μM (K_i)[a]	[32]
	CB2 receptor inverse agonist	CHO transfected cells	4.2 μM (K_i)[b]	[32]
	TRPV1 agonist	HEK-293 transfected cells	3.2 μM (EC_{50})	[33]
	FAAH/anandamide transporter inhibition	HEK-293 transfected cells, rat brain membranes	7.5–8.6/22 μM (IC_{50})	[33,34]
serotonin-related mechanisms	5-HT1A receptor agonist	CHO transfected cells	16 μM (increases receptor response by 67%)	[35]
	5-HT2A receptor agonist	CHO transfected cells	32 μM (IC_{50})	[35]
	5-HT3 receptor antagonist	*Xenopus laevis* oocytes	10–30 μM	[36]
	suppression of mitogen-induced IDO activity (decreasing tryptophan metabolism)	human blood cells	8.9 μM (IC_{50})	[37]
others	intracellular (Ca^{2+}) increase	hippocampal cell cultures/ hippocampal preparations	approximately 1 μM (effective concentration)	[38,39]
	allosteric modulation of μ and δ opioid receptors	cerebral cortex preparations	100 μM	[40]
	PPARγ receptors agonist	aorta preparations	5 μM (IC_{50})	[41]
	GPR55 antagonist	cell membranes of transfected cells	445 nM (IC_{50})	[42]
	blockade of adenosine uptake/indirect A2 agonist	microglia and macrophages cell cultures	less than 250 nM (K_i)/ 500 nM (effective concentration)	[43,44]
	TRPV2 agonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	3.7 μM (EC_{50})	[45]
	TRPM8 antagonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	80–140 nM(IC_{50})	[46]
	TRPA1 agonist	HEK-293 transfected cells/rat dorsal root ganglia (DRG) sensory neurons	96 nM(EC_{50})	[46]
	P38 MAPKinase inhibition	PC12 cells	10^{-6}–10^{-4} M (effective concentrations)	[47]
	NF-κB activation	PC12 cells	10^{-6}–10^{-4} M (effective concentrations)	[47]
	inhibition of mitochondrial superoxide production	vascular endotelial cells	4 μM (effective concentration)	[48]
	inhibition of inducible nitric oxide synthase (iNOS) expression	kidney	10 mg kg^{-1}	[49]

[a]CBD was able to antagonize the effects of the CB1 agonist CP55940-induced stimulation of [35S]GTPgS binding to mouse brain membranes at a much lower concentration ($K_B = 79$ nM) than the K_i for displacement of the CB1 ligand.
[b]CBD acts as an inverse agonist with a lower concentration ($K_B = 65$ nM) than the K_i for displacement of the CB2 ligand.

transporter [33,43,50], indirectly increasing the levels of these neurotransmitters.

Some of CBD effects involve intracellular pathways that play fundamental roles in neuronal physiology. For example, in hippocampal neurons, CBD increases intracellular calcium concentrations via mitochondrial uptake and release and/or activation of type-L voltage-gated calcium channels [38,39]. CBD has also a potent action in inhibiting oxidative and nitrosative stress, a mechanism that has been related to its neuroprotective effects with implications for the treatment of Alzheimer's, Huntington's and Parkinson's diseases. It decreases the neuronal damage promoted by β-amyloid protein deposit [47,51] and attenuates the depletion of tyrosine hydroxylase, dopamine and GABA levels by modulating the expression of the inducible nitric oxide synthase and reducing the production of reactive oxygen species (ROS)-generating NADPH oxidases [47,52–54]. Moreover, CBD pretreatment attenuated high-glucose-induced mitochondrial superoxide generation and NF-κB activation, along with the expression of adhesion molecules ICAM-1 and VCAM-1 [48]. Together, these results suggest that CBD can exert CB1- and

CB2-independent neuroprotective/antioxidant/anti-inflammatory effects [48].

The large majority of these possible mechanisms have been unveiled by *in vitro* studies. Their association to the behaviour effects of CBD is still not clear, a topic that is further complicated by the common bell-shaped dose-response curves produced by this compound in distinct biological systems [4].

In the last decade, however, several *in vivo* studies have helped us to understand the mechanisms of CBD central effects.

(d) In vivo *mechanisms of cannabidiol anxiolytic effects: 5-HT1A receptors*

Russo *et al.* [35] were the first to suggest that CBD could act as a 5HT1A receptor agonist. They observed that, at μM range, this drug displaces 8-OH-DPAT, a 5-HT1A receptor agonist, from cloned human 5-HT1A receptors expressed in cultured cells obtained from Chinese hamster ovary. *In vivo* experiments gave further support to the involvement of 5-HT1A receptors in the effects of CBD [18–20,55]. For instance, the neuroprotective effects of CBD in hepatic encephalopathy or cerebral infarction are mediated by these receptors [55,56]. Regarding the behavioural studies, the effects of CBD in a PTSD model (predator exposure) were prevented by WAY100635, a 5HT1A receptor antagonist [11]. This same antagonist prevented the anxiolytic- and panicolytic-like effects of CBD after injections into the DPAG [16,18], bed nucleus of the stria terminalis [19,20] and prefrontal cortex (M. V. Fogaça & F. S. Guimarães 2012, unpublished data; figure 1). In humans, although no study so far has investigated the involvement of 5-HT1A mechanisms in CBD effects, the anxiolytic profile of this drug in the public speaking model was remarkably similar to the positive control ipsapirone, a 5HT1A receptor partial agonist [24].

Other CBD effects also involve 5-HT1A receptors. It decreases nausea and vomiting probably by an indirect agonism at these receptors. Although the mechanism of this indirect action is unclear, it may involve interactions with allosteric sites or changes in different systems that would result in a facilitation of 5-HT1A-mediated responses [57]. Adding to the evidence that the interaction of CBD with 5-HT1A receptors could be complex, it was recently shown that this compound antagonizes food intake induced by 8-OH-DPAT [58]. Therefore, additional research is clearly needed to clarify how CBD facilitates 5-HT1A-mediated neurotransmission.

(e) In vivo *mechanisms of cannabidiol effects: the endocannabinoid system*

CBD could facilitate eCB-mediated neurotransmission by blocking the metabolism and uptake of anandamide [33]. However, AM251, a CB1 receptor antagonist, failed to prevent the anxiolytic effects of CBD injected into the DPAG observed in the elevated plus maze at the same dose that antagonized the anxiolytic effects of anandamide [18,59].

On the other hand, CB1, but not 5-HT1A, receptor antagonism was able to prevent CBD effects on both extinction and reconsolidation, indicating that its interference on aversive memories involves eCB-mediated mechanisms [15,23]. These results agree with the well-described facilitation of extinction by endogenous cannabinoids [60], suggesting that CBD interferes with aversive memories by facilitating the effects of eCBs [45].

Finally, AM251 blocked CBD effects in the marble burying model [14], whereas 5-HT1A-receptor antagonism was ineffective. This result corroborates the proposal that anxiety and OCD models engage distinct brain mechanisms, with the marble burying behaviour being related to repetitive behaviours instead of anxiety [61].

How facilitation of eCB-mediated neurotransmission decreases repetitive behaviour is unknown, but may involve attenuation of glutamate-mediated neurotransmission. eCBs can reduce the release of several neurotransmitters, including glutamate [62], a major neurotransmitter of the cortico-striato-thalamo-cortical circuitry that has been implicated in the pathophysiology of OCD [63]. Anti-glutamatergic drugs such as riluzole and memantine decrease marble burying behaviour [64,65] and are proposed to be clinically useful for OCD treatment [66,67].

An indirect anti-glutamatergic action via increased eCB neurotransmission may also be involved in other central effects of CBD such as anticonvulsant [3], an effect that could also be related to indirect CB1-mediated inhibition of glutamate release. Corroborating this proposal, anticonvulsant effects of other inhibitors of anandamide metabolism/uptake have recently been described [3]. Moreover, epileptic patients present a significant reduction in the fraction of CB1-positive glutamatergic, but not GABAergic, axon terminals, probably resulting in increased neural excitability [68].

(f) In vivo *mechanisms of cannabidiol effects: adult hippocampal neurogenesis*

Impairment in adult hippocampal neurogenesis has been associated with the pathogenesis of anxiety disorders and depression [69] and at least some of the behavioural effects of prototype antidepressant drugs depend on facilitation of this process [70]. CBD can also increase adult hippocampal neurogenesis, as first demonstrated by Wolf *et al.* [71]. They also showed that the proneurogenic effect of CBD was absent in CB1-knockout mice [71]. Because CBD is not a CB1-receptor agonist, this result suggested that CBD effect was mediated by an indirect activation of these receptors, possibly by inhibition of anandamide metabolism/uptake [33]. Corroborating this latter possibility, recent results from our group showed that CBD increases proliferation of hippocampal progenitor cells in culture, an effect mimicked by CB_1 or CB_2 receptor agonists and prevented by antagonists of these receptors [72]. Moreover, CBD effects were also inhibited by overexpression of the FAAH, reinforcing the proposal of anandamide involvement. These results agree with those previously reported by Jiang *et al.* [73] showing that a synthetic CB1 agonist is able to promote embryonic and adult hippocampus neurogenesis, an effect associated with the anxiolytic

and antidepressant properties of the drug. Similar to prototype antidepressants, the anxiolytic effect of repeated administered CBD (30 mg/daily for 14 days) in mice submitted to a chronic unpredictable stress model disappeared when hippocampal neurogenesis was inhibited [72], suggesting a causal link between its proneurogenic and anxiolytic effect after repeated administration (figure 1).

Other mechanisms could also be involved in CBD effects on adult hippocampal neurogenesis—for example, activation of peroxisome proliferator-activated receptors. This particular mechanism seems to be important during neuroinflammation and neurodegenerative process related to β-amyloid protein deposits in CNS [51]. Although the pro-neurogenic effect of CBD has not yet been studied in rats, it could help us to explain the recent report that repeated CBD treatment enhances contextual fear conditioning [22]. Immature newborn neurons are selectively activated by this task [74], and neurogenesis suppression impairs contextual fear memory [75]. Considering the important role proposed for hippocampal neurogenesis in several brain functions [76,77], the effects and mechanisms of CBD on this process is another important research venue to be pursued.

(g) *Cannabidiol and the vanilloid system*

CBD can activate transient receptor potential (TRP) channels [33]. These channels comprise a family of over 50 members and are present in different species, including yeast, worms, insects, fish and mammals [78]. The vanilloid receptor 1 or TRPV1 is one of the first identified members of the family, being a non-selective cation channel with a preference for calcium. It is activated by noxious stimuli, heat, protons ($pH < 5.9$) and various, mostly noxious, natural products such as capsaicin [79]. TRPV1 receptors are present in the brain, where anandamide has been proposed to act as an endogenous agonist or an endovanilloid [80]. These receptors can facilitate the release of glutamate [81], a neurotransmitter that induces defensive responses in brain areas such as the DPAG [82]. On the basis of these pieces of evidence, we hypothesized that TRPV1 activation could be at least partially responsible for the inverted U-shaped dose-response curves commonly observed with CBD. Accordingly, using intra-DPAG injections, we showed that local pretreatment with an ineffective dose of the TRPV1 antagonist capsazepine turned a higher, ineffective dose (60 nmol) of CBD into an anxiolytic one [83]. TRPV1 receptors are also involved in the bell-shaped dose responses curves of anandamide analogues [84,85].

In addition to TRPV1, CBD could also interfere with other members of the TRP family, activating TRPV2 and ankyrin type 1 (TRPA1) channels and antagonizing melastatin type 8 (TRPM8) channels [45,46]. The role played by these mechanisms on CBD behavioural effects, however, is unknown at the moment.

3. CANNABIDIOL AND PSYCHOSIS

Initial studies with laboratory animals suggested that CBD prevents some of the effects produced by THC [86]. Similar antagonism was also found in humans, where CBD attenuated the impairment of time production tasks and the euphoria induced by THC in healthy volunteers [87,88]. Confirming and extending these results, Zuardi *et al.* [31] demonstrated that CBD inhibits THC-induced anxiety and psychotic-like symptoms such as disconnected thoughts, perceptual disturbance, depersonalization and resistance to communication. In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa after the use of a variety of *Cannabis* virtually devoid of CBD showed a much higher frequency of acute psychotic episodes than in other countries [89], suggesting that the presence of CBD in *Cannabis* samples protects users against the occurrence of THC-induced acute psychotic episodes. Because experimental evidence indicates that the antagonistic effect of CBD did not result from a pharmacokinetic interaction between the two cannabinoids [90], these initial observations led to the hypothesis that CBD could possess antipsychotic properties.

An initial study in rats investigated whether this compound could attenuate stereotypies induced by the dopaminergic agonist apomorphine. CBD effects were compared with those of haloperidol [91]. Both drugs reduced apomorphine-induced stereotyped behaviour in a dose-related manner. Even though they increased plasma levels of prolactin, CBD had much lower potency, with significant increases only seen after the doses of 120 and 240 mg kg^{-1}. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg kg^{-1}. These results suggest that CBD exhibits a profile similar to atypical antipsychotic drugs. In another study, CBD was compared with haloperidol and clozapine, an atypical antipsychotic drug. The drug inhibited the hyperlocomotion induced by amphetamine and ketamine, an NMDA receptor antagonist, in mice [92]. As expected, while both haloperidol and clozapine inhibited hyperlocomotion, only haloperidol induced catalepsy. These results extend CBD antipsychotic-like effects to a glutamate-based model. In agreement with these results, CBD, similar to clozapine, reversed the disruption of prepulse inhibition (PPI) in mice and the hyperactivity and reduction of social interaction in rats caused by MK-801, another NMDA receptor antagonist [93,94]. Typical antipsychotics, on the other hand, are usually unable to restore the deficits in PPI and social interaction induced by NMDA receptor antagonists [95,96].

Extending findings from studies using single drug administration, chronic treatment with CBD attenuated amphetamine-induced hyperlocomotion [97]. Preliminary results from our group indicate that this treatment regime is also able to decrease the impairments in PPI and object recognition induced by repeated administration of MK-801 (F. V. Gomes, E. A. Del Bel & F. S. Guimarães, unpublished data). Despite these findings, there are also negative results regarding the possible antipsychotic effects of CBD. Chronic treatment with this drug failed to change behavioural changes such as locomotor hyperactivity and PPI deficits observed in transmembrane domain neuregulin 1 mutant (Nrg1) mice, a proposed model for a schizophrenia susceptibility gene [98]. A summary of

Table 3. Preclinical and clinical studies investigating the antipsychotic properties of CBD. ↓, antipsychotic-like effects; BPRS, brief psychiatric rating scale; CADSS, clinician administered dissociative states scale; PANSS, positive and negative syndrome scale; PPQ, Parkinson psychosis questionnaire.

model	species	effective doses	CBD effects	references
studies with laboratory animals				
apomorphine-induced stereotyped behaviour	rat	60 mg kg^{-1}	↓	[91]
D-amphetamine- and ketamine-induced hyperlocomotion	mouse	15–60 mg kg^{-1}	↓	[92]
MK-801-induced disruption of PPI	mouse	5 mg kg^{-1}	↓	[93]
D-amphetamine-induced hyperlocomotion	mouse	50 mg kg^{-1} (chronic – 21 days)	↓	[97]
MK-801-induced social withdrawal and isruption of PPI	rat	3–30 mg kg^{-1}	↓	[99]
MK-801-induced hyperlocomotion and deficits in social interaction and	rat	3 mg kg^{-1}	↓	[94]
locomotor hyperactivity and PPI	*Nrg 1* mutant mouse	1, 50 and 100 mg kg^{-1}	no effects	[98]
model/measures	subjects (*n*)	doses	CBD effects	references
clinical studies				
THC-induced impairment of time production task	healthy male volunteers (40)	15–60 mg (acute)	↓	[87]
THC-induced euphoria	healthy male volunteers (15)	0.15 mg kg^{-1} (inhalation; acute)	↓	[88]
THC-induced psychotic symptoms	healthy male volunteers (eight)	1 mg kg^{-1} (acute)	↓	[31]
nabilone-induced impairment of perception of binocular depth inversion	healthy male volunteers (nine)	200 mg (acute)	↓	[100]
THC-induced psychotic symptoms (PANSS)	healthy male and female volunteers (six)	5 mg (iv, acute)	↓	[101]
ketamine-induced psychotic symptoms (BPRS and CADSS)	healthy male volunteers (10)	600 mg (acute)	↓ (trend)	[102]
psychotic symptoms (BPRS)	schizophrenic female patient (one)	increasing oral doses of CBD, reaching 1500 mg d^{-1} (four weeks)	↓	[103]
psychotic symptoms (BPRS)	male patients with treatment-resistant schizophrenia (three)	increased from 40 up to 1280 mg d^{-1} (30 days)	one patient showed mild improvement	[104]
L-dopa-induced psychosis (BPRS and PPQ)	Parkinson's disease patients (six)	increased from 150 up to 600 mg d^{-1} depending on the clinical response (four weeks)	↓	[105]
psychotic symptoms (BPRS and PANSS)	acute paranoid schizophrenia patients (42)	600 mg d^{-1} (four weeks)	↓	[34]
Stroop Colour Word Test	schizophrenic patients (28)	300 and 600 mg (acute)	no effect	[106]

the studies investigating the antipsychotic-like effects of CBD in animal models can be seen in table 3.

(a) *Cannabidiol and psychosis: clinical studies*

The antipsychotic-effects of CBD have also been demonstrated in humans (table 3). In healthy volunteers, Leweke *et al.* [100] observed that the decrease of the perception of illusory image induced by nabilone, a synthetic cannabinoid drug with THC-like properties, was reduced by CBD. Another model used to evaluate antipsychotic-like activity of drugs in humans is the administration of sub-anaesthetic doses of ketamine. This drug induces psychotic symptoms that mimic both positive and negative symptoms of schizophrenia. An initial investigation in healthy subjects showed that CBD induced a non-significant trend to reduce ketamine-induced dissociative effects, but, at the same time, augmented the activating effects of ketamine

[102]. Because only a single dose of CBD was used, additional studies are needed to characterize the effects of CBD in this model [102].

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In an open, case-report study, a 19-year-old black schizophrenic female patient, who presented serious side effects after treatment with conventional antipsychotics, received increasing oral doses of CBD (up to 1500 mg d^{-1}) for four weeks [103]. A significant improvement with no side effects was observed in all items of the standard brief psychiatric rating scale (BPRS) during CBD treatment, with an efficacy similar to that of haloperidol. Symptom worsening was observed when the administration was interrupted. In another case study, CBD was administered to three 22- or 23-year-old male schizophrenic patients who had not responded to typical antipsychotic drugs for 30 days [104]. The dose of CBD was increased from 40 up to 1280 mg d^{-1}. One patient showed mild improvement, but only slight or no change was observed in the other two, suggesting that CBD may not be effective for the treatment of resistant schizophrenia. Moreover, CBD had no beneficial effects on the performance of schizophrenic patients in the Stroop colour word test, which can be used to assess attentional processes frequently impaired in schizophrenia [106]. It is still unknown whether chronic administration of CBD could improve the cognitive deficits in the disorder. No significant side effects were observed during CBD treatment in these clinical studies, suggesting that CBD is safe and well tolerated in schizophrenic patients.

In an open-label study evaluating CBD effects on psychotic symptoms associated with L-dopa use in Parkinson's patients [105], the drug decreased scores of a questionnaire developed to assess psychotic symptoms in Parkinson's disease (Parkinson psychosis questionnaire), improved total BPRS scores as well as scores specifically related to positive and negative symptoms. Confirming the lack of motor effects observed in animal studies, CBD did not affect motor function. On the contrary, it decreased the total scores of the unified Parkinson's disease rating scale, suggesting an improvement of this function.

Overall, therefore, even if there are negative results, most clinical studies with normal subjects or schizophrenic patients suggest that CBD has antipsychotic properties. Corroborating this possibility, a four-week double-blind controlled clinical trial in 42 acute schizophrenic and schizophreniform psychosis patients comparing the effects of CBD with those of amisulpride, an atypical antipsychotic, showed that both treatments were equally effective in reducing acute psychotic symptoms after two and four weeks of treatment [34]. Moreover, compared with amisulpride, CBD caused a lower incidence of extrapyramidal symptoms and increases in prolactin and weight gain.

The presence of antipsychotic properties in CBD is also supported by convergent evidence linking the habitual use of *Cannabis* to the risk of developing schizophrenia or schizophrenia-like psychosis, especially in vulnerable subjects [107]. This effect has been attributed to THC. In agreement with the initial reports showing antagonism of THC-induced psychotomimetic effects [31,87,88], the presence of CBD in *Cannabis* strains has been shown to be protective against the occurrence of psychotic-like reactions and cognitive impairment [108–110]. In this context, Di Forti *et al.* [111] found that the use of *Cannabis* containing high THC- and low CBD concentration was associated with a higher risk of a first psychotic episode. Furthermore, the presence of CBD protects from *Cannabis*-associated decrease in hippocampal volume [112]. This neuroprotective effect of CBD has also been reported in the human basal ganglia, where there was a strong positive correlation between *N*-acetylaspartate/total creatine ratio and the amount of CBD (as measured by its presence in hair samples) in the putamen/globus pallidum of recreational *Cannabis* users. This finding could reflect a CBD-induced enhancement of neuronal and axonal integrity in these regions [113]. More recently, Bhattacharyya *et al.* [114], investigating the effects of THC and CBD during attentional salience processing, have also showed that these two cannabinoids produce opposite effects on prefrontal, striatal and hippocampal functions.

(b) *Brain sites and mechanisms of cannabidiol antipsychotic effects*

Few studies in laboratory animals have investigated the possible brain sites and mechanisms of CBD antipsychotic effects. Consistent with the behavioural data described earlier, both CBD and clozapine, but not haloperidol, increased neuronal activation (measured by cFos-protein expression) in the prefrontal cortex. Probably reflecting its motor side effects, only haloperidol increased cFos in the dorsal striatum. CBD, and, in addition, increased cFos in the nucleus accumbens [115], an effect shared by typical and atypical antipsychotic drugs [116]. Intracerebroventricular administration of CBD (10 μg) also enhanced cFos expression in waking-related brain areas such as hypothalamus and dorsal raphe nucleus [117], but the relation between this finding and its antipsychotic properties is unclear.

A number of neuroimaging studies in healthy volunteers have compared the effects of CBD and high doses of THC. Consistent with the behavioural findings in humans and rodents, these drugs caused opposite effects on brain activity in the striatum, anterior cingulate, prefrontal cortex, parahippocampal gyrus, amygdala, right posterior superior temporal gyrus, middle occipital gyrus and cerebellum [27, 101,114,118–120]. Behavioural measurements in these studies indicated that some of these changes (decreased activation of ventral and dorsal striatum, anterior cingulate gyrus, right temporal lobe) are associated with the psychotic-like effects of THC, suggesting that these regions could be possible brain suites of CBD action [121]. No study using direct injections into key brain regions associated with the pathophysiology of schizophrenia, such as the prefrontal cortex and nucleus accumbens, has been performed so far to investigate CBD antipsychotic properties.

Regarding the pharmacological mechanisms, intracerebroventricular administration of CBD enhanced extracellular levels of dopamine in the nucleus accumbens [122]. A similar finding was found after

Table 4. Antidepressant-like effects of CBD. Studies with laboratory animals. FST, forced swimming test; TST, tail suspension test.

model	species	effective doses	CBD effects	references
restraint stress	rat	10–20 mg kg^{-1}	↓ cardiovascular and behavioural effects of stress	[17]
FST	mouse	200 mg kg^{-1}	↓ immobility	[127]
TST	mouse	20–200 mg kg^{-1}	no effect	[127]
FST	mouse	30 mg kg^{-1}	↓ immobility	[128]
chronic unpredictable stress	mouse	30 mg kg^{-1} (daily, chronic treatment)	↓ the behavioural consequences of stress through enhancement of hippocampal neurogenesis	[72]

microdialysis perfusion of CBD (30, 60 or 90 nM) into the rat lateral hypothalamus [117], a procedure that also enhanced alertness. It is unclear how this effect would relate to the antipsychotic properties of CBD because usual antipsychotic drugs act by antagonizing dopamine-2 receptors [123]. Moreover, studies with animal models that involve dopaminergic stimulation suggest that the antipsychotic-like doses of CBD (60–120 mg kg^{-1}) are higher than those needed to induce anxiolytic-like effects [7,91,92] and reverse behavioural deficits induced by the NMDA receptor antagonist MK-801 [93,94,99]. These findings indicate that the mechanisms of CBD effects on glutamate- or dopamine-based models could be at least partially distinct. This possibility needs to be further explored.

Recently, Leweke *et al.* [34] showed that schizophrenic patients treated with CBD present higher anandamide serum levels compared with those receiving the antipsychotic amisulpride. Moreover, in the CBD group, there was a significant association between anandamide levels and improvement of psychotic symptoms. In the same study, they confirmed, *in vitro*, that CBD inhibits FAAH activity in a concentration (10 μM) that does not interact with receptors (dopamine, GABA, serotonin and glutamate) commonly associated with schizophrenia. However, by indirectly activating CB1 receptors via increased levels of anandamide, CBD could potentially modulate neurotransmitters systems related to these receptors [121,124]. Moreover, as previously discussed, facilitation of CB1-mediated neurotransmission by CBD also increases adult hippocampal neurogenesis, a mechanism that could be related to the cognitive deficits found in schizophrenic patients [124].

As discussed already, CBD and anandamide can also activate TRPV1 channels. This mechanism, probably by facilitating the pre-synaptic release of glutamate [80], is involved in the ability of CBD to reverse the disruption of PPI induced by the NMDA receptor antagonist MK-801 [93].

Other mechanisms that could also help us to explain CBD anti-psychotic effects are facilitation of 5-HT1A-mediated neurotransmission, an effect shared by the atypical anti-psychotic aripiprazole, which acts as a partial agonist at these receptors, and anti-inflammatory/neuroprotective action [124].

4. CANNABIDIOL AND DEPRESSION

Cannabis sativa exerts significant effects upon humour, which include euphoria and mood elevation [125]. THC may account for most of these effects through activation of CB1 receptors. Considering these observations, as well as the effects of synthetic cannabinoids and drugs that increase eCB levels, a putative role for the eCB system in mood disorders has been proposed [126]. The effects of CBD, however, have been scarcely investigated (table 4). The fact that this compound, in addition to facilitating eCB activity [33], may facilitate the activation of 5-HT1A receptors [35] suggests that it might also have antidepressant-like properties. 5HT1A receptors modulate responses to stressful stimuli and are proposed to mediate the effects of antidepressant drugs [129].

Stress exposure is a key aetiological factor in depression [130] and animal models used to study antidepressant-like effects are generally based on acute responses to inescapable aversive stimuli, which are prevented by antidepressants [131]. Alternatively, considering the nature of depression as a chronic psychiatric disorder, some models investigate drug effects upon the diverse consequences of chronic stress, including anhedonia and changes in exploratory activity [132].

One of the first studies that indicate the presence of antidepressant-like properties in CBD focused on its ability to prevent the autonomic and behavioural consequences of inescapable stress [17]. Rats were submitted to restraint stress during 60 min, which increases heart rate and blood pressure and caused anxiogenic-like responses in rats exposed to the elevated plus maze 24 h later. CBD was injected 30 min before the stress at the doses of 1, 10 or 20 mg kg^{-1}. The doses of 10 and 20 mg kg^{-1} attenuated the changes in autonomic parameters, whereas at 10 mg kg^{-1} CBD also prevented the late anxiogenic-like effect of stress. There were no changes in motor activity or basal cardiovascular parameters, discarding any possible confounding factor [17]. Similar effects were observed after intra-cisterna magna administration of CBD [12], thus suggesting that these effects are centrally mediated.

Another behavioural model widely used to assess antidepressant-like effects, mainly due to its pharmacological predictability, is the forced swim test. In this assay, rats or mice exposed to inescapable swimming assume a posture of immobility, which is reversed by antidepressants [131]. We tested in mice the effects of CBD (3–100 mg kg^{-1}) injected 30 min prior to the test [128]. The drug produced an inverted U-shaped dose-response curve. At the dose of 30 mg kg^{-1}, it reduced immobility similar to the tricyclic antidepressant imipramine (30 mg kg^{-1}). Our behavioural

findings in the forced swimming test were confirmed by another study, published in the same year. CBD was tested at the doses of 20, 100 and 200 mg kg^{-1} [127], with the higher dose being effective. The drug had no effect, however, in the mouse tail suspension test. One drawback common to all these studies is that the animals received only acute injections. Depression, however, is a chronic disorder that requires long-lasting drug treatment [130]. CBD has been recently tested against the consequences of chronic unpredictable stress, which includes anhedonia and anxiety-like behaviour [130]. Chronic treatment with CBD was able to prevent these behavioural changes, an effect that depends on hippocampal neurogenesis, similar to antidepressant drugs [72]. This observation further strengthens the notion that this natural cannabinoid should be considered as a potential approach for the treatment of mood disorders.

Despite this body of evidence, no clinical study has investigated whether CBD can decrease depressive symptoms in patients. This compound has been tested, however, in patients suffering from bipolar disorders, a subtype of mood disorder, in whom it was not effective in treating manic episodes [133]. Actually, this is in line with animal models, in which CBD failed to prevent hyperactivity in rodents [134].

To summarize, although the data are scarce, preclinical studies so far do provide evidence that this compound could induce antidepressant-like effects. Clinical studies are important to confirm this possibility.

(a) *Mechanisms of cannabidiol antidepressant effects*

Similar to findings with animal models of anxiety, the attenuation of the behavioural consequences of restraint stress and the antidepressant-like effects of CBD in the forced swimming test were attenuated by a 5-HT1A receptor antagonist [17,128]. In the latter model, despite the association between increased expression of neurotrophic factors and antidepressant activity [130], CBD failed to modify brain-derived neurotrophic factor hippocampal levels [128].

As discussed earlier, CBD can also facilitate hippocampal neurogenesis, probably by facilitation of eCB neurotransmission [72]. The involvement of this mechanism on its antidepressant-like properties after repeated administration remains to be investigated.

5. CONCLUSIONS

CBD is a safe compound with a wide range of therapeutic applications, including the treatment of psychiatric disorders [3,4]. These findings make this drug an attractive candidate for future clinical use. Its therapeutic use, however, has some limiting factors. In addition to its low and variable oral bioavailability in humans [135], it causes bell-shaped dose-response curves and, judging from the studies with laboratory animals, possesses a narrow therapeutic dose range. A clear target of future research, therefore, is to try to develop compounds with similar safety and clinical profile but with larger effective dose ranges. To this aim, a better understanding of the mechanisms responsible for the unique properties of CBD is essential.

The behaviour studies reviewed here clearly indicate that more than one mechanism is involved, depending on the effects being measured (anxiolytic, anti-compulsive, antidepressant or antipsychotic-like) and the drug regime (single versus repeated administration). Facilitation of 5-HT1A-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex, seems responsible for CBD acute anxiolytic-like effects. Other CBD effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, facilitation of adult hippocampal neurogenesis and blockade of the anxiogenic consequences of chronic unpredictable stress could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. In addition to these mechanisms, CBD can interfere in several other important biological processes (e.g. inhibition of adenosine uptake, inverse agonism at CB2 receptor, CB1 receptor antagonism, GPR55 antagonism, PPARγ receptors agonism, intracellular (Ca^{2+}) increase, etc.). Additional *in vivo* studies are clearly needed to investigate their possible involvement on CBD behavioural effects.

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REVIEW

Cannabidiol as a Potential Treatment for Anxiety Disorders

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Abstract Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Keywords Cannabidiol · Endocannabinoids · Anxiety · Generalized anxiety disorder · Post-traumatic stress disorder

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Introduction

Fear and anxiety are adaptive responses essential to coping with threats to survival. Yet excessive or persistent fear may be maladaptive, leading to disability. Symptoms arising from excessive fear and anxiety occur in a number of neuropsychiatric disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive–compulsive disorder (OCD). Notably, PTSD and OCD are no longer classified as anxiety disorders in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders-5; however, excessive anxiety is central to the symptomatology of both disorders. These anxiety-related disorders are associated with a diminished sense of well-being, elevated rates of unemployment and relationship breakdown, and elevated suicide risk [1–3]. Together, they have a lifetime prevalence in the USA of 29 % [4], the highest of any mental disorder, and constitute an immense social and economic burden [5, 6].

Currently available pharmacological treatments include serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressant drugs, and partial 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonists. Anticonvulsants and atypical antipsychotics are also used to treat PTSD. These medications are associated with limited response rates and residual symptoms, particularly in PTSD, and adverse effects may also limit tolerability and adherence [7–10]. The substantial burden of anxiety-related disorders and the limitations of current treatments place a high priority on developing novel pharmaceutical treatments.

Cannabidiol (CBD) is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ^{9}-tetrahydrocannabinol (THC). CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions [11, 12]. In recent

years, CBD has attracted increasing interest as a potential anxiolytic treatment [13–15]. The purpose of this review is to assess evidence from current preclinical, clinical, and epidemiological studies pertaining to the potential risks and benefits of CBD as a treatment for anxiety disorders.

Methods

A search of MEDLINE (PubMed), PsycINFO, Web of Science Scopus, and the Cochrane Library databases was conducted for English-language papers published up to 1 January 2015, using the search terms "cannabidiol" and "anxiety" or "fear" or "stress" or "anxiety disorder" or "generalized anxiety disorder" or "social anxiety disorder" or "social phobia" or "post-traumatic stress disorder" or "panic disorder" or "obsessive compulsive disorder". In total, 49 primary preclinical, clinical, or epidemiological studies were included. Neuroimaging studies that documented results from anxiety-related tasks, or resting neural activity, were included. Epidemiological or clinical studies that assessed CBD's effects on anxiety symptoms, or the potential protective effects of CBD on anxiety symptoms induced by cannabis use (where the CBD content of cannabis is inferred via a higher CBD:THC ratio), were included.

CBD Pharmacology Relevant to Anxiety

General Pharmacology and Therapeutic Profile

Cannabis sativa, a species of the *Cannabis* genus of flowering plants, is one of the most frequently used illicit recreational substances in Western culture. The 2 major phyto- cannabinoid constituents with central nervous system activity are THC, responsible for the euphoric and mind-altering effects, and CBD, which lacks these psychoactive effects. Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties (see [11, 12, 16–19] for reviews). A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted [20].

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviors, specifically the cannabinoid type 1 receptor (CB_1R), the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor [11, 12, 19, 21]. In addition, CBD may also regulate, directly or indirectly, the peroxisome proliferator-activated receptor-γ, the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, the adenosine transporter, additional TRP channels, and glycine receptors [11, 12, 19, 21]. In the current review of primary studies, the following receptor-specific actions were found to have been investigated as potential mediators of CBD's anxiolytic action: CB_1R, TRPV1 receptors, and 5-HT_{1A} receptors. Pharmacology relevant to these actions is detailed below.

The Endocannabinoid System

Following cloning of the endogenous receptor for THC, namely the CB_1R, endogenous CB_1R ligands, or "endocannabinoids" (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The CB_1R is an inhibitory $G_{i/o}$ protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ-aminobutryic acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and Ca^{2+} influx, via cleavage of membrane phospholipids. The primary mechanism by which eCBs regulate synaptic function is retrograde signaling, wherein eCBs produced by depolarization of the postsynaptic neuron activate presynaptic CB_1Rs, leading to inhibition of neurotransmitter release [23]. The "eCB system" includes AEA and 2-arachidonoylglycerol; their respective degradative enzymes fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase; the CB_1R and related CB_2 receptor (the latter expressed mainly in the periphery); as well as several other receptors activated by eCBs, including the TRPV1 receptor, peroxisome proliferator-activated receptor-γ, and G protein-coupled 55 receptor, which functionally interact with CB_1R signaling (reviewed in [21, 24]). Interactions with the TRPV1 receptor, in particular, appear to be critical in regulating the extent to which eCB release leads to inhibition or facilitation of presynaptic neurotransmitter release [25]. The TRPV1 receptor is a postsynaptic cation channel that underlies sensation of noxious heat in the periphery, with capsacin (hot chili) as an exogenous ligand. TRPV1 receptors are also expressed in the brain, including the amygdala, periaqueductal grey, hippocampus, and other areas [26, 27].

The eCB system regulates diverse physiological functions, including caloric energy balance and immune function [28]. The eCB system is also integral to regulation of emotional behavior, being essential to forms of synaptic plasticity that determine learning and response to emotionally salient, particularly highly aversive events [29, 30]. Activation of CB_1Rs produces anxiolytic effects in various models of unconditioned fear, relevant to multiple anxiety disorder symptom domains (reviewed in [30–33]). Regarding conditioned fear, the effect of CB_1R activation is complex: CB_1R activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, CB_1R activation potently enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

CB_1R activation are anxiogenic [35], and individuals with eCB system gene polymorphisms that reduce eCB tone—for example, FAAH gene polymorphisms—exhibit physiological, psychological, and neuroimaging features consistent with impaired fear regulation [36]. Reduction of AEA–CB_1R signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and CB_1R activation is essential to negative feedback of the neuroendocrine stress response, and protects against the adverse effects of chronic stress [38, 39]. Finally, chronic stress impairs eCB signaling in the hippocampus and amygdala, leading to anxiety [40, 41], and people with PTSD show elevated CB_1R availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, CB_1R activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing CB_1R activation include THC, which is a potent and direct agonist; synthetic CB_1R agonists; FAAH inhibitors and other agents that increase eCB availability, as well as nonpsychoactive cannabis phytocannabinoids, including CBD. While CBD has low affinity for the CB_1R, it functions as an indirect agonist, potentially via augmentation of CB_1R constitutional activity, or via increasing AEA through FAAH inhibition (reviewed in [21]).

Several complexities of the eCB system may impact upon the potential of CBD and other CB_1R-activating agents to serve as anxiolytic drugs. First, CB_1R agonists, including THC and AEA, have a biphasic effect: low doses are anxiolytic, but higher doses are ineffective or anxiogenic, in both preclinical models in and humans (reviewed in [33, 45]). This biphasic profile may stem from the capacity of CB_1R agonists to also activate TRPV1 receptors when administered at a high, but not low dose, as demonstrated for AEA [46]. Activation of TRPV1 receptors is predominantly anxiogenic, and thus a critical balance of eCB levels, determining CB1 *versus* TRPV1 activation, is proposed to govern emotional behavior [27, 47]. CBD acts as a TRPV1 agonist at high concentrations, potentially by interfering with AEA inactivation [48]. In addition to dose-dependent activation of TRPV1 channels, the anxiogenic *versus* anxiolytic balance of CB_1R agonists also depends on dynamic factors, including environmental stressors [33, 49].

5-HT_{1A} Receptors

The 5-HT_{1A} receptor (5-$HT_{1A}R$) is an established anxiolytic target. Buspirone and other 5-$HT_{1A}R$ agonists are approved for the treatment of GAD, with fair response rates [50]. In preclinical studies, 5-$HT_{1A}R$ agonists are anxiolytic in animal models of general anxiety [51], prevent the adverse effects of stress [52], and enhance fear extinction [53]. Both pre- and postsynaptic 5-$HT_{1A}Rs$ are coupled to various members of the $G_{i/o}$ protein family. They are expressed on serotonergic neurons in the raphe, where they exert autoinhibitory function, and various other brain areas involved in fear and anxiety [54, 55]. Mechanisms underlying the anxiolytic effects of 5-$HT_{1A}R$ activation are complex, varying between both brain region, and pre- *versus* postsynaptic locus, and are not fully established [56]. While in vitro studies suggest CBD acts as a direct 5-$HT_{1A}R$ agonist [57], in vivo studies are more consistent with CBD acting as an allosteric modulator, or facilitator of 5-HT_{1A} signaling [58].

Preclinical Evaluations

Generalized Anxiety Models

Relevant studies in animal models are summarized in chronological order in Table 1. CBD has been studied in a wide range of animal models of general anxiety, including the elevated plus maze (EPM), the Vogel-conflict test (VCT), and the elevated T maze (ETM). See Table 1 for the anxiolytic effect specific to each paradigm. Initial studies of CBD in these models showed conflicting results: high (100 mg/kg) doses were ineffective, while low (10 mg/kg) doses were anxiolytic [59, 60]. When tested over a wide range of doses in further studies, the anxiolytic effects of CBD presented a bell-shaped dose–response curve, with anxiolytic effects observed at moderate but not higher doses [61, 90]. All further studies of acute systemic CBD without prior stress showed anxiolytic effects or no effect [62, 65], the latter study involving intracerebroventricular rather than the intraperitoneal route. No anxiogenic effects of acute systemic CBD dosing in models of general anxiety have yet been reported. As yet, few studies have examined chronic dosing effects of CBD in models of generalized anxiety. Campos et al. [66] showed that in rat, CBD treatment for 21 days attenuated inhibitory avoidance acquisition [83]. Long et al. [69] showed that, in mouse, CBD produced moderate anxiolytic effects in some paradigms, with no effects in others.

Anxiolytic effects of CBD in models of generalized anxiety have been linked to specific receptor mechanisms and brain regions. The midbrain dorsal periaqueductal gray (DPAG) is integral to anxiety, orchestrating autonomic and behavioral responses to threat [91], and DPAG stimulation in humans produces feelings of intense distress and dread [92]. Microinjection of CBD into the DPAG produced anxiolytic effects in the EPM, VGC, and ETM that were partially mediated by activation of 5-$HT_{1A}Rs$ but not by CB_1Rs [65, 68]. The bed nucleus of the stria terminalis (BNST) serves as a principal output structure of the amygdaloid complex to coordinate sustained fear responses, relevant to anxiety [93]. Anxiolytic effects of CBD in the EPM and VCT occurred upon microinjection into the BNST, where they depended on 5-$HT_{1A}R$

Table 1 Preclinical studies

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Silveira Filho et al. [59]	WR	i.p.	**100** mg/kg, acute	GSCT	No effect	NA
Zuardi et al. [60]	WR	i.p.	**10**mg/kg, acute	CER	Anxiolytic	NA
Onaivi et al. [61]	ICR mice	i.p.	0.01, 0.10, **0.50**, **1.00**, **2.50**, **5.00**, **10.00**, **50.00**, 100.00 mg/kg, acute	EPM	Anxiolytic	Effects ↓ by IP flumazenil, unchanged by naloxone
Guimaraes et al. [61]	WR	i.p.	**2.5**, **5.0**, **10.0** and 20.0 mg/kg, acute	EPM	Anxiolytic	NA
Moreira et al. [62]	WR	i.p.	2.5, 5.0 and **10.0**mg/kg, acute	VCT	Anxiolytic	Effect unchanged by IP flumazenil
Resstel et al. [63]	WR	i.p.	**10**mg/kg, acute	CFC	Anxiolytic	NA
Campos et al. [64]	WR	dlPAG	15.0, **30.0**, 60.0 nmol/0.2 μl, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra-dlPAG WAY100635 but not intra-dlPAG AM251
Bitencourt et al. [65]	WR	i.c.v.	**2.0** μg/μl 5 min before extinction, acute	CFC extinction EPM before and 24 h after CFC	Anxiolytic No effect before CFC Anxiolytic following CFC	Extinction effect ↓ by SR141716A but not capsazepine
Campos et al. [66]	WR	dlPAG	**30**, 60 mg/kg, acute	EPM	Anxiolytic	Intra-dlPAG capsazepine renders 60 mg/kg anxiolytic
Resstel et al. [67]	WR	i.p.	1, **10** or 20 mg/kg, acute	RS EPM 24 h following RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	All effects ↓ by systemic WAY100635
Soares et al. [68]	WR	dlPAG	15, **30** or **60**nmol, acute	ETM PAG E-stim	Anxiolytic Panicolytic Panicolytic	All effects ↓ by intra-dlPAG WAY100635 but not AM251
Long et al. [69]	C57BL/6 J mice	i.p.	**1**, 5, 10, **50**mg/kg, chronic, daily/21 d	EPM L-DT SI OF	No effect 1 mg/kg anxiolytic No effect 50 mg/kg anxiolytic	NA
Lemos et al. [70]	WR	i.p. PL IL	**10**mg/kg IP, **30**nmol intra-PL and intra-IL, acute	CFC	IP and PL anxiolytic IL anxiogenic	NA
Casarotto et al. [71]	C57BL/6 J mice	i.p.	15, **30**, and 60 mg/kg, acute, or subchronic, daily/7 d	MBT	Anticompulsive	Effect ↓ by IP AM251 but not WAY100635
Gomes et al. [72]	WR	BNST	15, **30**, and 60 nmol, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra BNST WAY100635
Granjeiro et a l. [73]	WR	Intracisternal	15, **30**, and 60 nmol, acute	RS EPM 24 h after RS	Anxiolytic, ↓Pressor ↓Tachycardia Anxiolytic	NA
Deiana et al. [74]	SM	i.p. Oral	**120**mg/kg, acute	MBT	Anticompulsive	NA
Uribe-Marino et al. [75]	SM	i.p.	0.3, **3.0**, **30.0**mg/kg, acute	PS	Panicolytic	NA

Table 1 (continued)

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Stern et al. [76]	WR	i.p.	3, **10**, 30 mg/kg immediately after retrieval, acute	Reconsolidation blockade	Anxiolytic 1 and 7 d old fear memories disrupted	Effect ↓ by AM251 but not WAY100635
Campos et al. [77]	WR	i.p.	**5** mg/kg, subchronic, daily/7 d	EPM following PS	Anxiolytic	Effects ↓ by IP WAY100635
Hsiao et al. [78]	WR	CeA	**1** μg/μl	REM sleep time EPM OF	↓ REM sleep suppression Anxiolytic Anxiolytic	NA
Gomes et al. [79]	WR	BNST	**15**, **30**, **60**nmol, acute	CFC	Anxiolytic	Both effects ↓ by intra-BNST WAY100635
El Batsh et al. [80]	LE-H R	i.p.	**10**mg/kg, chronic, daily/14 d	CFC	Anxiogenic	NA
Campos et al. [81]	C57BL/6 mice	i.p.	**30**mg/kg 2 h after CUS, chronic daily/14 d	EPM NSF	Anxiolytic Anxiolytic	Both effects ↓ by AM251
Do Monte et al. [82]	L-E HR	IL	1 μg or **0.4**μg/0.2 μl 5 min before extinction daily/4 d	Extinction of CFC	Anxiolytic	Effect ↓ by IP rimonabant
Campos et al. [83]	Rat	i.p.	**5**mg/kg, chronic, daily/21 d	ETM	Anxiolytic Panicolytic	Panicolytic effect ↓ by intra-dlPAG WAY100635
Almeida et al. [84]	Rat	i.p.	**1**, 5, 15 mg/kg, acute	SI	Anxiolytic	NA
Gomes et al. [85]	WR	BNST	**30** and 60 nmol, acute	RS	Anxiogenic ↑ Tachydardia	Effect ↓ by WAY100635
Twardowschy et al. [86]	SM	i.p.	**3**mg/kg, acute	PS	Panicolytic	Effects ↓ by IP WAY100635
Focaga et al. [87]	WR	PL	15, **30**, 60 nmol, acute	EPM EPM after RS CFC	Anxiogenic Anxiolytic Anxiolytic	All effects ↓ by intra PL WAY100635 Anxiolytic EPM effect post-RS ↓ by IP metyrapone
Nardo et al. [88]	SM	i.p.	**30** mg/kg, acute	MBT	Anticompulsive	NA
da Silva et al. [89]	WR	SNpr	**5**μg/**0.2**μl	$GABA_A$ blockade in dlSC	Panicolytic	Both effects ↓ by AM251

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 (CB_1R) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = CB_1R antagonist; rimonabant = CB_1R antagonist; capsazepine = transient receptor potential vanilloid type 1 antagonist; naloxone = opioid antagonist; flumazenil = $GABA_A$ receptor antagonist

Anxiolytic effects in models used: CER = reduced fear response; CFC = reduced conditioned freezing; CFC extinction = reduced freezing following extinction training; EPM = reduced % time in open arm; ETM = decreased inhibitory avoidance; L-DT = increased % time in light; VCT = increased licks indicating reduced conflict; NSF = reduced latency to feed; OF = increased % time in center; SI = increased social interaction

Anticomplusive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; $GABA_A$ blockade in dlSC = defensive immobility, and explosive escape; PAG-E-Stim = increased threshold for escape; PS = reduced explosive escape

WR = Wistar rats; SM = Swiss mice; L-E HR = Long–Evans hooded rats; i.p. = intraperitoneal; dlPAG = dorsolateral periaqueductal gray; i.c.v. = intracerebroventricular; PL = prelimbic; IL = infralimbic; BNST = bed nucleus of the stria terminalis; CeA = amygdala central nucleus; SNpr = substantia nigra pars reticularis; CUS = chronic unpredictable stress; GSCT = Geller–Seifter conflict test; CER = conditioned emotional response; EPM = elevated plus maze; VCT = Vogel conflict test; CFC = contextual fear conditioning; RS = restraint stress; ETM = elevated T maze; PAG E-stim = electrical stimulation of the dlPAG; L-DT = light–dark test; SI = social interaction; OF = open field; MBT = marble-burying test; PS = predator stress; NSF = novelty suppressed feeding test; $GABA_A$ = γ-aminobutyric acid receptor A; dlSC = deep layers superior colliculus; REM = rapid eye movement; NA = not applicable

activation [79], and also upon microinjection into the central nucleus of the amygdala [78]. In the prelimbic cortex, which drives expression of fear responses via connections with the amygdala [94], CBD had more complex effects: in unstressed rats, CBD was anxiogenic in the EPM, partially via 5-HT_{1A}R receptor activation; however, following acute restraint stress, CBD was anxiolytic [87]. Finally, the anxiolytic effects of systemic CBD partially depended on $GABA_A$ receptor activation in the EPM model but not in the VCT model [61, 62].

As noted, CBD has been found to have a bell-shaped response curve, with higher doses being ineffective. This may reflect activation of TRPV1 receptors at higher dose, as blockade of TRPV1 receptors in the DPAG rendered a previously ineffective high dose of CBD as anxiolytic in the EPM [66]. Given TRPV1 receptors have anxiogenic effects, this may indicate that at higher doses, CBD's interaction with TRPV1 receptors to some extent impedes anxiolytic actions, although was notably not sufficient to produce anxiogenic effects.

Stress-induced Anxiety Models

Stress is an important contributor to anxiety disorders, and traumatic stress exposure is essential to the development of PTSD. Systemically administered CBD reduced acute increases in heart rate and blood pressure induced by restraint stress, as well as the delayed (24 h) anxiogenic effects of stress in the EPM, partially by 5-HT_{1A}R activation [67, 73]. However intra-BNST microinjection of CBD *augmented* stress-induced heart rate increase, also partially via 5-HT_{1A}R activation [85]. In a subchronic study, CBD administered daily 1 h after predator stress (a proposed model of PTSD) reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT_{1A}R activation [77]. In a chronic study, systemic CBD prevented increased anxiety produced by chronic unpredictable stress, in addition to increasing hippocampal AEA; these anxiolytic effects depended upon CB_1R activation and hippocampal neurogenesis, as demonstrated by genetic ablation techniques [81]. Prior stress also appears to *modulate* CBD's anxiogenic effects: microinjection of CBD into the prelimbic cortex of unstressed animals was anxiogenic in the EPM but following restraint stress was found to be anxiolytic [87]. Likewise, systemic CBD was anxiolytic in the EPM following but not prior to stress [65].

PD and Compulsive Behavior Models

CBD inhibited escape responses in the ETM and increased DPAG escape electrical threshold [68], both proposed models of panic attacks [95]. These effects partially depended on 5-HT_{1A}R activation but were not affected by CB_1R blockade. CBD was also panicolytic in the predator–prey model, which assesses explosive escape and defensive immobility in response to a boa constrictor snake, also partially via 5-HT_{1A}R activation; however, more consistent with an anxiogenic effect, CBD was also noted to decrease time spent outside the burrow and increase defensive attention (not shown in Table 1) [75, 86] . Finally, CBD, partially via CB_1Rs, decreased defensive immobility and explosive escape caused by bicuculline-induced neuronal activation in the superior colliculus [89]. Anticompulsive effects of CBD were investigated in marble-burying behavior, conceptualized to model OCD [96]. Acute systemic CBD reduced marble-burying behavior for up to 7 days, with no attenuation in effect up to high (120 mg/kg) doses, and effect shown to depend on CB_1Rs but not 5-HT_{1A}Rs [71, 74, 88].

Contextual Fear Conditioning, Fear Extinction, and Reconsolidation Blockade

Several studies assessed CBD using contextual fear conditioning. Briefly, this paradigm involves pairing a neutral context, the conditioned stimulus (CS), with an aversive unconditioned stimulus (US), a mild foot shock. After repeated pairings, the subject learns that the CS predicts the US, and subsequent CS presentation elicits freezing and other physiological responses. Systemic administration of CBD prior to CS re-exposure reduced conditioned cardiovascular responses [63], an effect reproduced by microinjection of CBD into the BNST, and partially mediated by 5-HT_{1A}R activation [79]. Similarly, CBD in the prelimbic cortex reduced conditioned freezing [70], an effect prevented by 5-HT_{1A}R blockade [87]. By contrast, CBD microinjection in the infralimbic cortex *enhanced* conditioned freezing [70]. Finally, El Batsh et al. [80] reported that repeated CBD doses over 21 days, that is chronic as opposed to acute treatment, *facilitated* conditioned freezing. In this study, CBD was administered prior to conditioning rather than prior to re-exposure as in acute studies, thus further directly comparable studies are required.

CBD has also been shown to enhance extinction of contextually conditioned fear responses. Extinction training involves repeated CS exposure in the absence of the US, leading to the formation of a new memory that inhibits fear responses and a decline in freezing over subsequent training sessions. Systemic CBD administration immediately before training markedly enhanced extinction, and this effect depended on CB_1R activation, without involvement of TRPV1 receptors [65]. Further studies showed CB_1Rs in the infralimbic cortex may be involved in this effect [82].

CBD also blocked reconsolidation of aversive memories in rat [76]. Briefly, fear memories, when reactivated by re-exposure (retrieval), enter into a labile state in

which the memory trace may either be reconsolidated or extinguished [97], and this process may be pharmacologically modulated to achieve reconsolidation blockade or extinction. When administered immediately following retrieval, CBD prevented freezing to the conditioned context upon further re-exposure, and no reinstatement or spontaneous recovery was observed over 3 weeks, consistent with reconsolidation blockade rather than extinction [76]. This effect depended on CB_1R activation but not 5-$HT_{1A}R$ activation [76].

Summary and Clinical Relevance

Overall, existing preclinical evidence strongly supports the potential of CBD as a treatment for anxiety disorders. CBD exhibits a broad range of actions, relevant to multiple symptom domains, including anxiolytic, panicolytic, and anticompulsive actions, as well as a decrease in autonomic arousal, a decrease in conditioned fear expression, enhancement of fear extinction, reconsolidation blockade, and prevention of the long-term anxiogenic effects of stress. Activation of 5-$HT_{1A}Rs$ appears to mediate anxiolytic and panicolytic effects, in addition to reducing conditioned fear expression, although CB_1R activation may play a limited role. By contrast, CB_1R activation appears to mediate CBD's anticompulsive effects, enhancement of fear extinction, reconsolidation blockade, and capacity to prevent the long-term anxiogenic consequences of stress, with involvement of hippocampal neurogenesis.

While CBD predominantly has acute anxiolytic effects, some species discrepancies are apparent. In addition, effects may be contingent on prior stress and vary according to brain region. A notable contrast between CBD and other agents that target the eCB system, including THC, direct CB_1R agonists and FAAH inhibitors, is a lack of anxiogenic effects at a higher dose. Further receptor-specific studies may elucidate the receptor specific basis of this distinct dose response profile. Further studies are also required to establish the efficacy of CBD when administered in chronic dosing, as relatively few relevant studies exist, with mixed results, including both anxiolytic and anxiogenic outcomes.

Overall, preclinical evidence supports systemic CBD as an acute treatment of GAD, SAD, PD, OCD, and PTSD, and suggests that CBD has the advantage of not producing anxiogenic effects at higher dose, as distinct from other agents that enhance CB_1R activation. In particular, results show potential for the treatment of multiple PTSD symptom domains, including reducing arousal and avoidance, preventing the long-term adverse effects of stress, as well as enhancing the extinction and blocking the reconsolidation of persistent fear memories.

Human Experimental and Clinical Studies

Evidence from Acute Psychological Studies

Relevant studies are summarized in Table 2. The anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC. CBD reduced THC-induced anxiety when administered simultaneously with this agent, but had no effect on baseline anxiety when administered alone [99, 100]. Further studies using higher doses supported a lack of anxiolytic effects at baseline [101, 107]. By contrast, CBD potently reduces experimentally induced anxiety or fear. CBD reduced anxiety associated with a simulated public speaking test in healthy subjects, and in subjects with SAD, showing a comparable efficacy to ipsapirone (a 5-$HT_{1A}R$ agonist) or diazepam [98, 105]. CBD also reduced the presumed anticipatory anxiety associated with undergoing a single-photon emission computed tomography (SPECT) imaging procedure, in both healthy and SAD subjects [102, 104]. Finally, CBD enhanced extinction of fear memories in healthy volunteers: specifically, inhaled CBD administered prior to or after extinction training in a contextual fear conditioning paradigm led to a trend-level enhancement in the reduction of skin conductance response during reinstatement, and a significant reduction in expectancy (of shock) ratings during reinstatement [106].

Evidence from Neuroimaging Studies

Relevant studies are summarized in Table 3. In a SPECT study of resting cerebral blood flow (rCBF) in normal subjects, CBD reduced rCBF in left medial temporal areas, including the amygdala and hippocampus, as well as the hypothalamus and left posterior cingulate gyrus, but increased rCBF in the left parahippocampal gyrus. These rCBF changes were not correlated with anxiolytic effects [102]. In a SPECT study, by the same authors, in patients with SAD, CBD reduced rCBF in overlapping, but distinct, limbic and paralimbic areas; again, with no correlations to anxiolytic effects [104].

In a series of placebo-controlled studies involving 15 healthy volunteers, Fusar-Poli et al. investigated the effects of CBD and THC on task-related blood-oxygen-level dependent functional magnetic resonance imaging activation, specifically the go/no-go and fearful faces tasks [109, 110]. The go/no-go task measures response inhibition, and is associated with activation of medial prefrontal, dorsolateral prefrontal, and parietal areas [111]. Response activation is diminished in PTSD and other anxiety disorders, and increased activation predicts response to treatment [112]. CBD produced no changes in predicted areas (relative to placebo) but reduced activation in the left insula, superior temporal gyrus, and transverse temporal gyrus. The fearful faces task activates the amygdala, and other medial temporal areas involved in

Table 2 Human psychological studies

Study	Subjects, design	CBD route, dose	Measure	Effect
Karniol et al. [99]	HV, DBP	Oral, 15, 30, 60 mg, alone or with THC, acute, at 55, 95, 155, and 185 min	Anxiety and pulse rate after THC and at baseline	↓ THC-induced increases in subjective anxiety and pulse rate No effect at baseline
Zuardi et al., [100]	HV, DBP	Oral 1 mg/kg alone or with THC, acute, 80 min	STAI score after THC	↓ THC-induced increases in STAI scores
Zuardi et al. [98]	HV, DBP	Oral 300 mg, acute, 80 min	VAMS, STAI and BP following SPST	↓ STAI scores ↓ VAMS scores ↓ BP
Martin-Santos et al. [101]	HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	Baseline anxiety and pulse rate	No effect
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	VAMS before SPECT SPECT	↓ VAMS scores
Bhattacharyya et al. [103]	15 HV DBP	Oral 600 mg, acute, 1, 2, 3 h	STAI scores VAMS scores	↓ STAI scores ↓ VAMS scores
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	VAMS before SPECT SPECT	↓ VAMS scores
Bergamaschi et al. [105]	SAD and HC DBP	Oral 600 mg, acute, 1, 2, 3 h	VAMS, SSPS-N, cognitive impairment, SCR, HR after SPST	↓ VAMS, SSPS-N and cognitive impairment, no effect on SCR or HR
Das et al. [106]	HV DBP	Inhaled, 32 mg, acute, immediately following, before, after extinction	SCR and shock expectancy following extinction	CBD after extinction training produced trend level reduction in SCR and decreased shock expectancy
Hindocha et al. [107]	Varying in schizotypy and cannabis use, DBP	Inhaled, 16 mg, acute	Baseline VAS anxiety	No significant effect of CBD

HV = healthy volunteers; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; THC = $^{\Delta}$9-tetrahydrocannabinol; STAI = Spielberger's state trait anxiety inventory; VAMS = visual analog mood scale; BP = blood pressure; SPST = simulated public speaking test; SCR = skin conductance response; SPECT = single-photon emission computed tomography; SSPS-N = negative self-evaluation subscale; HR = heart rate; VAS = visual analog scale, CBD = cannabidiol

Table 3 Neuroimaging studies

Study	Subjects, design	CBD route, dose, timing	Measure	Effect of CBD
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	SPECT, resting (rCBF)	↓ rCBF in left medial temporal cluster, including amygdala and HPC, also ↓ rCBF in the HYP and posterior cingulate gyrus ↑ rCBF in left PHG
Borgwardt et al. [108]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI during oddball and go/no-go task	↓ Activation in left insula, STG and MTG
Fusar-Poli et al. [109]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI activation during fearful faces task	↓ Activation in left medial temporal region, including amygdala and anterior PHG, and in right ACC and PCC
Fusar-Poli et al. [110]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI functional connectivity during fearful faces task	↓ Functional connectivity between L) AMY and ACC
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	SPECT, resting (rCBF)	↓ rCBF in the left PHG, HPC and ITG. ↑ rCBF in the right posterior cingulate gyrus

CBD = cannabidiol; HV = healthy controls; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; SPECT = single-photo emission computed tomography; rCBF = regional cerebral blood flow; fMRI = functional magnetic resonance imaging; HPC = hippocampus; HYP = hypothalamus; PHG = parahippocampal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex

emotion processing, and heightened amygdala response activation has been reported in anxiety disorders, including GAD and PTSD [113, 114]. CBD attenuated blood-oxygen-level dependent activation in the left amygdala, and the anterior and posterior cingulate cortex in response to intensely fearful faces, and also reduced amplitude in skin conductance fluctuation, which was highly correlated with amygdala activation [109]. Dynamic causal modeling analysis in this data set further showed CBD reduced forward functional connectivity between the amygdala and anterior cingulate cortex [110].

Evidence from Epidemiological and Chronic Studies

Epidemiological studies of various neuropsychiatric disorders indicate that a higher CBD content in chronically consumed cannabis may protect against adverse effects of THC, including psychotic symptoms, drug cravings, memory loss, and hippocampal gray matter loss [115–118] (reviewed in [119]). As THC acutely induces anxiety, this pattern may also be evident for chronic anxiety symptoms. Two studies were identified, including an uncontrolled retrospective study in civilian patients with PTSD patients [120], and a case study in a patient with severe sexual abuse-related PTSD [121], which showed that chronic cannabis use significantly reduces PTSD symptoms; however, these studies did not include data on the THC:CBD ratio. Thus, overall, no outcome data are currently available regarding the chronic effects of CBD in the treatment of anxiety symptoms, nor do any data exist regarding the potential protective effects of CBD on anxiety potentially induced by chronic THC use.

Summary and Clinical Relevance

Evidence from human studies strongly supports the potential for CBD as a treatment for anxiety disorders: at oral doses ranging from 300 to 600 mg, CBD reduces experimentally induced anxiety in healthy controls, without affecting baseline anxiety levels, and reduces anxiety in patients with SAD. Limited results in healthy subjects also support the efficacy of CBD in acutely enhancing fear extinction, suggesting potential for the treatment of PTSD, or for enhancing cognitive behavioral therapy. Neuroimaging findings provide evidence of neurobiological targets that may underlie CBD's anxiolytic effects, including reduced amygdala activation and altered medial prefrontal amygdala connectivity, although current findings are limited by small sample sizes, and a lack of independent replication. Further studies are also required to establish whether chronic, in addition to acute CBD dosing is anxiolytic in human. Also, clinical findings are currently limited to SAD, whereas preclinical evidence suggests CBD's potential to treat multiple symptom domains relevant to GAD, PD, and, particularly, PTSD.

Conclusions

Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB_1Rs and 5-HT_{1A}Rs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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Original Article

Cannabis Use in HIV for Pain and Other Medical Symptoms

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Abstract
Despite the major benefits of antiretroviral therapy on survival during HIV infection, there is an increasing need to manage symptoms and side effects during long-term drug therapy. Cannabis has been reported anecdotally as being beneficial for a number of common symptoms and complications in HIV infections, for example, poor appetite and neuropathy. This study aimed to investigate symptom management with cannabis. Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control. J Pain Symptom Manage 2005;29:358–367.

Key Words
Cannabis, HIV, pain, symptoms

Introduction

HIV or AIDS affects over 40 million people in the world[1] and more than 49,500 in the UK.[2] Although there is still no cure available for this disease, remarkable improvements in the survival of HIV-infected individuals have been achieved.[3] This survival has lead to an increasing prevalence of individuals with HIV infection, many on long-term treatment with combinations of antiretroviral therapies. This has increased the clinical focus on the management of chronic symptoms associated with both HIV and the side effects of antiretroviral medication. Recently, in small sample studies of HIV patients, the medicinal use of cannabis has been documented as a treatment for varied symptoms.[4–7]

Symptoms associated with HIV occur as both direct and indirect consequences of the disease process and as a side effect of the antiretroviral drugs used in the treatment of the disease. These symptoms include nausea and vomiting, pain (e.g., in a nerve distribution), reduced appetite, weight loss, headaches, diarrhea, constipation, anxiety, and depression. Flu-like symptoms and severe myalgia can result directly

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from seroconversion early in the disease. Central pain and peripheral neuropathy can occur as a result of viral-mediated neurotoxicity, secondary to either mitochondrial damage, demyelination, or low B_{12} levels, all of which have been observed in patients with HIV. The inflammation that occurs as a result of the mitochondrial damage can result in HIV-related encephalopathy or HIV-related colitis. Symptoms may also occur secondary to infections or tumors, which have resulted from HIV-related immunosuppression. Examples of this include nausea and dysphagia from esophageal candida, or pain from a gastrointestinal lymphoma. Symptoms commonly occurring as a side effect of HIV treatment include renal colic from nephrolithiasis associated with the protease inhibitor, indinavir; painful peripheral neuropathy from use of stavudine, a nucleoside analogue; or sleep disturbances from the non-nucleoside inhibitor, efavirenz. Thus, a wide range of symptoms can significantly affect the quality of life of individuals living with HIV as a long-term chronic infection.[8,9]

It has been recognized that cannabinoids such as delta-9-tetrahydrocannabinol (THC), which is now available as a licensed pharmaceutical preparation, can improve appetite and relieve nausea and vomiting.[10] Cannabis plant material not only contains THC but also other cannabinoids, such as cannabidiol (CBD), that may mitigate psychotic mood effects of THC.[11]

The aim of this study was to measure the patterns and prevalence of cannabis use in patients presenting at a large HIV clinic and to evaluate its beneficial or detrimental effect on symptom control.

Methods

Subjects

Following Ethics Committee approval, HIV-positive patients were recruited into an anonymous cross-sectional questionnaire survey using a single center. The outpatient clinic provided a walk-in service as well as pre-arranged appointments, including pharmacy and phlebotomy sections. All patients entering the clinic were asked to verbally consent to participate in the study. Written consent was not obtained in order to protect patient anonymity. The number of patients who refused to take part was recorded. Many patients were regular clinic users, had discussed their symptoms with HIV and pain specialists, and were able to distinguish between the various types of pain described on the questionnaire. A researcher was available to answer questions (e.g., on the interpretation of words). Patients completed the questionnaire while waiting and confidentiality was maintained by enumerating the papers without patient identification.

Questionnaire

The questionnaire was piloted to refine its content, word use, and format and then issued to patients attending the clinic. The questionnaire (see Appendix) was designed to contain close-ended questions with defined yes/no or categorical responses. It was divided into sections. The first included demographics (age, sex, number of years with HIV) and a validated scale to measure degree of disability described by Sharrack and Hughes.[12] The second had specific questions concerning the patient's use of cannabis medically to treat symptoms of HIV. These symptoms included those directly related to HIV plus those resulting from their medication. Those who did not use cannabis for medicinal purposes, including those who used it solely for recreation, were not required to continue completing the questionnaire, although their demographic details were recorded. The next section included questions relating to frequency, patterns, and reasons for cannabis use. Then in tabular form, a range of symptoms were listed (Table 1), and against

Table 1
Order of Symptom List in Questionnaire as Scored by Patients for Benefit or Detriment

Lack of appetite
Feeling sick (i.e., nausea)
Tremor
Depression
Anxiety
Weight loss
Weakness
Tiredness
Vision dimness
Slurred speech
Memory loss
Constipation
Headaches
Diarrhea
Pain in muscles
Nerve pain
Tingling
Numbness

each one, the patient was invited to score benefit or detriment as 'much better,' 'little better,' 'unchanged,' 'a little worse,' and 'much worse'. For the symptoms of pain and sensory changes, the questionnaire also contained 'body diagrams', that is, pain maps, so that the patients could mark where they identified their nerve or muscle pain, tingling and numbness.

Analysis

Data from the questionnaires were entered into an Access database (Windows 98 version) and analyzed using the Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago). Categorical data comparing the sex differences between the two groups and symptom severity were analyzed using the Fisher's exact test. Because the distribution of age and the number of years with HIV were not normal and had some outliers, the differences in these variables between the two groups were analyzed using the Mann-Whitney U test. Both simple frequency analysis and the sign test were used in assessing the percentage improvement or deterioration in symptoms.

Results

A total of 523 questionnaires were completed from 565 patients approached. This was a 93% response rate. Of those who completed the study, 143 (27%) used cannabis to treat symptoms associated with HIV.

Physical Data

The sex, age, years with HIV, disability, and cannabis user status are shown in Tables 2 and 3. About 1 in 10 patients were female and few were severely disabled in this outpatient setting. Compared with females, males were statistically significantly likely to be cannabis users ($P < 0.01$) and those who had the disease for longer and were more disabled were also more likely to be users ($P < 0.01$).

When nerve pain was reported on the pain map, it was experienced mainly in the legs, and less in the feet and hands (27, 19, and 15 patients, respectively). Muscle pain was predominantly localized to the legs, but also to the lower back, shoulders and neck (46, 19, and 19 patients, respectively). Tingling and numbness was experienced in the periphery, with the hands and feet being affected (34 and 26 patients, respectively).

Patient Choice of Route and Timing for Symptom Control

Of the 143 patients who had used cannabis to treat HIV symptoms, 107 (75%) were current users. Within the whole group, smoking was the single route of administration in 101 (71%), and was combined with eating and drinking the plant in 39 (27%); ingestion was the only route in 3 (2%). On a day that cannabis was used, 50 patients (36%) would take it once, 33 (23%) twice, 23 (16%) three times, and 35 (24%) four or more times. Most patients (79/143 [55%]) were daily users and 15 (11%) used it weekly. Others reported intermittent administration during the week. Thus, all patients reported using cannabis at least once a week to relieve symptoms.

Throughout the day, the majority of patients (91/143 [64%]) took cannabis after 6 p.m. and

Table 2
Demographic Data, Disability Scores, and the Number of Patients Using Cannabis to Treat Symptoms

	Females $n = 43$ (8%)	Males $n = 480$ (92%)	All Subjects $n = 523$
Age (years)[a]	38 [32–43] (20–65)	39 [35–44] (20–69)	39 [35–44] (20–69)
Years with HIV[a]	6 [2–9] (0–18)	9 [4–13] (0–25)	8 [4–13] (0–25)
Disability[b]			
0	12 (28%)	164 (34%)	176 (34%)
1	14 (33%)	136 (28%)	150 (29%)
2	10 (23%)	100 (21%)	110 (21%)
3	4 (9%)	74 (15%)	78 (15%)
4	3 (7%)	5 (1%)	8 (2%)
5	0	1 (0.2%)	1 (0.2%)
Number that used cannabis to treat symptoms	4/43 (9%)	139/480 (29%)	143/523 (27%)

[a]Median [IQR] (range).
[b]0 = none; 1 = mild; 2 = moderate not requiring help from others; 3 = moderate requiring help from others; 4 = severe with almost total loss of function; and 5 = total loss of function.

Table 3
Demographic Differences Between Users and Non-Users of Cannabis for Symptom Control

	Users $n = 143$	Non-Users $n = 380$	Statistical Significance
Males:Females	139:4	341:39	$P < 0.01$
Age[a]	40 [36–44] (26–61)	38 [34–44] (20–69)	$P = 0.046$
Years with HIV[a]	10 [6–15] (0–25)	7 [3–12] (0–20)	$P < 0.01$
No disability:Disability	17:126	159:221	$P < 0.01$

[a]Median [IQR] (range).

before midnight. However, an overlapping group (66/143 [46%]) also reported use at any time if necessary. The reasons for taking the cannabis at these times were reported in a structured format, as detailed in Table 4. A number of reasons related to the time of administration, not least of which was recreational use together with medicinal use. Relief of symptoms of anxiety and depression was common, as was general symptom relief. The reported use for relaxation may reflect the time at which it was taken, namely, during the evening.

Effect on Symptoms

A lack of appetite was the most frequent symptom reported (Table 5) and 97% experienced improvement with cannabis use. Pain was the next most frequent, being present in 45% of patients and improved in 94% of them. The collective results demonstrated statistically significant improvement in half or more patients in symptoms of nausea, anxiety, nerve pain, depression, tingling, numbness, weight loss, headaches, tremor, constipation, and tiredness. Symptoms that were not improved included weakness and slurred speech, and statistically significant memory deterioration was recorded in 47% of users.

Discussion

The demographic characteristics of our cohort of patients (male:female, 11.2:1) is comparable with the UK population of HIV-positive patients, which has a male:female ratio of 11.5:1. In addition, their ages and duration of HIV disease were comparable with the general UK data for such patients.[13] Our sample of 523 patients has the highest response rate and is the largest study of its kind. It compares with previous studies, which have had samples ranging from 72 subjects[7] to 442.[6] This detailed report of cannabis use for symptom control in a clinically significantly large group of patients can form the basis for more extensive investigations using purified and standardized cannabis extracts.

Table 4
Reasons for Using Cannabis

Purpose	*n*	%
Treat symptoms	77	54
Aid relaxation	121	85
Reduce anxiety	94	66
Relieve depression	75	52
Reduce symptom frequency	29	20
Increase energy levels	15	11
For a 'high'	62	43

Despite the fact that cannabis is still illegal, its use for medical purposes appears to be quite widespread. A report from the British Medical Association[14] stated "many normally law abiding citizens—probably many thousands in the developed world" use cannabis illegally for therapy. Wesner[15] reported from an anonymous mail survey of 123 HIV-positive patients in Honolulu that 36.9% of them used cannabis for therapeutic reasons. Approximately one-quarter of 228 HIV-positive men in the Sydney Men and Sexual Health study reported therapeutic use of cannabis.[16] Thirty-two percent (32%) of 72 patients at a clinic in Alabama reported the medical use of marijuana.[7] These results are comparable to a more recent study carried out in Northern California, in which 33.3% of HIV-positive patients who responded to an anonymous mailed questionnaire used cannabis to treat symptoms associated with their disease.[6] Our study expanded these findings in a large city clinic population by focusing on the patient's perceived improvement or worsening of symptoms for which cannabis was considered the origin.

The large number of patients using cannabis as medicinal therapy for symptoms related to HIV raises a number of issues. First, patients are being left with no alternative but to use a non-medical source of supply, which has the

Table 5
Effect of Cannabis on Complaint of Symptoms in 143 HIV Patients

Symptom	Number of Complaints	% Responding					
		Much Better	Little Better	No Change	Little Worse	Much Worse	P-value
Lack of appetite	111	79	18	2	0	1	0.000
Pain in muscles	65	63	31	6	0	0	0.000
Nausea	62	56	37	3	2	*2*	0.000
Anxiety	98	64	29	3	2	2	0.000
Nerve pain	53	51	40	9	0	0	0.000
Depression	94	56	30	9	4	1	0.000
Tingling	46	37	48	9	7	0	0.000
Numbness	42	36	36	24	5	0	0.000
Weight loss	62	45	24	31	0	0	0.000
Headaches	46	35	30	33	2	0	0.000
Tremor	24	37	29	21	13	0	0.004
Constipation	24	21	29	46	4	0	0.003
Tiredness	60	17	33	33	15	2	0.002
Diarrhea	48	13	23	56	6	2	0.007
Vision dimness	22	9	27	55	9	0	0.109
Weakness	48	10	21	54	15	0	0.134
Memory loss	38	13	5	34	34	13	0.043
Slurred speech	9	11	0	78	11	0	1.00

Note: In ranked order of those demonstrating improvement (recorded as % much better, little better) in comparison to those recorded with no change, little worse, or much worse. The *P*-value in the last column is the exact 2-sided *P*-value for the sign test of no change.

potential for heterogeneity of active cannabinoids, toxic contaminants, inappropriate dose, and drug misuse. Second, if part of the plant material has therapeutic efficacy, the source of this material should be standardized and subjected to clinical trials so that safe and effective use is advocated. Third, the patient is unlikely to divulge cannabis use to their medical team, so that potential drug interactions with prescribed antiretroviral medications may be occurring. In addition, in this study, the number of purely recreational users was not determined so that the overall incidence of drug interactions may be far greater. The type of drug interactions to be considered include loss of cognitive function because it is well-recognized that this is an effect of both cannabis[17] and antiretroviral drugs such as efavirenz.[18] Certainly, the loss of memory reported by these patients is of clinical significance, particularly in the methodological design of clinical trials, and if it is the result of combining preparations, this may be investigated using known standardized cannabinoid therapies. This approach may be one way to reduce additive effects and prevent patients being subject to the effects of unpredictable concentrations of illicit drugs.

The positive responses to symptom control recorded in this study, as exemplified in Table 5, suggest that it is highly probable that cannabinoid medications have a medicinal role in this condition for a number of reasons. First, they are reported by patients to improve appetite, reduce weight loss, and alleviate nausea.[19–23] These effects have been recognized and synthetic THC (dronabinol) is licensed for use in the U.S. for this indication. However, no direct comparison has been attempted with a cannabis plant extract that will contain not only THC but also other cannabinoids, of which CBD is reputed to reduce the adverse effects of THC.[24] Secondly, pain relief appears to be significant in cannabis users, thereby suggesting a potential target for investigation in the use of cannabinoids as analgesics in HIV patients.

Patients have reported various forms of pain with HIV, such as muscular and neuropathic pain, and these were characterized in the pain maps drawn by the patients. Currently available analgesic drugs have limited efficacy, particularly for neuropathic pain.[25] Clearly, there is a need to develop alternative analgesic agents, such as cannabinoids, to improve the choice of therapies. There is animal evidence that cannabinoids have analgesic effects that operate in models of hyperalgesia and allodynia, both indicators of neuropathic pain states,[26,27] and the discovery of the endogenous cannabinoid system has led scientists to explore the role of endocannabinoids in chronic pain models.[28,29] However, in clinical practice the choice of natural or synthetic phyto- or endo-cannabinoids for clinical trials is very limited. There have been several anecdotal and clinical trial reports that

cannabis plant extract and synthetic THC and related analogues produce pain relief in humans.[30–33] For this present select group of HIV patients, given the reported symptoms experienced using cannabis plant material, there is a strong concern from the medical community managing these patients to limit adverse side effects from self-administered drugs and to provide cannabinoids in a formulation and dosing schedule that avoids harm to the patient. For example, there is strong evidence that the smoking route of administration of cannabis is not safe long-term because of the carcinogenic properties of a cannabis cigarette.[34]

A pattern of cannabis use emerges from this study that is regular, ongoing, and treats the symptoms of HIV patients to their satisfaction. Given the sedative properties of cannabis, it is important to assess whether evening dosing for cannabinoid therapies is more useful or appropriate. Its sedative effects may be helpful at this time but none were reported as predominant. Presumably there is tolerance to these types of effects.[29] More importantly, reduction of pain, anxiety, and gastrointestinal upset appears to be the constellation of symptom control sought by these HIV patients, as shown in Tables 4 and 5.

In relation to HIV, there have been anecdotal reports[35] of patients who were already recreational users of cannabis reporting that it improved certain symptoms, such as loss of appetite and nausea, as well as pain and general well being. A small, uncontrolled study of 10 symptomatic AIDS patients reported that dronabinol might be effective in reducing nausea and increasing appetite.[10] Where patients are also medicating with antiretroviral agents, the combination of cannabis and protease inhibitors may be detrimental by altering viral loads. Thus, the effect of smoking on the viral load of HIV-infected patients was investigated by a short-term randomized placebo controlled trial.[36] No adverse effects of either therapy were measured with respect to RNA levels, $CD4^+$ and $CD8^+$ cell counts, or protease inhibitor levels. This brief trial suggests that there are no obvious harmful effects, but these need to be determined using an appropriate route of drug administration and a longer-term study.

There is accumulating evidence that suggests that cannabinoids have therapeutic applications in a variety of neurodegenerative diseases, such as multiple sclerosis,[37,38] Huntington's disease,[39] and brain injury.[40] So far, in terms of HIV, the evidence for therapeutic efficacy of cannabinoids is still mainly anecdotal. We have sought to establish if an improvement from cannabis use, albeit self-administered and not standardized, is seen in symptoms such as pain, appetite, and nausea in a large sample of HIV patients. To do this, we expanded on previous research by determining specifically the variety and groups of symptoms that patients select to modify by their use of cannabis. We also secured a therapeutic timetable in order to predict the frequency of drug administration for the patient's selected symptoms. These results will be important in the design of a randomized, placebo-controlled clinical trial comparing conventional treatments to cannabis for symptoms of HIV.

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Appendix

Questionnaire

HIV Symptoms and the Use of Cannabis

This questionnaire is designed to establish the current use of cannabis for the management of symptoms from HIV in our patients. We would be grateful for some personal details (but not details of identification) and your past and present experiences (if any) with cannabis.

Please complete the following:

General Details:

Sex: MALE/FEMALE (encircle as necessary)
Age: ……years
Number of years with HIV: ……..

Degree of Disability

Please choose ONE of the following statements which best describes how severely you are affected by the HIV disease, and how it affects your activities of daily living:

None
Mild symptoms
Moderate symptoms—not requiring help from others
Moderate symptoms—requiring help from others
Severe symptoms—almost total loss of function
Total loss of function

Cannabis use
Have you ever used cannabis to relieve your symptoms (as listed below) of HIV? Y/N
If **"NO"** we thank you for answering this questionnaire and you are not required to complete any more of the questionnaire.

If **"YES"** please complete the following details:

How do you take the cannabis?

Smoke Y/N
Drink Y/N
Eat Y/N
Other (state)……..

How many years have you used cannabis relieve some of your symptoms?……..years
How many times a day do you use cannabis?……
How many days a week do you take cannabis?……

When do you take cannabis: [*Please choose only ONE*]

After 6 pm and before midnight	Y/N
Between 6 am and midday	Y/N
Midday to 6 pm	Y/N
At any time when necessary	Y/N
Just before going to bed	Y/N
At regular intervals during the day	Y/N

Do you take cannabis to: [*You may choose MORE THAN ONE*]

Relieve symptoms	Y/N
Aid relaxation	Y/N
Relieve anxiety	Y/N
Relieve depression	Y/N
Reduce symptom frequency	Y/N
Obtain energy	Y/N
To get a 'high' / Recreational	Y/N

For each symptom in the left-hand column state if the symptom is now present. Then mark for each symptom, whether past or present, its response to cannabis use, i.e., better or worse.
Diagrams are provided below for the question relating to sites of pain, etc.

Symptom (past or present)	Present	Response to cannabis *[Please tick ONE box]*				
	Y/N	Much better	Little better	Not changed	Little worse	Much worse
Lack of appetite						
Feeling sick, i.e., Nausea						
Anxiety						
Depression						
Tremor						
Headaches						
Weight loss						
Weakness						
Tiredness						
Vision dimness						
Slurred speech						
Tremor						
Memory loss						
Constipation						
Diarrhea						
Muscle pain (please mark on Diagram 1 where you are affected by this)						
Nerve pain (please mark on Diagram 2 where in your body this is)						
Tingling (draw on Diagram 3 where this is)						
Numbness (draw on Diagram 4 where this is)						
Others (please state)						

N.B. Please do not forget to fill in the body diagrams on the next page if you suffer from MUSCLE PAIN, NERVE PAIN, TINGLING OR NUMBNESS.

Once completed please hand over this questionnaire to the reception desk.

THANK YOU.

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report

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ABSTRACT

Introduction: Anxiety and sleep disorders are often the result of posttraumatic stress disorder and can contribute to an impaired ability to focus and to demonstration of oppositional behaviors.

Case Presentation: These symptoms were present in our patient, a ten-year-old girl who was sexually abused and had minimal parental supervision as a young child under the age of five. Pharmaceutical medications provided partial relief, but results were not long-lasting, and there were major side effects. A trial of cannabidiol oil resulted in a maintained decrease in anxiety and a steady improvement in the quality and quantity of the patient's sleep.

Discussion: Cannabidiol oil, an increasingly popular treatment of anxiety and sleep issues, has been documented as being an effective alternative to pharmaceutical medications. This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder.

INTRODUCTION

Cannabidiol (CBD) oil is a naturally occurring constituent of industrial hemp and marijuana, which are collectively called cannabis. CBD oil is 1 of at least 85 cannabinoid compounds found in cannabis and is popular for its medicinal benefits. After tetrahydrocannabinol (THC), CBD oil is the second-most-abundant component of cannabis. Other names for CBD oil include CBD-rich hemp oil, hemp-derived CBD oil, or CBD-rich cannabis oil. Considered to be generally safe, CBD has been used medicinally for decades. However, CBD is not medical marijuana and should be distinguished from high-CBD strains of medical marijuana, which do contain THC, such as "Charlotte's Web."

The most abundant compound in cannabis, THC is also a cannabinoid. The THC component induces the psychoactive effect, "high." A cannabis plant has different amounts of CBD and THC depending on the strain and thus provides different recreational or medicinal effects. The cannabinoid profile of industrial hemp or medical marijuana is ideal for people looking for the medical benefits of CBD without the "high" of the THC.

The mechanism of action of CBD is multifold.[1-3] Two cannabinoid receptors are known to exist in the human body: CB1 and CB2 receptors. The CB1 receptors are located mainly in the brain and modulate neurotransmitter release in a manner that prevents excessive neuronal activity (thus calming and decreasing anxiety), as well as reduces pain, reduces inflammation, regulates movement and posture control, and regulates sensory perception, memory, and cognitive function.[a2] An endogenous ligand, anandamide, which occurs naturally in our bodies, binds to the CB1 receptors through the G-protein coupling system. CBD has an indirect effect on the CB1 receptors by stopping the enzymatic breakdown of anandamide, allowing it to stay in the system longer and provide medical benefits.[4] CBD has a mild effect on the CB2 receptors, which are located in the periphery in lymphoid tissue. CBD helps to mediate the release of cytokines from the immune cells in a manner that helps to reduce inflammation and pain.[2]

Other mechanisms of action of CBD include stimulation of vanilloid pain receptors (TRPV-1 receptor), which are known to mediate pain perception, inflammation, and body temperature.[5] In addition, CBD may exert its anti-anxiety effect by activating adenosine receptors which play a significant role in cardiovascular function and cause a broad anti-inflammatory effect throughout the body.[5] At high concentrations, CBD directly activates the 5-HT1A serotonin receptor, thereby conferring an antidepressant effect.[6] Cannabidiol has been found to be an antagonist at the potentially new third cannabinoid receptor, GPR55, in the caudate nucleus and putamen, which if stimulated may contribute to osteoporosis.[7]

Since the 1940s, a considerable number of published articles have dealt with the chemistry, biochemistry, pharmacology, and clinical effects of CBD.[8] The last decade has shown a notable increase in the scientific literature on CBD, owing to its identification for reducing nausea and vomiting, combating psychotic disorders, reducing inflammation, decreasing anxiety and depression, improving sleep, and increasing a sense of well-being.[9-12] Findings presented at the 2015 International Cannabinoid Research Society at its 25th Annual Symposium reported the use of CBD as beneficial for kidney fibrosis and inflammation, metabolic syndrome, overweight and obesity, anorexia-cachexia syndrome, and modification of osteoarthritic and other musculoskeletal conditions.[13-16]

Although studies have demonstrated the calming, anti-inflammatory, and relaxing effects of CBD, clinical data from actual cases is minimal. This case study offers evidence that CBD is effective as a safe alternative treatment to traditional psychiatric medications for reducing anxiety and insomnia.[17]

CASE PRESENTATION

A ten-year-old girl presented in January 2015 for a reevaluation of behaviors related to her diagnosis of posttraumatic stress disorder (PTSD) secondary to sexual

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abuse. Her chief issues included anxiety, insomnia, outbursts at school, suicidal ideation, and self-destructive behaviors. Her grandmother, who has permanent custody of the patient and her younger brother, accompanied her.

Our patient had been seen for an initial evaluation in January 2012 and received a diagnosis of PTSD secondary to sexual abuse on the basis of her history, clinical observations, and behaviors (Table 1). Her father had died 6 months earlier in a motor vehicle accident, and our patient's maternal grandparents became her permanent guardians. Before her father's death, our patient had no supervision from her father and very little supervision from her mother. An 11-year-old boy had molested her when she was 3 years old. Her medical history included her mother having methadone addiction, alcoholism, bipolar disorder, and depression. Her mother used marijuana her entire pregnancy with the girl. The patient presented in January 2012 as displaying aggressive, disobedient, impulsive, and sexually inappropriate behaviors. She also demonstrated low self-esteem and anxiety and had poor sleep (restless, interrupted, and unable to sleep alone).

Workup during 2012 included laboratory studies, which ruled out a thyroid dysfunction and an iron or vitamin D deficiency. The patient was started on a

Table 1. Timeline

Date	Presentation	Medications	Supplements	Other
January 31, 2012	New evaluation: 7.5-year-old girl. History of sexual abuse and neglect. Issues: Insomnia, sexual behaviors. Diagnosis: PTSD secondary to sexual abuse.	None	Melatonin, 1 mg/night	February 14, 2012, laboratory values: TSH, 2.46 mIU/L (reference range, 0.47-4.68 mIU/L); ferritin: 21 ng/mL (reference range, 10-150 ng/mL). February 16, 2012, laboratory values: Vitamin D_3: 39 ng/mL (reference range, 20-50 ng/mL)
February 20, 2012	Sleeping 2-3 hours/night. Started counseling; Cooperative and good behavior at counseling session. Anxious, traumatized.	Clonidine, 0.05 mg (half tablet) at bedtime	Inositol, 3 g 3 times/d; EPA fish oil, 500 mg/d	Eye movement desensitization and reprocessing therapy recommended
February 22, 2012	Did not do well with clonidine because of hallucinations, so she discontinued that treatment. Behavior still very rough; sleep poor.	Started imipramine therapy, 25 mg at bedtime		March 7, 2012: ECG was normal
August 8, 2012[a]	Good summer. In play therapy. Overall better sleep and energy with imipramine therapy. Patient's 6-year-old brother also now in therapy.	Imipramine, 25 mg at bedtime		
January 21, 2015	Returned for evaluation and treatment after 3 years. Suicidal ideation; cut self on leg; defiant and stubborn. Had psychotherapy 3 years straight twice a month. Sleeps with brother; can't sleep alone.	Off all medications for past 18 months	Melatonin, 5 mg; St John's wort, 450 mg twice/d; magnesium, 300 mg/d; diphenhydramine, 25 mg/night	
February 16, 2015	Hard to manage. Has outbursts at school.		Magnesium and St John's wort: stopped treatment; EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	February 11, 2015: Normal cortisol and DHEA levels
March 16, 2015	Better overall. Started animal-assisted therapy.		EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	Started a regimen of CBD oil, 25 mg (1 capsule)/d at 6 pm
April 14, 2015	Sleeping better with CBD treatment. Getting biofeedback. Has stomachaches. Mood is more at ease.		EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	CBD oil, 25 mg (1 capsule)/d at 6 pm
May 26, 2015	"Ghosts" waking patient up at night.		EPA fish oil, 750 mg/d	CBD oil, 25 mg (1 capsule)/d at 6 pm
July 22, 2015	Sleeping better; able to sleep in own room 3-4 nights/wk.		EPA fish oil, 750 mg/d	CBD liquid, 12 mg (in 4 sublingual sprays)/night; 12 mg more (in 4 sublingual sprays) during the day as needed for anxiety, typically 3 or 4 times/wk
August 24, 2015	Sleeping well. Handling school well.		EPA fish oil, 750 mg/d	CBD oil, 25 mg (1 capsule)/night; CBD liquid, 6-12 mg (in 2-4 sublingual sprays) as needed for anxiety, typically 2 or 3 times/wk

[a] There were additional visits in 2012 with no substantial changes.

CBD = cannabidiol; DHEA = dehydroepiandrosterone; ECG = electrocardiogram; EPA = eicosapentaenoic acid; PTSD = posttraumatic stress disorder; TSH = thyroid stimulating hormone.

regimen of 1 mg/night of melatonin, which helped her sleep duration. Three grams of inositol 3 times a day and 500 mg/d of eicosapentaenoic fish oil were also helpful in reducing her anxiety. A trial of clonidine was implemented, which resulted in hallucinations and thus was discontinued. The patient was switched to a regimen of 25 mg of imipramine at bedtime to decrease her anxiety, which appeared to be helpful. Counseling sessions were started. The patient continued psychotherapy for 3 years, but she was not seen again in our clinic until the return visit in January 2015, when she was not receiving any of her medications and supplements.

CBD oil can be an effective compound to reduce anxiety and insomnia secondary to PTSD.

At the patient's return in January 2015, she demonstrated the same prominent symptoms as at her initial presentation. At that time, the initial treatment included the following supplements and medications to assist with her sleep and anxiety: melatonin, 5 mg/night; magnesium, 300 mg/d; and diphenhydramine (Benadryl), 25 mg/night. Our patient demonstrated slight gains but was still having outbursts at school and was reportedly difficult to manage at home. In addition, her underlying anxiety continued.

Cannabidiol oil was explored as a potential additional treatment to help her insomnia and anxiety, but we deferred for two months while we waited for a response from other interventions. The grandmother preferred reducing the pharmacologic load given her granddaughter's failure to respond long term to psychiatric medications.

In March 2015, CBD oil was recommended as a potential additional treatment to help her insomnia and anxiety, and her grandmother provided full informed consent. Our patient was administered the Sleep Disturbance Scale for Children[18] and the Screen for Anxiety Related Disorders (SCARED)[19] before taking the CBD oil and each month afterward for the next 5 months. Test scores on the Sleep Disturbance Scale for Children and Screen for Anxiety Related Disorders demonstrated an improvement (Table 2).

A trial of CBD supplements (25 mg) was then initiated at bedtime, and 6 mg to 12 mg of CBD sublingual spray was administered during the day as needed for anxiety. A gradual increase in sleep quality and quantity and a decrease in her anxiety were noted. After 5 months, the patient was sleeping in her own room most nights and handling the new school year with no difficulties. No side effects were observed from taking the CBD oil.

DISCUSSION

Studies repeatedly recognize the prevalence of an anxiety-provoked sleep disorder after a traumatic experience.[20] Our patient was definitely experiencing this phenomenon, which was aggravated by daily stressful activities.

The main finding from this case study is that CBD oil can be an effective compound to reduce anxiety and insomnia secondary to PTSD. A review of the literature suggests some benefits from the use of CBD because of its anxiolytic and sleep-inducing effects.[9] Animal studies support use of this treatment and report that "CBD may block anxiety-induced [rapid eye movement] sleep alteration via its anxiolytic effect on the brain."[21]

The strength of this particular case is that our patient was receiving no pharmaceutical medications (other than nonprescription diphenhydramine) but only nutritional supplements and the CBD oil to control her symptoms. Her scores on the sleep scale and the anxiety scale consistently and steadily decreased during a period of 5 months (see Table 2). She was ultimately able to sleep through the night most nights in her own room, was less anxious at school and home, and displayed appropriate behaviors. The patient's grandmother (her caregiver) reported: "My granddaughter's behaviors are definitely better being on the CBD. Her anxiety is not gone, but it is not as intense and she is much easier to be around. She now sleeps in her own room most of the time, which has never happened before."

Table 2. Patient's clinical progress in sleep and anxiety

Date of visit	Sleep scale score[a]	SCARED score[b]
March 16, 2015	59	34
May 25, 2015	42	24
July 22, 2015	41	19
August 24, 2015	37	16
September 22, 2015	38	18

[a] A score of more than 50 is considered indicative of a sleep disorder on the Sleep Disturbance Scale for Children.
[b] A SCARED score over 25 indicates a high probability of a childhood anxiety disorder.
SCARED = Screen for Anxiety Related Disorders.

Further study will need to be conducted to determine the permanency of our patient's positive behaviors and how long she will need to continue taking the CBD oil. We do not have a reasonable foundation to recommend dosing from the scientific literature. However, in our experience, this supplement given 12 mg to 25 mg once daily appears to provide relief of key symptoms with minimal side effects. Our patient did not voice any complaints or discomfort from the use of CBD. We routinely asked about headache, fatigue, and change in appetite or agitation in addition to conducting a routine psychiatric evaluation. Although CBD is considered generally safe,[17] the long-term effects are yet to be studied.

The ultimate goal is to gradually taper her off the use of CBD oil and transition our patient into lifelong coping strategies such as yoga, meditation, and various other therapeutic activities. ❖

[a] GW Pharmaceuticals is the founder of the Cannabinoid Research Institute, directed by Philip Robson, MD. Further research articles listed.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Marijuana and Medicine

Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily [tetrahydrocannabinol], for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude [tetrahydrocannabinol] delivery system that also delivers harmful substances.

— Joy JE, Watson SJ Jr, Benson JA Jr. Marijuana and medicine: Assessing the science base. Washington, DC: National Academies Press; 1999.

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Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics†

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Abstract — Marijuana is a currently illegal psychoactive drug that many physicians believe has substantial therapeutic uses. The medical literature contains a growing number of studies on cannabinoids as well as case studies and anecdotal reports suggesting therapeutic potential. Fifteen states have passed medical marijuana laws, but little is known about the growing population of patients who use marijuana medicinally. This article reports on a sample of 1,746 patients from a network of nine medical marijuana evaluation clinics in California. Patients completed a standardized medical history form; evaluating physicians completed standardized evaluation forms. From this data we describe patient characteristics, self-reported presenting symptoms, physician evaluations, other treatments tried, other drug use, and medical marijuana use practices. Pain, insomnia, and anxiety were the most common conditions for which evaluating physicians recommended medical marijuana. Shifts in the medical marijuana patient population over time, the need for further research, and the issue of diversion are discussed.

Keywords — anxiety, cannabis therapeutics, insomnia, medical marijuana, pain

Medicinal preparations containing marijuana (cannabis) were widely used in many societies for centuries. Dr. William O'Shaughnessy introduced it as a modern medicine in Europe in 1839. Marijuana was prescribed for therapeutic use in American medical practice for a variety of conditions from the mid-nineteenth century into the twentieth. Marijuana was admitted to the *United States Pharmacopoeia* in 1850 and listed in the *National Formulary* and the *US Dispensatory*. Major pharmaceutical companies including Lilly, Burroughs-Wellcome, and Parke-Davis produced cannabis-based therapeutic agents (Brecher et al. 1972).

In 1936, the Federal Bureau of Narcotics advocated a law prohibiting its use, which Congress passed in 1937, against the advice of the American Medical Association (Grinspoon & Bakalar 1993:9–11). This law, along with increased prescribing of aspirin and barbiturates, pushed cannabis out of the *United States Pharmacopoeia* and common medical practice by 1942.

After nonmedical cannabis use spread in the 1960s, the number of Americans reporting lifetime prevalence

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increased sharply. Recent estimates from the National Survey on Drug Use and Health show that 102,404,000 Americans have used this drug, 41% of the population aged 12 and over, or about half the adult population (SAMHSA 2010). This widespread use led to a gradual rediscovery of the therapeutic uses of cannabis, albeit largely without physician involvement.

Alongside the spread of nonmedical use, in 1964 scientists determined the precise chemical structure of delta-9 tetrahydrocannabinol (THC), thought to be the most significant psychoactive ingredient in cannabis (Gaoni & Mechoulam 1964). This stimulated research in the clinical pharmacology of cannabinoids. Many physicians in clinical practice also recognized the therapeutic potential of cannabis (Irvine 2006; Charuvastra, Freidmann & Stein 2005), specifically, for example, for pain (Woolridge et al. 2005), as an antiemetic for chemotherapy patients (Doblin & Kleiman 1991), or for symptoms of AIDS (Abrams et al. 2003). More recently a broader medical literature documenting the therapeutic properties of endogenous cannabinoids has developed (e.g., Nicoll & Alger 2004; Lehmann et al. 2002; Hall, Degenhart & Currow 2001). Numerous case reports in the medical literature also have suggested that cannabis has therapeutic potential for a variety of conditions. But rigorous experimental research that might determine more precisely the therapeutic efficacy of cannabis for specific conditions has been blocked by the Drug Enforcement Administration (see Zeese 1999; *Alliance for Cannabis Therapeutics v. Drug Enforcement Administration* 1994).

This combination of increasing therapeutic use and federal government opposition ultimately led to passage of new state laws providing for the medical use of cannabis upon physician recommendation. Since 1996, 15 U.S. states and the District of Columbia have passed such laws: California, Alaska, Oregon, Washington, Nevada, Colorado, Maine, Montana, Michigan, and Washington, DC by ballot initiative; Rhode Island, New Mexico, Vermont, Hawaii, and New Jersey by state legislation.

The first of these laws was California's Proposition 215, the Compassionate Use Act, passed in 1996 (*San Francisco Chronicle* 1996). This act made it legal under state law for patients to possess and use cannabis if recommended by their physicians. Numerous medical and scientific associations endorsed medical use of cannabis and/or supported further research into its therapeutic potential. These included the American College of Physicians (2008), the American Public Health Association (1995), the British Medical Association (1997), the Canadian Medical Association (2005), and the Institute of Medicine of the National Academy of Sciences (1999).

Such elections and endorsements notwithstanding, the Bush Administration's Office of National Drug Control Policy threatened to revoke the licenses of physicians who recommended cannabis to patients. One physician challenged this policy and the U.S. Court of Appeals ruled (in *Conant v. Walters)* in 2002 that it unconstitutionally infringed physicians' First Amendment rights to freedom of speech with their patients (McCarthy 2004). Subsequent legislation and case law have left medical marijuana (MM) patients and their physicians in legal limbo:

- In 2003, the California legislature passed SB 420 to provide specific implementation guidelines for Proposition 215, including how counties should handle MM patient ID cards.
- Most drug law enforcement is done by local police who enforce state, not federal, drug laws. In 2005, The California Attorney General ruled that Proposition 215 is the legitimate will of the voters and is therefore valid under the California Constitution for purposes of *state* law enforcement. He advised the Highway Patrol and other state law enforcement agencies that under California law MM patients were legally entitled to possess and use cannabis for therapeutic purposes (Hoge 2005).
- In 2006, Bush administration Attorney General Gonzales sought to invalidate state MM laws, and the U.S. Supreme Court ruled (*Gonzales v. Raich* 2006) that the Compassionate Use Act—its legitimate electoral provenance notwithstanding—neither supersedes nor invalidates federal laws that prohibit marijuana use (see Mikos 2009 for a legal analysis of the states' neglected power to legalize behavior that is criminalized under federal law).
- In 2008 the Supreme Court denied without comment an appeal by two California counties that had refused to implement Proposition 215 (*County of San Diego v. San Diego NORML* 2008), thereby letting stand a lower court ruling that upheld SB 420's provisions regarding counties issuing MM identification cards.
- In 2009, Attorney General Eric Holder issued a policy stating that federal drug control agencies would no longer raid MM dispensaries if they operated within state and local laws (Moore 2009).
- That policy notwithstanding, the DEA has continued to raid MM dispensaries in California into 2011 (e.g., Blankstein 2009).

Within this grey area between conflicting state and federal laws, the number of patients who have received recommendations for medical marijuana from physicians has continued to grow, albeit by how much remains unknown. Over 1,000 MM dispensaries, delivery services, and cooperatives are said to be operating in California to meet the demand (NORML 2007). A rough estimate of the number of MM patients in California can be extrapolated from Oregon figures. Unlike California's Compassionate Use Act, Oregon's MM law set up an Oregon Medical Marijuana Program that requires centralized record keeping. As of July, 2009, some 2,983 Oregon-licensed physicians had approved 20,307 applications for MM (Oregon

Department of Human Services 2008). The population of California is 9.7 times that of Oregon (U.S. Census 2007), which yields a crude estimate of 196,978 MM patients in California. This is likely an underestimate because the California statute affords greater latitude to physicians regarding the conditions for which they can recommend MM (". . . any other illness for which marijuana provides relief"). Americans for Safe Access (2008), a MM patient advocacy group, has estimated that there are well over 200,000 physician-sanctioned MM patients in California.

Despite their growing numbers, however, the ambiguous legal status of MM patients renders them a half-hidden population whose characteristics are not well documented, with the partial exception of the San Francisco Bay Area (O'Connell & Bou-Matar 2007; Reiman 2007a). Medical marijuana will likely continue to be a contentious issue, but across fifteen states and the District of Columbia several hundred thousand people are using marijuana as a medicine recommended by physicians, and yet little is known about them as a patient population.

We intend this study as a modest contribution toward filling this gap. It presents data on the demographic characteristics, presenting symptoms, physician evaluations, conventional treatments tried, and MM use practices of patients from a network of MM assessment clinics in California.

METHODS

These data were drawn from 1,746 consecutive admissions to nine MM assessment clinics operating in California in July, August, and September 2006. These assessment clinics are not dispensaries and are not connected to dispensaries. They were located throughout the state—in the north and south, coast and central valley, and large and small cities: Modesto, Oakland, Sacramento, Hollywood, San Diego, Santa Cruz, Ukiah, San Francisco, and Santa Rosa. They charged $100 to $125 for an assessment. At the time our sample was drawn, these assessment clinics had evaluated over 54,000 MM patients. Without a comprehensive patient database or representative household surveys, there is no way to determine precisely how representative this sample is of the overall population of MM patients. Moreover, there is a large albeit unknown number of people who use marijuana medicinally but who have not sought physician recommendations or official patient ID cards, perhaps because of the expense of the assessment.[1]

Evaluating physicians interviewed potential patients and evaluated their patient medical histories for purposes of recommending MM and issuing patient identification cards under the Compassionate Use Act and SB 420. The evaluation instruments were (1) a basic patient-administered medical history questionnaire covering demographics, presenting symptoms or conditions, brief medical history, conventional and alternative medical treatments tried, drug use history, and MM use practices; and (2) a physician evaluation form using International Classification of Diseases codes (ICD-9). Each patient received and signed an extensive informed consent form noting confidentiality, which was approved by the clinics' IRB.

Most prior studies of MM patients are based on small, symptom-specific samples. Initially, the population of MM patients in the San Francisco Bay Area were people with HIV/AIDS and cancer (e.g., Harris, Mendelson & Jones 1998). Later, physicians began to recommend cannabis to patients with chronic pain, mood disorders and other psychiatric conditions (Gieringer 2002). The data reported here describe what is among the largest and most symptomatically and demographically diverse samples of medical cannabis patients to date (cf., O'Connell & Bou-Matar 2007).

RESULTS

As Table 1 indicates, the MM patients are three-fourths male and three-fifths White. Compared to the US Census of California, the patients in this sample are on average somewhat younger, report slightly more years of formal education, and are more often employed. The comparison also indicates that women, Latinos, and Asian Americans are underrepresented. Given the limitations of our data, we can offer only informed speculation as to why.

The underrepresentation of women may be in part an epidemiological artifact of the gender distribution of certain kinds of injuries (e.g., workplace, sports, and motorcycle accidents). It may also have to do with the double stigma women face in seeking MM—for using an illicit drug and for violating gender-specific norms against illegal behavior in general. Moreover, as with alcohol use, pregnant women and women considering pregnancy are likely to have health concerns and many may fear that MM could put them in jeopardy if discovered by child protection agencies.

Given the high poverty rate among Latinos and their concentration in the manual labor end of the occupational structure, Latinos are exposed to equal or greater risks of work-related injuries and to no less epidemiologic risk of other conditions for which MM is sometimes used. It seems likely that their under-representation has to do with the undocumented status of many Latinos in California. The undocumented often avoid contact with government agencies for fear of apprehension by law enforcement, for beyond arrest and incarceration this carries the risk of deportation. Such fears reduce the likelihood of Latinos accessing health care in general and MM in particular. Asian Americans are also underrepresented, but this may be because they have lower prevalence of marijuana use than other racial/ethnic groups and/or because they have their own venerable traditions of herbal medicine.

TABLE 1
Demographic Characteristics of California Medical Marijuana Patients Compared to California Census 2000, Age 18 and Over {n = 1746}

	MM Patients	U.S. Census 2000 – California
Female	27.1%	50.7%
Male	72.9%	49.3%
White	61.5%	59.5%
Latino	14.4%	32.4%
African American	11.8%	6.7%
Native American	4.5%	1.0%
Asian/Pacific Islander	4.2%	11.2%
Other	4.3%	*
18–24 Years Old	17.9%	~17.1%
25–34 "	27.5%	15.4%
35–44 "	21.3%	16.2%
45–54 "	20.4%	12.8%
55> "	12.6%	18.4%
<High School	8.8%	*
High School Graduate	42.2%	*
Some College	27.1%	*
College Graduate>	23.8%	*
Employed	64.8%	57.5%
Health Insurance	73.4%	*

*Data not available in California Census.

TABLE 2
Patient Self-Reports of Therapeutic Benefits from Medicinal Marijuana*

	Percent
To Relieve:	
Pain	82.6
Muscle Spasms	41.1
Headaches	40.7
Anxiety	37.8
Nausea/Vomiting	27.7
Depression	26.1
Cramps	19.0
Panic Attacks	16.9
Diarrhea	5.0
Itching	2.8
To Improve:	
Sleep	70.7
Relaxation	55.1
Appetite	37.7
Concentration/Focus	22.9
Energy	15.9
To Prevent:	
Medication Side Effects	22.5
Anger	22.4
Involuntary Movements	6.2
Seizures	3.2
As Substitute for:	
Prescription Medication	50.9
Alcohol	13.0

*N = 1,745; patients could report more than one benefit in more than one category.

African-Americans, conversely, are over-represented in this sample. This does not appear to stem from their prevalence of marijuana use, for representative national surveys show that Blacks generally do not have significantly higher prevalence of marijuana use than Whites (SAMHSA 2005). African-Americans may be more likely to seek MM for any of several reasons: because they are disproportionately poor, more often lack health insurance, are significantly less likely to be prescribed other medication for pain (Pletcher et al. 2008) or to receive treatment for cancer (Gross et al. 2008), and because African-Americans are a growing proportion of HIV/AIDS cases. Some of these same reasons may help to explain why Native Americans are also overrepresented, although their proportion of both this sample and the general population is too small to judge representativeness accurately.

In their medical history questionnaires, patients were asked "Which of the following best describe the therapeutic benefit you receive from medicinal cannabis? (Check the most important)." Patients typically reported more than one therapeutic benefit (mean = 3). Early studies showed most patients used MM to relieve symptoms of HIV/AIDS (Woolridge et al. 2005) or cancer, and it is likely that the majority of patients in our sample who reported "nausea" were cancer patients receiving chemotherapy. However, Table 2 suggests that cancer and AIDS patients are now a significantly smaller proportion of the total (e.g., "to relieve nausea/vomiting" 27.7%, "to improve appetite" 37.7%) and that the MM patient population has become more diverse since the Compassionate Use Act was passed in 1996 (cf. Ware, Adams & Guy 2005, on MM use in the UK, and Grotenherman 2002 on MM use in Germany).

Instead, relief of pain, muscle spasms, headache, and anxiety, as well as to improve sleep and relaxation were the most common reasons patients cited for using MM. Chronic pain also topped the list of maladies for which MM was used in another California clinical sample (Reiman 2007b).

Table 3 shows the ICD-9 diagnostic codes most frequently recorded by evaluating physicians. Pain from back and neck injuries was the most frequently coded. This appears consistent with a nationally representative Medical Expenditure Panel Survey, which found a 19.3% increase in the prevalence of spine problems between 1997 and 2005 (Martin et al. 2008). Back and neck pain was followed in frequency by sleep disorders (also increasing), anxiety/depression, muscle spasms, and arthritis. Fully half of this sample reported using MM as a substitute

TABLE 3
Conditions Most Frequently Recorded by Physicians As Reasons for Approving Medical Marijuana Patient Identification Cards*

	Percent	ICD-9 Codes
Back/Spine/Neck Pain	30.6%	[722.1–724.2]
Sleep Disorders	15.7%	[307.42, 327.0]
Anxiety/Depression	13.0%	[300.0, 311.0]
Muscle Spasms	9.5%	[728.85]
Arthritis	8.5%	[715.0, 721.2, 721.2]
Injuries (Knee, Ankle, Foot)	4.5%	[959.7]
Joint Disease/Disorders	4.4%	[716.1–719.49]
Narcolepsy	3.7%	[347.0]
Nausea	3.4%	[787.02]
Inflammation (Spine, Nerve)	2.9%	[724.4]
Headaches/Migraines	2.7%	[784.0, 346.0, 346.2]
Eating Disorders	1.1%	[783.0]

*N = 1746; some patients reported multiple symptoms and/or conditions.

TABLE 4
Other Treatment Modalities Tried for the Medical Condition(s) for Which Patients Seek Medical Marijuana*

	%	N
Prescription Medication	79.3%	1383
Physical Therapy	48.7	850
Chiropractic	36.3	633
Surgery	22.3	389
Counseling	21.0	366
Acupuncture	19.4	338
Therapeutic Injection	15.4	269
Homeopathy	12.0	209
Other Types of Treatment	11.9	208

*N = 1746; patients could report multiple other treatments.

for prescription drugs, consistent with other studies (e.g., Reiman 2007a).

Table 4 indicates that the MM patients in the sample had tried a variety of other treatments, conventional and alternative, for the conditions for which they were seeking a MM identification card. Four in five (79.3%) reported having tried other medications prescribed by their physicians (almost half were opiates); about half (48.7%) had tried physical therapy; over a third (36.3%) had tried chiropractic; nearly one-fourth (22.3%) reported having had surgery for their condition.

Table 5 compares patient responses to the drug use questions to those in the 2006 National Survey on Drug Use and Health (SAMHSA 2007). Prevalence of tobacco

TABLE 5
Medical Marijuana Patients' Self-Reported Current Nonmedical Drug Use, Compared to 2006 National Survey on Drug Use And Health (SAMHSA 2007)

	MM Patients	NSDUH*
Tobacco	29.4%	25.0%
Alcohol	47.5	61.9
Cocaine	0.3	1.9
Methamphetamine	0.4	0.5
Heroin	0.1	0.3
Other Opiates	1.2	**

Note: Participants were asked "Do you currently use . . ."; answers are percent responding "yes." N = 1745; patients could report more than one drug. Of smokers, 65.5% used ten or less cigarettes/day; of drinkers, 58.7% used</= one or less drinks/day.
*NSDUH figures for "past month" prevalence used as a proxy for "current use".
**Data not available in comparable form.

use was somewhat higher than in the general population, but prevalence of alcohol use was significantly lower. Many patients reported that they valued MM because it allowed them to reduce their alcohol use. It is possible that self-reports on a self-administered instrument will underestimate illicit drug use, particularly if patients felt that admitting illicit drug use could reduce their chances of obtaining a MM identification card. Rigorous assessments of the reliability of such data must await further research, but limitations aside, these data suggest low prevalence of other illicit drug use among MM patients. While it is true that the great majority of our respondents had used marijuana recreationally, in response to a separate question over two-fifths (41.2%) reported that they had *not* been using it recreationally prior to trying it for medicinal purposes.

Table 6 presents data on patients' medical marijuana use practices. Amounts used per week varied from three grams or less (40.1%) to seven or more grams (23.3%). Two-thirds (67%) reported using MM daily while one-fourth (26%) reported using less than once a week. Half (52.9%) reported using one or two times per day while one in ten (10%) reported using three or more times per day. Patients consumed MM primarily in the evenings (52.3%) or prior to sleep (56.1%). More than two in five (42.3%) reported that when they used depended on their medical symptoms. Patients ingested MM predominantly by smoking (86.1%), although one-fourth (24.4%) reported ingesting orally and nearly a fourth (21.8%) reported using a vaporizer. These latter figures suggest that at least some of the time, many MM patients are choosing modes of ingestion that reduce the perceived risk of harms from smoking (Tan et al. 2009; Hashibe et al. 2006).

TABLE 6
Medical Marijuana Use Practices

Frequency of Medical Marijuana Use (N = 1583)*	
Daily	67.0% (1065)
<Once A Week	26.0% (409)
<Once A Month	7.0% (109)
On Days Used, Frequency per Day (N = 1574)	
1 To 2 Times Per Day	52.9% (833)
2 To 3 Times Per Day	29.0% (457)
>3 Times Per Day	10.0% (284)
Time Of Day Typically Used (N = 1745)	
Prior To Sleep	56.1% (979)
Evenings	52.3% (913)
Depends on Symptoms	42.3% (739)
Mornings	25.7% (448)
Afternoons	20.1% (350)
After Work	12.4% (217)
Middle of the Night	6.5% (114)
All Day	5.3% (93)
Mode of Ingestion (N = 1745)	
Smoke	86.1% (1503)
Oral Ingestion	24.4% (426)
Vapor	21.8% (380)
Topical	2.8% (49)
Amount Used per Week (N = 1431)	
0–3 Grams	40.1% (574)
4–7 Grams	36.5% (523)
>7 Grams	23.3% (334)

*Total n = 1745, but N's vary across questions because patients could choose more than one response and because not all responded to each question.

DISCUSSION

Rediscovery of Medicinal Utility and Diversifying Patient Population

Compared to earlier studies of MM patients, these data suggest that the patient population has evolved from mostly HIV/AIDS and cancer patients to a significantly more diverse array. The diffusion of marijuana as a medicine may have been slower than that of other medicines in conventional clinical practice because the flow of information from physician to patient is impeded by MM's ambiguous legal status. Thus, information about the potential therapeutic utility of cannabis is spread mostly via word of mouth and other informal means. This suggests that the patient population is likely to continue evolving as new patients and physicians discover the therapeutic uses of cannabis. Ironically, this trend toward increasing therapeutic uses is bringing marijuana back to the position it held in the U.S. Pharmacopeia prior to its prohibition in 1937.

Further Research

Like other medicines, marijuana's therapeutic efficacy varies across conditions and patient groups. This variation seems more likely when supplies remain illicit because standardized dosages or other quality controls are more difficult to achieve. To gain maximum therapeutic potential across the growing range of conditions for which MM is being recommended, more systematic research is needed. Longitudinal, case control, and double-blind studies are required to rigorously assess marijuana's therapeutic efficacy for specific patient groups, conditions, and diseases. With regard to shifts in the patient population, it also would be very useful to have follow-up studies of patients accessing the assessment clinics in our sample and others drawn from similar assessment clinics.

Diversion

Critics have argued that some MM patients are "gaming the system" to get marijuana for nonmedical use. Neither our data nor any other data we are aware of allow any clear-cut, empirical estimate of the scale of such diversion. Given the widespread nonmedical use marijuana in the general population (102,404,000 Americans report lifetime prevalence; see SAMHSA 2010) and the risk of arrest (847,864 Americans were arrested for marijuana offenses in 2008, 754,224 or 88.96% of them for possession alone; FBI 2009), it seems likely that at least some MM patients use MM dispensaries as sources of supply for nonmedical use.

Defining and measuring such diversion, however, is complicated at best. Given the high prevalence of nonmedical use, it is not surprising that most MM patients in our sample reported having used it recreationally before using it therapeutically. But as noted above, two-fifths had *not* been using marijuana recreationally prior to trying it for medicinal purposes. Their self-reported rates of other illicit drug use are slightly lower than those found among the general population, and their levels of educational attainment and rate of employment are comparable to the California population. Our data have clear limitations, but they contain no obvious signs that MM patients differ from the general population.

Nor is drug diversion unique to medical marijuana. A significant albeit unknown proportion of other patients obtain prescriptions for numerous drugs through legal medical channels that they then use for nonmedical purposes, for example, Valium and other benzodiazepines (Haafkens 1997), Ritalin and other stimulants prescribed for ADHD, and Oxycontin and other opiates prescribed for pain.

The diversion issue will likely become more important as the line between medical and nonmedical drug use is increasingly blurred (Murray, Gaylin & Macklin 1984). Beyond the spread of MM, Prozac and other SSRI-type antidepressants, for example, are often prescribed

for patients who do not meet DSM criteria for clinical depression but who simply feel better when taking it. Such "cosmetic psychopharmacology" (Kramer 1993) is likely to grow as new psychiatric medications come to market. The line between medical and nonmedical drug use has also been blurred by performance enhancing drugs such as steroids, so-called "smart drugs" that combine vitamins with psychoactive ingredients, and herbal remedies like *ma huang* (ephedra) available in health food stores (Burros & Jay 1996).

These examples suggest that despite the best intentions of physicians and law makers, much drug use does not fit into two neat boxes, medical and nonmedical, but rather exists on a continuum where one shades into the other as patients' purposes shift to suit situational exigencies in their health and their daily lives. It is not clear where a border line between medical and nonmedical marijuana or other drug use might be drawn nor how it might be effectively policed (see Reinarman & Levine 1997: 334–44).

NOTE

1. We are grateful to one anonymous reviewer for pointing out that the cost of these assessments may well have prevented some potential MM patients—including many impoverished HIV/AIDS patients—from obtaining ID cards, which may have affected the demographics of this sample.

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Therapeutic Benefits of Cannabis: A Patient Survey

Charles W. Webb MD and Sandra M. Webb RN, BSN

Abstract

Clinical research regarding the therapeutic benefits of cannabis ("marijuana") has been almost non-existent in the United States since cannabis was given Schedule I status in the Controlled Substances Act of 1970. In order to discover the benefits and adverse effects perceived by medical cannabis patients, especially with regards to chronic pain, we hand-delivered surveys to one hundred consecutive patients who were returning for yearly re-certification for medical cannabis use in Hawai'i.

The response rate was 94%. Mean and median ages were 49.3 and 51 years respectively. Ninety-seven per cent of respondents used cannabis primarily for chronic pain. Average pain improvement on a 0-10 pain scale was 5.0 (from 7.8 to 2.8), which translates to a 64% relative decrease in average pain. Half of all respondents also noted relief from stress/anxiety, and nearly half (45%) reported relief from insomnia. Most patients (71%) reported no adverse effects, while 6% reported a cough or throat irritation and 5% feared arrest even though medical cannabis is legal in Hawai'i. No serious adverse effects were reported.

These results suggest that Cannabis is an extremely safe and effective medication for many chronic pain patients. Cannabis appears to alleviate pain, insomnia, and may be helpful in relieving anxiety. Cannabis has shown extreme promise in the treatment of numerous medical problems and deserves to be released from the current Schedule I federal prohibition against research and prescription.

Introduction

Research into the therapeutic benefits of cannabis has been severely limited by the federal Schedule I classification, which essentially prohibits any ability to acquire or to provide cannabis for studies investigating possible therapeutic effects. Limited studies have been done in Canada and in Europe, as well as several in California.

Hawai'i is one of twenty states (plus the District of Columbia) which allow certifications for use of medical cannabis. The authors have been certifying patients for use of medical cannabis in Hawai'i for more than four years. In an attempt to discover the perceived benefits and adverse effects of medical cannabis, we conducted a survey of medical cannabis patients.

Methods

Sample Selection

Between July of 2010 and February of 2011, we hand-delivered questionnaires to one hundred consecutive patients who had been certified for the medical use of cannabis for a minimum of one year and were currently re-applying for certification.

Survey Design and Administration

The subjects were verbally instructed to complete the questionnaire in the office at the time of re-certification or were provided a stamped and addressed envelope so they could complete the questionnaire at home. All patients were instructed to remain anonymous and to answer the questions as honestly as possible.

A universal pain scale was used to assess pain before and after treatment (0 = no pain, 10 = worst pain ever). Open-ended questions were asked to ascertain the following:

(1) "Any adverse effects you have had from using medical cannabis?"
(2) "Does medical cannabis help you with any other problems? If so, what?"

The purpose of the last question was to explore benefits outside the parameters of the state of Hawai'i's medical cannabis qualifying conditions.

Results

The overall response rate was 94%. The mean age was 49.3 years and the median age was 51. No data was collected on sex or race/ethnicity. Almost all respondents (97%) used medical cannabis primarily for relief of chronic pain.

Average reported pain relief from medical cannabis was substantial. Average pre-treatment pain on a zero to ten scale was 7.8, whereas average post-treatment pain was 2.8, giving a reported average improvement of 5 points. This translates to a 64% average relative decrease in pain.

Other reported therapeutic benefits included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia. Other reported benefits did not extend to 5% or more of respondents.

Six patients (6%) wrote brief notes relating how cannabis helped them to decrease or to discontinue other medications. Comments included the following: "Medical cannabis replaced my need for oxycodone. Now I don't need them at all." "I do not need Xanax anymore." "In the last two years I have been able to drop meds for anxiety, sleep, and depression." "I've cut back 18 pills on my morphine dosage."

A majority (71%) reported no adverse effects, while 6% reported a cough and/or throat irritation and 5% reported a fear of arrest. All other adverse effects were less than 5%. No serious adverse effects were reported.

Discussion

According to the Institute of Medicine, chronic pain afflicts 116 million Americans and costs the nation over $600 billion every year in medical treatment and lost productivity.[1] Chronic pain is a devastating disease that frequently leads to major depression and even suicide.[2] Unfortunately, the therapeutic options for chronic pain are limited and extremely risky.

Spurred by efforts to encourage physicians to become more pro-active in treating chronic pain, US prescription opioids (synthetic derivatives of opium) have increased ten-fold since 1990.[3] By 2009 prescription opioids were responsible for almost half a million emergency department visits per year.[4] In 2010 prescription opioid overdoses were responsible for well over 16,000 deaths.[5] A 2010 article in the *New England Journal of Medicine* addressing this problem is aptly titled "A Flood of Opioids, a Rising Tide of Deaths."[3] Drugs such as OxyContin[R] are so dangerous that the manufacturer's boxed warning states that "respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused."[6] Clearly safer analgesics are needed.

The Hippocratic Oath reminds to "first, do no harm." It cannot be over-emphasized that there has never been a death from overdose attributed to cannabis.[7] In fact, no deaths whatsoever have been attributed to the direct effects of cannabis.[7] Cannabis has a safety record that is vastly superior to all other pain medications.

Many physicians worry that cannabis smoke might be as dangerous as cigarette smoke; however, epidemiologic studies have found no increase in oropharyngeal or pulmonary malignancies attributable to marijuana.[8-10] Still, since smoke is something best avoided, medical cannabis patients are encouraged to use smokeless vaporizers which can be purchased on-line or at local "smoke-shops." In states that (unlike Hawai'i) allow cannabis dispensaries, patients can purchase "vapor pens," analogous to e-cigarettes and fully labeled regarding doses of THC and other relevant cannabinoids.

Tests have proven that smoke-free vaporizers deliver THC as well or even more efficiently than smoking, and that most patients prefer vaporizers over smoking.[11] Like smoking, vaporizers allow patients to slowly titrate their medicine just to effect, analogous to IV patient-controlled analgesia (PCA) that has been so successful in hospital-based pain control. This avoids the unwanted psychoactive side-effects often associated with oral medication such as prescription Marinol[R] (100% THC in oil) capsules which tend to be slowly and erratically absorbed and are often either ineffectually weak or overpoweringly strong.[12,13] Because inhaled cannabis is rapid, reliable, and titratable, most patients strongly prefer inhaled cannabis over Marinol[R] capsules.[14]

While the relative safety of cannabis as medication is easily established, the degree of efficacy is still being established. The reported pain relief by patients in this survey is enormous. One reason for this is that patients were already self-selected for success: they had already tried cannabis and found that it worked for them. For this sample, the benefits of cannabis outweighed any negative effects. The study design may therefore lend itself to over-estimating the benefits and under-estimating the negative side-effects if extrapolated to the general population.

Another reason that the reported pain relief is so significant is that cannabis has been proven effective for many forms of recalcitrant chronic pain. A University of Toronto systematic review of randomized controlled trials (RCT's) examining cannabinoids in the treatment of chronic pain found that fifteen of eighteen trials demonstrated significant analgesic effect of cannabinoids and that there were no serious adverse effects.[15]

While opioids are generally considered to have little benefit in chronic neuropathic pain, several RCT's have shown that cannabinoids can relieve general neuropathic pain,[16] as well as neuropathic pain associated with HIV and with multiple sclerosis (MS).[17,18] One study found that cannabis had continuing efficacy at the same dose for at least two years.[19]

Even low dose inhaled cannabis has been proven to reduce neuropathic pain. In a randomized, double-blind, placebo-controlled crossover trial involving patients with refractory neuropathic pain, Ware, et al, found that therapeutic blood levels of THC (mean 45 ng/ml achieved by a single inhalation three times a day) were much lower than those necessary to produce a cannabis euphoria or "high"(> 100 ng/ml).[19]

Cannabis is relatively non-addicting, and patients who stop using it (eg, while traveling) report no withdrawal symptoms. One author (Webb C.) worked for 26 years in a high volume emergency department where he never witnessed a single visit for cannabis withdrawal symptoms, whereas dramatic symptoms from alcohol, benzodiazepine, and/or opioid withdrawal were a daily occurrence.

So why is cannabis still held hostage by the DEA as a Schedule I substance? On June 18, 2010, the Hawai'i Medical Association passed a resolution stating in part that:

> "Whereas, 1) Cannabis has little or no known withdrawal syndrome and is therefore considered to be minimally or non-addicting; and
>
> Whereas, 2) Cannabis has many well-known medical benefits (including efficacy for anorexia, nausea, vomiting, pain, muscle spasms, and glaucoma) and is currently recommended by thousands of physicians; and
>
> Whereas 3) Cannabis has been used by millions of people for many centuries with no history of recorded fatalities and with no lethal dosage ever discovered; and
>
> Whereas, Cannabis therefore fulfills none of the required three criteria (all of which are required) to maintain its current restriction as a Schedule I substance…

The Hawai'i Medical Association recommends that Medical Cannabis be re-scheduled to a status that is either equal to or less restrictive than the Schedule III status of synthetic THC (Marinol[R]), so as to reduce barriers to needed research and to humanely increase availability of cannabinoid medications to patients who may benefit."[20]

Medical cannabis remains controversial mainly because the federal government refuses to recognize cannabis as an accepted medication. To this we would echo the words of Melanie Thernstrom in her excellent book *The Pain Chronicles*,[2] "How could treating pain be controversial?" one might ask, " Why wouldn't it be treated? Who are the opponents of relief?"

Conclusions

Cannabis is an extremely safe and effective medication for many patients with chronic pain. In stark contrast to opioids and other available pain medications, cannabis is relatively non-addicting and has the best safety record of any known pain medication (no deaths attributed to overdose or direct effects of medication). Adverse reactions are mild and can be avoided by titration of dosage using smokeless vaporizers.

More research needs to be pursued to discover degrees of efficacy in other areas of promise such as in treating anxiety, depression, bipolar disorder, autism, nausea, vomiting, muscle spasms, seizures, and many neurologic disorders. Patients deserve to have cannabis released from its current federal prohibition so that scientific research can proceed and so that physicians can prescribe cannabis with the same freedom accorded any other safe and effective medications.

Conflict of Interest

None of the authors identify a conflict of interest.

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Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization

William D. Troutt, N.M.D. & Matthew D. DiDonato, Ph.D.

Abstract — Many advances have been made toward understanding the benefits of medical cannabis. However, less is known about medical cannabis patients themselves. Prior research has uncovered many important patient characteristics, but most of that work has been conducted with participants in California, who may not represent medical cannabis patients throughout the United States. Furthermore, it is unknown if medical cannabis legalization, which typically imposes strict regulations on cannabis cultivation and sale, impacts patients' experiences acquiring and using cannabis. The goal of this study was to address these limitations by (1) examining the characteristics, perceptions, and behaviors of medical cannabis patients in Arizona; and (2) questioning participants with a history of cannabis use regarding their experiences with cannabis before and after legalization. Patients in Arizona share many characteristics with those in California, but also key differences, such as average age and degree of cannabis consumption. Participants also had positive perceptions of the effect of medical cannabis legalization, reporting that feelings of safety and awareness were higher after legalization compared to before. The results are discussed in relation to evidence from patients in other states and in terms of their potential policy implications.

Keywords — Arizona, medical cannabis, medical cannabis legalization, patient characteristics, perceptions

Support for the use of cannabis for medical purposes is growing throughout the United States. To date, 23 states and the District of Columbia have enacted laws legalizing medical cannabis, and 16 states have similar legislation under consideration. Recent polls also show that the majority of Americans believe that cannabis should be legalized for medical purposes (Anderson Robbins Research & Shaw & Company Research 2013; Associated Press-CNBC 2010), and the popularity of this sentiment has increased over time (Anderson Robbins Research & Shaw & Company Research 2013).

Support may be on the rise, in part, due to research that shows the potential therapeutic effects of medical cannabis. Animal studies, for example, show that cannabis-derived extracts mitigate cancer cell proliferation and tumor growth (Aviello et al. 2012) and have antidepressant-like effects (Jiang et al. 2005). Studies also show that cannabis may be beneficial for humans. Bar-Sela and colleagues (2013) found that nausea, vomiting, weight loss, sleep disorders, and pain were reduced in cancer patients after 6–8 weeks of cannabis use. Studies also show that cannabis significantly reduces chronic pain (see Lynch and Campbell 2011),

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inflammatory bowel disease (Allegretti et al. 2013), post-traumatic stress disorder (Greer, Grob, and Halberstadt 2014), and seizure disorders (Lorenz 2004).

Although many advances have been made in understanding the benefits of medical cannabis, less is known about US medical cannabis patients themselves. Demographically, most patients are White, male, and approximately 35 to 45 years of age (Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinarman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O'Connell and Bou-Matar 2007; Harris et al. 2000). Most patients report medicating with cannabis daily (Bonn-Miller et al. 2014; Ilgen et al. 2013; Reinarman et al. 2011; O'Connell and Bou-Matar 2007), consuming six to nine grams of cannabis per week (Bonn-Miller et al. 2014; Reinarman et al. 2011; O'Connell and Bou-Matar 2007), and prefer inhalation as the method of consumption (O'Connell and Bou-Matar 2007).

Studies also show that the majority of patients use medical cannabis to relieve pain. However, patients also report using cannabis to treat a variety of other conditions, including anxiety, sleep apnea, hypertension, incontinence, and depression (Aggarwal et al. 2013; Nunberg et al. 2011; Reinarman et al. 2011). Generally, patients report that medical cannabis is effective for helping them manage their condition(s) (Bonn-Miller et al. 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Harris et al. 2000). For example, Aggarwal and colleagues (2013) found that, on a scale from 1 to 10, where 10 indicated absolute symptom control, patients reported that cannabis provided symptom control in the range of 7 to 10 across a variety of conditions. Patients also often reduce their use of other medications (i.e., prescription and over-the-counter drugs) when using medical cannabis (Nunberg et al. 2011; Aggarwal et al. 2009; Reiman 2009, 2007).

Though these studies are informative, one limitation is that most were conducted with samples of patients living in California. California patients may not represent those living in other areas of the country because the regulations that govern patients in California are different from those in other states. For example, residents of California may legally obtain medical cannabis to treat a number of ailments, including any chronic or persistent condition that considerably limits major life activities or that, if not alleviated, may compromise the patient's safety or health (California Senate Bill 420 2003). Because the list of conditions for which the legal medical use of cannabis is granted in other states is often less inclusive, patients from these states may differ from those in California.

Considering that medical cannabis has been legalized in many states, there is an opportunity to paint a more comprehensive picture of American medical cannabis patients by conducting similar studies in other geographic locations. Scientists have begun to conduct such research through the examination of patients living in Washington State (Aggarwal et al. 2013, 2009) and Michigan (Ilgen et al. 2013). Our first goal was to continue this line of research by studying medical cannabis patients in Arizona. To aid comparisons with previous research, we assessed patient characteristics, behaviors, and perceptions that have been examined in prior studies. These included patterns of use (e.g., frequency of consumption, amount of consumption, preferred method of consumption), degree of relief experienced when using medical cannabis, and use of other medications.

In addition to the limited research on medical cannabis patients outside of California, to our knowledge there has been no systematic examination of patients' perceptions of the outcomes of medical cannabis legalization. One objective of legalizing cannabis for medical use is to safeguard its acquisition and production, which often involves strict regulation of its cultivation and sale. For instance, the rules and regulations of the Arizona Medical Marijuana Program require that those authorized to operate medical cannabis dispensaries and cultivation facilities enact strict security policies and procedures (Arizona Department of Health Services Medical Marijuana Rules 2012). In addition, many dispensaries and facilities employ third-party laboratories to test cannabis products for possible contaminants. However, it is unknown if such regulations translate to changes in patient safety or product quality.

Because individuals who use cannabis medicinally are those most affected by these regulations, surveying patients regarding their experiences purchasing and using medical cannabis may uncover the changes legalization has had on patient safety and product quality. In particular, patients with a history of using cannabis medicinally prior to legalization can provide their perspective on the changes that legalization has generated. The second goal of the present study was to determine the effectiveness of measures invoked to regulate and secure the cultivation and sale of medical cannabis by examining the perceptions of patients that used cannabis medicinally prior to legalization. Patients were asked to compare their perceptions of safety, product knowledge, and the effectiveness of cannabis for treating their condition(s) before and after legalization. Because of the regulations imposed with the legalization of medical cannabis, we hypothesized that patients would feel greater safety, have better knowledge, and that cannabis effectiveness would be greater after legalization.

METHOD

Participants and Procedures

Participants were 367 patients recruited from four medical cannabis dispensaries located throughout Arizona. The majority of the patients were male (63.8%), and

ranged from 18 to 83 years of age (M = 45.78 years; SD = 13.76 years). Most of the patients were White (86.4%), whereas the rest were Hispanic (6.3%), Black (2.5%), Native American (1.9%), Asian (0.8%), or Other (2.1%). These figures are similar to those reported by the Arizona Department of Health Services (2014) for this patient population.

To protect patient confidentiality, the authors did not directly contact patients, but approached dispensary owners to request assistance in recruiting participants. Dispensary owners informed their patients of the study, and interested patients were directed to a website that provided information about the research, including a description of the study, an explanation of patients' rights as participants, and information regarding the collection and storage of participant responses (i.e., responses were anonymous and would be stored on a password-protected server and/or computer only accessible to the researchers). If the patient agreed to participate, he or she checked a box indicating his or her agreement and the survey questions appeared.

Measures

Patient conditions. Participants were asked to select from an extensive list of conditions for which they use medical cannabis to control or treat. For each condition selected, participants completed subsequent questions and rated them on five-point Likert-type scales regarding the degree of relief experienced overall (1 = No relief at all; 5 = Almost complete relief), the degree of relief compared to other medications (1 = Much less relief; 5 = Much more relief), and the use of other medications since using medical cannabis (1 = I use other medications much less frequently; 5 = I use other medications much more frequently). Higher scores indicated greater relief or more frequent use of other medications.

Patterns and methods of cannabis use. Patients reported on the frequency ("On average, how frequently do you medicate with medical cannabis?": "Less than once per month" to "Several times per day") and amount ("On average, how much medical cannabis do you consume in a month?": "Less than one gram" to "More than one ounce") of consumption. Patients also completed a single-item measure regarding their preferred method of consumption (smoking, edibles, tinctures, vaporizing, raw consumption, or oils).

Perceptions of prior medical cannabis users. Participants were asked if they had used cannabis to treat their condition(s) before its legalization in Arizona. Those who replied "yes" were asked to complete four additional items. These items included the perceived safety of acquiring cannabis ("Compared to when you did not have a medical marijuana card, acquiring cannabis as a medical marijuana card holder feels": 1 = Much more dangerous; 5 = Much safer), knowledge of strain characteristics ("Compared to when you did not have a medical marijuana card, your knowledge of what strain you are acquiring and its characteristics is": 1 = Much worse; 5 = Much better), confidence in a safe product ("Compared to when you did not have a medical marijuana card, your confidence that you are receiving a safe, uncontaminated product is": 1 = Much lower; 5 = Much higher), and product effectiveness for treating their condition(s) ("Compared to when you did not have a medical marijuana card, the effectiveness of the cannabis you receive to treat your condition is": 1 = Much worse; 5 = Much better).

RESULTS

The conditions for which patients reported using medical cannabis are displayed in Table 1. Consistent with previous research, the majority of patients reported suffering from chronic pain. Other commonly reported conditions included anxiety, depression, headaches, insomnia, muscle spasms, nausea, and stress.

Figure 1 shows the distributions of patients for frequency of cannabis use (Figure 1A), amount of cannabis consumed per month (Figure 1B), and preferred method of cannabis consumption (Figure 1C). The large majority of patients (83.7%) reported using medical cannabis several times per week or more, with most using medical cannabis daily (61%). Most patients consumed one-half of an ounce of cannabis or less per month (78.1%), and the most popular method of consumption was inhalation (i.e., smoking or vaporizing; 67.2%).

Perceived Effectiveness of Medical Cannabis

Patients' perceptions of the effectiveness of medical cannabis for treating their condition(s) are presented in Table 1. The values reflect the percent of patients who reported experiencing, overall, *a lot of relief* or *almost complete relief* from their symptoms and conditions when using medical cannabis (second column), *a little more relief* or *much more relief* from medical cannabis compared to other medications (third column), and using other medications *a little less frequently* or *much less frequently* when medicating with cannabis (fourth column).

For many of the conditions, patients reported that cannabis was effective for helping them manage their ailments. For example, at least 70% of patients reported experiencing *a lot of relief* or *almost complete relief* for 24 of the 42 conditions. Similarly, for 27 of the 42 conditions, at least 70% of patients reported experiencing *a little more relief* or *much more relief* from medical cannabis compared to other medications. Finally, at least 70% of patients reported using other medications *a little less frequently* or *much less frequently* for 24 of the 42 conditions.

TABLE 1
Percent of Patients Who Experience Relief and Less Frequently Use other Medications Due to Medical Cannabis Use, by Condition

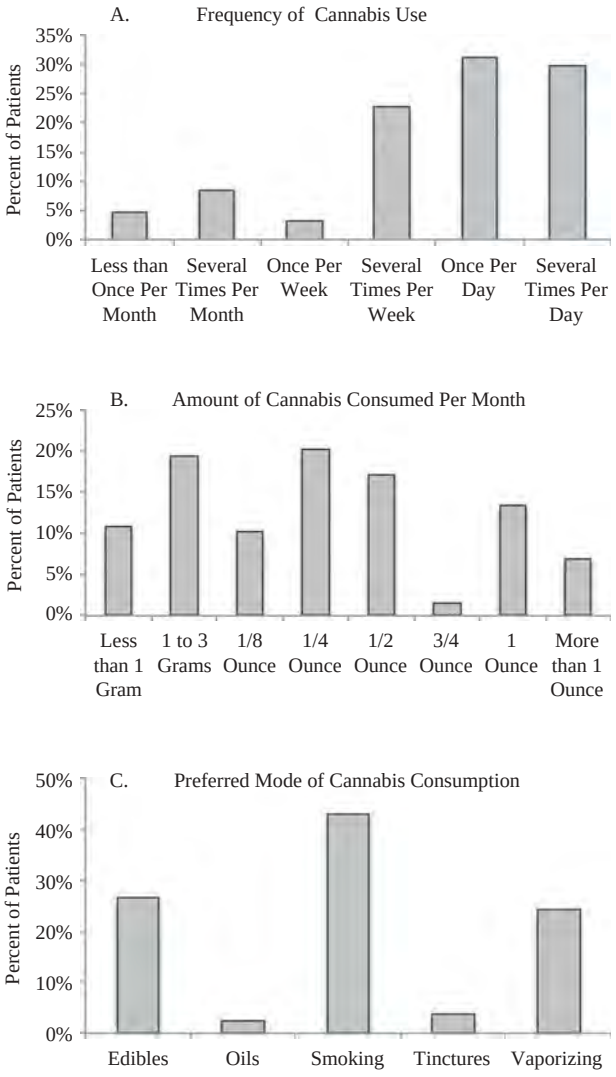
Condition	Number of patients (%)	General relief[a]	Relief compared to other medications[b]	Less frequent use of other medications[c]
Alcohol Dependency	23 (6.3%)	91.30%	100%	100%
Anxiety	181 (49.3%)	82.90%	79.30%	85.90%
Arthritis	90 (24.5%)	63.30%	68.30%	81.20%
Asthma	13 (3.5%)	61.50%	50%	80.00%
ADHD	32 (8.7%)	81.20%	65%	84.60%
Bipolar Disorder	23 (6.3%)	60.90%	90.00%	56.30%
Bowel Distress	38 (10.4%)	78.90%	88.40%	95.40%
Cancer	17 (4.6%)	88.30%	54.60%	78.60%
Carpal Tunnel	15 (4.1%)	40.00%	80.00%	100%
Chronic Pain	318 (86.6%)	76.70%	73.50%	90.20%
Diabetes	26 (7.1%)	38.40%	37.50%	54.10%
Crohn's Disease	14 (3.8%)	85.70%	75%	81.80%
Depression	106 (28.9%)	82.10%	86.90%	65.10%
Fibromyalgia	26 (7.1%)	76.90%	76.20%	93.80%
Glaucoma	9 (2.5%)	55.50%	50.00%	60%
Headaches	106 (28.9%)	68.90%	73.70%	93.80%
Hepatitis C	11 (3.0%)	45.50%	85.80%	28.60%
HIV	1 (0.3%)	100%	100%	—
Huntington's Disease	1 (0.3%)	100%	—	—
Hypertension	26 (7.1%)	65.40%	60.00%	46.60%
Insomnia	145 (39.5%)	82.70%	77.40%	81.90%
Loss of Appetite	67 (18.3%)	79.10%	92.30%	88.90%
Multiple Sclerosis	5 (1.4%)	100%	75.00%	33.30%
Muscle Spasms	130 (35.4%)	76.20%	82.10%	91.40%
Muscular Dystrophy	1 (0.3%)	100%	100%	—
Nausea	105 (28.6%)	85.70%	87.30%	94.80%
Neuropathy	45 (12.3%)	51.10%	69.70%	60.70%
OCD	17 (4.6%)	64.70%	62.50%	33.40%
Opioid Dependency	8 (2.2%)	75%	60.00%	50.00%
Osteoarthritis	39 (10.6%)	61.50%	66.60%	84%
PTSD	28 (7.6%)	67.90%	92.90%	44.40%
Schizophrenia	2 (0.5%)	100%	100%	—
Seizures	15 (4.1%)	80.00%	61.60%	84.70%
Skin Conditions	5 (1.4%)	60.00%	50.00%	50.00%
Sleep Apnea	31 (8.5%)	58.10%	85.00%	66.60%
Stress	164 (44.7%)	87.20%	91.60%	79.10%
Tourette's Syndrome	4 (1.1%)	100%	100%	—
Tremors	6 (1.6%)	50.00%	100%	100%
Vomiting	31 (8.4%)	71.00%	87.50%	82.40%
Wasting	6 (1.6%)	50.00%	66.70%	100%
Weight Loss	24 (6.5%)	62.50%	80.00%	70.00%

[a]The percent of patients with this condition who reported that they experienced a lot or almost complete overall relief.
[b]The percent of patients with this condition who reported that they experienced a lot or almost complete overall relief.
[c]The percent of patients with this condition who reported that they use other medications a little or much less frequently.

Perceived Effects of Medical Cannabis Legalization

Nearly two-thirds of participants ($n = 239$) reported using cannabis medicinally prior to legalization. These patients were asked to compare their current experiences acquiring, their knowledge of, and their experiences using medical cannabis to their experiences and knowledge before legalization. Distributions of the patient's responses are shown in Figure 2. Compared to their experiences

FIGURE 1
Distributions of patient responses, by percentage, for cannabis-related behaviors and perceptions: (A) the frequency of patient's cannabis use; (B) the amount of cannabis consumed by patients per month; (C) patient's preferred mode of cannabis consumption.



before legalization, 89.1% of patients reported that acquiring cannabis after legalization felt *somewhat safer* or *much safer*, 80.3% reported that their knowledge of the cannabis strains they acquired was *somewhat better* or *much better*, 85.4% reported that they had *somewhat more confidence* or *much more confidence* that they were purchasing a safe and uncontaminated product, and 79.5% reported that the medical cannabis was *somewhat more effective* or *much more effective* for treating their condition(s).

DISCUSSION

The goals of this study were to (1) examine the characteristics, perceptions, and behaviors of medical cannabis patients in Arizona; and (2) question participants with a history of cannabis use regarding their perceptions of safety acquiring cannabis, the quality of the cannabis they have obtained, their knowledge of the cannabis, and its perceived effectiveness, before and after legalization.

Patient Characteristics, Perceptions, and Behaviors

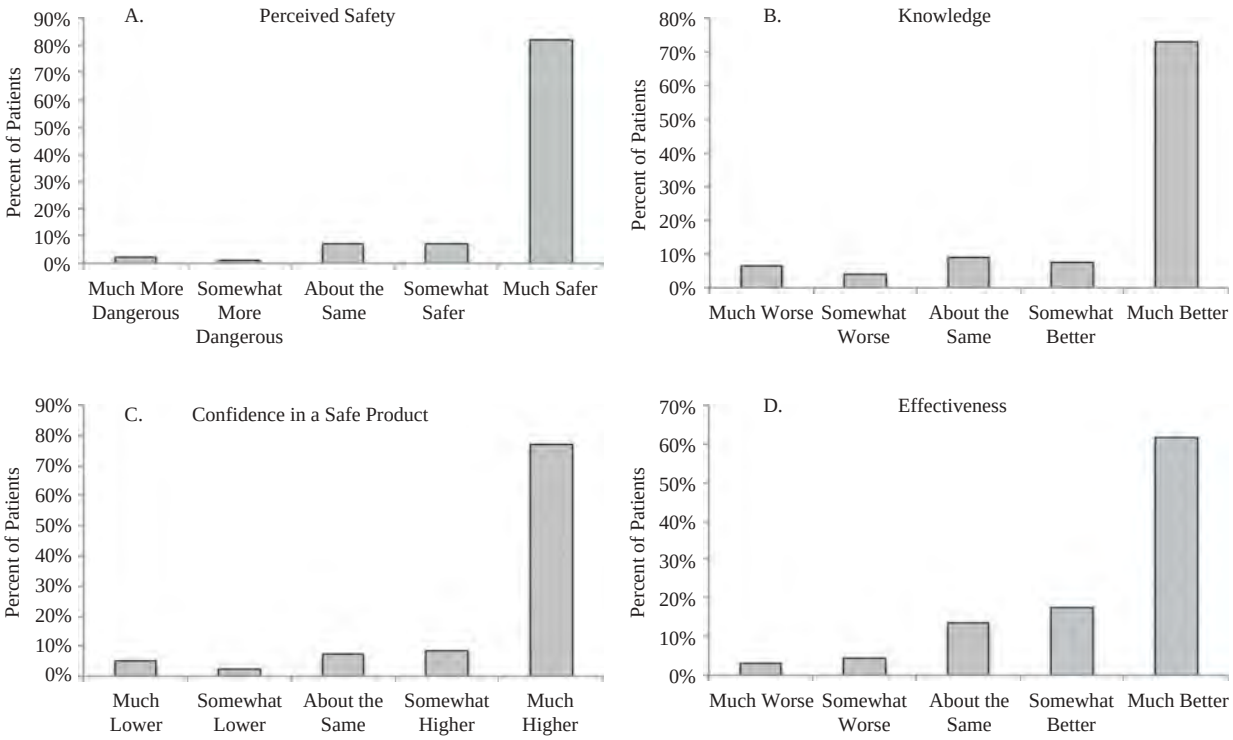
Consistent with research in other states (Bonn-Miller et al. 2014; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinarman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O'Connell and Bou-Matar 2007; Harris et al. 2000), participants in the present study were mostly White men. Average patient age, approximately 46 years, differed from that in other states. For example, average ages reported in studies of patients from California range from 28 to 41 years (Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Reiman 2009, 2007; Harris et al. 2000). Average patient age is somewhat higher in Colorado (42 years of age; Colorado Department of Public Health and Environment 2014) and Washington State (41 to 47 years of age; Aggarwal et al. 2013, 2009). In Michigan (46 years of age; Murphy 2013) and Montana (47 years of age; Montana Department of Public Health and Human Services 2014), average patient age more closely approximates that of Arizona.

State-level variation in the average age of medical cannabis patients may in part be explained by the conditions that qualify a person to use medical cannabis in each state. For example, the qualifying conditions in Arizona, Colorado, Montana, Michigan, and Washington State are less inclusive than those in California, and are generally limited to more debilitating diseases. Individuals who suffer from more serious conditions may also be older, which may account for higher average patient ages in states other than California. The variability in these statistics underscores the risk of generalizing findings from patients living in California to those residing in other states and highlights the importance of studying patients throughout the United States. State-level differences in regulations also present an opportunity to explore how such regulations shape patient characteristics. A potential avenue for future work may be to study and compare patients in all states that have legalized the medical use of cannabis, ideally using a national sample to aid state-level comparisons.

Participants in the present study reported that, on average, they consumed cannabis on a daily basis and that inhalation was the preferred method of consumption, patterns of use that reflect those found in prior work (Bonn-Miller et al. 2014; Ilgen et al. 2013; Reinarman et al. 2011; O'Connell and Bou-Matar 2007). However, previous research shows that patients consume between

FIGURE 2

Distributions of patient responses, by percentage, of their current experiences acquiring and knowledge of medical cannabis compared to their experiences before legalization: (A) the perceived safety of acquiring cannabis; (B) knowledge of medical cannabis characteristics; (C) perceived confidence in a safe product; and (D) perceived effectiveness of cannabis for treating their condition(s).



six and nine grams of cannabis per week or, equivalently, 0.85 to 1.25 ounces per month (Bonn-Miller et al. 2014; Reinarman et al. 2011; O'Connell and Bou-Matar 2007). This is in contrast to the findings of the present study, which show that 78% of patients consumed 0.5 ounces of cannabis per month or less.

State-level differences in average patient age, in particular, may affect variation in consumption. Patients in Arizona are, on average, older than those in California, and older patients may consume less cannabis than younger patients. Evidence from the present study supports this hypothesis, as there is a small, but significant, negative correlation between age and the amount of cannabis consumed per month ($r = -.11$, $p < .05$). Relatedly, Grella and colleagues (2014) found that younger patients visited dispensaries more frequently than older patients. Although there are likely other factors that contribute to consumption disparities, these findings also highlight the importance of studying medical cannabis patients across the US.

Patients reported using medical cannabis to treat a variety of conditions. The most commonly reported conditions included chronic pain, muscle spasms, nausea, anxiety, arthritis, depression, headaches, insomnia, and stress. Patients also reported that cannabis was effective for treating the symptoms of many of these conditions, findings that are consistent with previous research (Bonn-Miller et al. 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Harris et al. 2000). This effectiveness included feelings of general relief and relief compared to other medications. The conditions for which the highest proportions of patients reported relief included alcohol dependency, anxiety, bowel distress, depression, insomnia, muscle spasms, and stress. Furthermore, patients reported using other medications less frequently when using cannabis. This is consistent with findings from other studies of patient perceptions (Reiman 2007, 2009; Nunberg et al. 2011; Reinarman et al. 2011), as well as a study of opiate overdose mortality, which showed that states with legalized medical cannabis had significantly lower opiate overdose mortality compared

to those without legalized medical cannabis (Bachhuber et al. 2014).

Medical cannabis may benefit Arizona patients suffering from a variety of conditions. This conclusion has potential policy implications, as patients report deriving benefit not only for conditions that fall under the list of conditions that qualify a person to use medical cannabis (e.g., cancer, chronic pain, muscle spasms), but also for conditions that are not listed (e.g., anxiety, depression, insomnia). Officials in Arizona previously considered research on post-traumatic stress disorder (PTSD; Greer, Grob, and Halberstadt 2014) in their decision to include PTSD among Arizona's qualifying conditions. Thus, officials may consider the findings from the present study, in conjunction with other research, to determine the suitability of expanding the list of qualifying conditions in Arizona.

Legalization and Patient Experiences

The present study was, to our knowledge, the first to examine the effect of legalization on patient's experiences with medical cannabis. Regarding safety, the majority of patients reported feeling safer acquiring medical cannabis after legalization, and their confidence that they were acquiring a safe, uncontaminated product was higher. Patients also reported that their knowledge of the strains they acquired was better and that the cannabis they acquired after legalization was more effective for treating their condition(s) than the cannabis they acquired before legalization.

These findings show that the Arizona medical cannabis program has had some success, as regulations have provided a safe environment for patients to acquire a safe and high-quality product. However, the potential negative effects of medical cannabis legalization were not assessed in the present study. For example, participants in other studies have reported difficulties affording legal medical cannabis (Aggarwal et al. 2009), a factor which may preclude some individuals from taking advantage of the program, leaving them seeking other, potentially illegal means of cannabis acquisition. Other factors, such as limits on the amount of cannabis that can be purchased or legal issues related to medical cannabis use, may also have negative consequences for some segments of the patient population.

The results of this study should be considered in light of some limitations. First, participant recruitment was conducted through medical cannabis dispensaries. Although this is a common method of recruitment (e.g., Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Aggarwal et al. 2013; Reiman 2009, 2007; Harris et al. 2000), such samples may have a positive bias for medical cannabis, as individuals who medicate with cannabis but for whom it was not effective are unlikely to be available to participate. However, at least one study using a large, representative sample of current and former medical cannabis users reported similar findings (Ryan-Ibarra, Induni, and Ewing 2015), lending validity to the results of the present study and those of previous research. Second, relatively few patients reported using medical cannabis for some of the conditions. Although this is not surprising, given the low incidence of some conditions, conclusions should be tempered for these conditions with respect to the effectiveness of medical cannabis for providing relief and/or for use as a substitute for other medications. Finally, patients' experiences acquiring and their knowledge of medical cannabis before and after legalization were assessed retrospectively, using a single measurement time-point.

Despite these limitations, this study has significance for understanding the characteristics, behaviors, and perceptions of Arizona medical cannabis patients. Additionally, it highlights the importance of studying patients throughout the US and understanding the potential effects of state-level regulatory differences on patient populations. The findings regarding the effectiveness of cannabis for treating various conditions have potential policy implications for the state of Arizona, as patients reported that cannabis was effective for treating conditions that currently do not qualify individuals for medical cannabis use. Furthermore, the results showed that the majority of patients report positive experiences as a result of legalization, although more work is needed to fully understand the consequences of Arizona's medical cannabis program.

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Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

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Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since 1964, when Raphael Mechoulam isolated and synthesized it. More recently, the synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated. Other phytocannabinoids, including tetrahydrocannabivarin, cannabigerol and cannabichromene, exert additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study. This review will explore another echelon of phytotherapeutic agents, the cannabis terpenoids: limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol and phytol. Terpenoids share a precursor with phytocannabinoids, and are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits ng·mL^{-1}. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant *Staphylococcus aureus*). Scientific evidence is presented for non-cannabinoid plant components as putative antidotes to intoxicating effects of THC that could increase its therapeutic index. Methods for investigating entourage effects in future experiments will be proposed. Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant.

LINKED ARTICLES

This article is part of a themed issue on Cannabinoids in Biology and Medicine. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2011.163.issue-7

Abbreviations

2-AG, 2-arachidonoylglycerol; 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AEA, arachidonoylethanolamide (anandamide); AI, anti-inflammatory; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; Ca^{++}, calcium ion; CB_1/CB_2, cannabinoid receptor 1 or 2; CBC, cannabichromene; CBCA, cannabichromenic acid; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol; CBGA, cannabigerolic acid; CBGV, cannabigerivarin; CNS, central nervous system; COX, cyclo-oxygenase; DAGL, diacylglycerol lipase; ECS, endocannabinoid system; EO, essential oil; FAAH, fatty acid amidohydrolase; FDA, US Food and Drug Administration; FEMA, Food and Extract Manufacturers Association; fMRI, functional magnetic resonance imaging; GABA, gamma aminobutyric acid; GPCR, G-protein coupled receptor; GPR, G-protein coupled receptor; HEK, human embryonic kidney; IC_{50}, 50% inhibitory concentration; i.p., intraperitoneal; MAGL, monoacylglycerol lipase; MIC, minimum inhibitory concentration; MS, multiple sclerosis; NGF, nerve growth factor; NIDA, US National Institute on Drug Abuse; PG, prostaglandin; PTSD, post-traumatic stress disorder; RCT, randomized clinical trial; SPECT, single photon emission computed tomography; SSADH, succinic semialdehyde dehydrogenase; Sx, symptoms; $T_{1/2}$, half-life; TCA, tricyclic antidepressant; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV, tetrahydrocannabivarin; TNF-α, tumour necrosis factor-alpha, TRPV, transient receptor potential vanilloid receptor

The roots of cannabis synergy

Cannabis has been a medicinal plant of unparalleled versatility for millennia (Mechoulam, 1986; Russo, 2007; 2008), but whose mechanisms of action were an unsolved mystery until the discovery of tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1964a), the first cannabinoid receptor, CB_1 (Devane *et al.*, 1988), and the endocannabinoids, anandamide (arachidonoylethanolamide, AEA) (Devane *et al.*, 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995). While a host of phytocannabinoids were discovered in the 1960s: cannabidiol (CBD) (Mechoulam and Shvo, 1963), cannabigerol (CBG) (Gaoni and Mechoulam, 1964b), cannabichromene (CBC) (Gaoni and Mechoulam, 1966), cannabidivarin (CBDV) (Vollner *et al.*, 1969) and tetrahydrocannabivarin (THCV) (Gill *et al.*, 1970), the overwhelming preponderance of research focused on psychoactive THC. Only recently has renewed interest been manifest in THC analogues, while other key components of the activity of cannabis and its extracts, the cannabis terpenoids, remain understudied (McPartland and Russo, 2001b; Russo and McPartland, 2003). The current review will reconsider essential oil (EO) agents, their peculiar pharmacology and possible therapeutic interactions with phytocannabinoids. Nomenclature follows conventions in Alexander *et al.* (2009).

Phytocannabinoids and terpenoids are synthesized in cannabis, in secretory cells inside glandular trichomes (Figure 1) that are most highly concentrated in unfertilized female flowers prior to senescence (Potter, 2004; Potter, 2009). Geranyl pyrophosphate is formed as a precursor via the deoxyxylulose pathway in cannabis (Fellermeier *et al.*, 2001), and is a parent compound to both phytocannabinoids and terpenoids (Figure 2). After coupling with either olivetolic acid or divarinic acid, pentyl or propyl cannabinoid acids are produced, respectively, via enzymes that accept either substrate (de Meijer *et al.*, 2003), a manifestation of Mechoulam's postulated 'Nature's Law of Stinginess'. Although having important biochemical properties in their own right, acid forms of phytocannabinoids are most commonly decarboxylated via heat to produce the more familiar neutral phytocannabinoids (Table 1). Alternatively, geranyl pyrophosphate may form limonene and other monoterpenoids in secretory cell plastids, or couple with isopentenyl pyrophosphate in the cytoplasm to form farnesyl pyrophosphate, parent compound to the sesquiterpenoids, that co-localizes with transient receptor potential vanilloid receptor (TRPV) 1 in human dorsal root ganglion, suggesting a role in sensory processing of noxious stimuli (Bradshaw *et al.*, 2009), and which is the most potent endogenous ligand to date on the G-protein coupled receptor (GPR) 92 (Oh *et al.*, 2008).

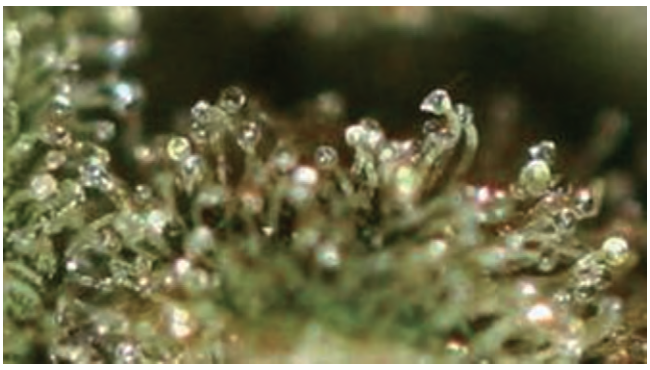


Figure 1

Cannabis capitate glandular (EBR by permission of Bedrocan BV, Netherlands).

An obvious question pertains to the chemical ecology of such syntheses that require obvious metabolic demands on the plant (Gershenzon, 1994), and these will be considered.

Is cannabis merely a crude vehicle for delivery of THC? Might it rather display herbal synergy (Williamson, 2001) encompassing potentiation of activity by active or inactive components, antagonism (evidenced by the ability of CBD to reduce side effects of THC; Russo and Guy, 2006), summation, pharmacokinetic and metabolic interactions? Recently, four basic mechanisms of synergy have been proposed (Wagner and Ulrich-Merzenich, 2009): (i) multi-target effects; (ii) pharmacokinetic effects such as improved solubility or bioavailability; (iii) agent interactions affecting bacterial resistance; and (iv) modulation of adverse events. Cannabis was cited as an illustration.

Could phytocannabinoids function analogously to the endocannabinoid system (ECS) with its combination of active and 'inactive' synergists, first described as an entourage (Ben-Shabat *et al.*, 1998), with subsequent refinement (Mechoulam and Ben-Shabat, 1999) and qualification (p. 136): 'This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them'. Support derives from studies in which cannabis extracts demonstrated effects two to four times greater than THC (Carlini *et al.*, 1974); unidentified THC antagonists and synergists were claimed (Fairbairn and Pickens, 1981), anticonvulsant activity was observed beyond the cannabinoid fraction (Wilkinson *et al.*, 2003), and extracts of THC and CBD modulated effects in hippocampal neurones distinctly from pure compounds (Ryan *et al.*, 2006). Older literature also presented refutations: no observed differences were noted by humans ingesting or smoking pure THC versus herbal cannabis (Wachtel *et al.*, 2002); pure THC seemed to account for all tetrad-type effects in mice (Varvel *et al.*, 2005); and smoked cannabis with varying CBD or CBC content failed to yield subjective differences combined with THC (Ilan *et al.*, 2005). Explanations include that the cannabis employed by Wachtel yielded 2.11% THC, but with only 0.3% cannabinol (CBN) and 0.05% CBD (Russo and McPartland, 2003), and Ilan's admission that CBN and CBD content might be too low to modulate THC. Another factor is apparent in that terpenoid yields from vaporization of street cannabis were 4.3–8.5 times of those from US National Institute on Drug Abuse cannabis (Bloor *et al.*, 2008). It is undisputed that the black market cannabis in the UK (Potter *et al.*, 2008), Continental Europe (King *et al.*, 2005) and the USA (Mehmedic *et al.*, 2010) has become almost exclusively a high-THC preparation to the almost total exclusion of other phytocannabinoids. If – as many consumers and experts maintain (Clarke, 2010) – there are biochemical, pharmacological and

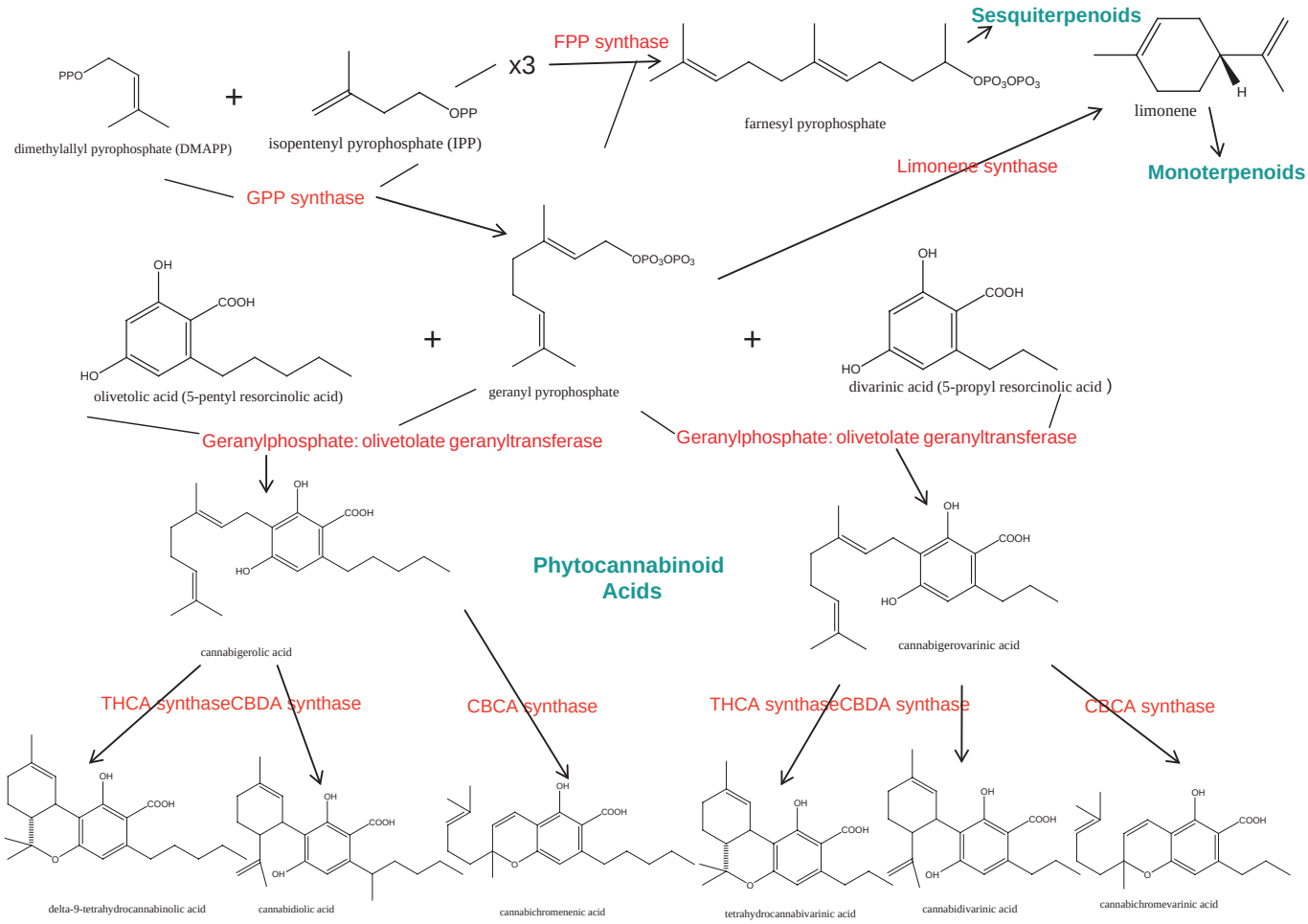


Figure 2
Phytocannabinoid and cannabis terpenoid biosynthesis.

phenomenological distinctions between available cannabis 'strains', such phenomena are most likely related to relative terpenoid contents and ratios. This treatise will assess additional evidence for putative synergistic phytocannabinoid-terpenoid effects exclusive of THC, to ascertain whether this botanical may fulfil its promise as, 'a neglected pharmacological treasure trove' (Mechoulam, 2005).

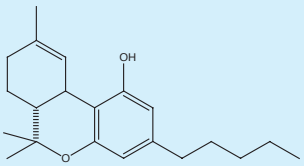
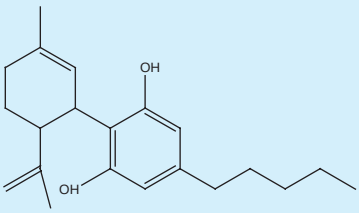
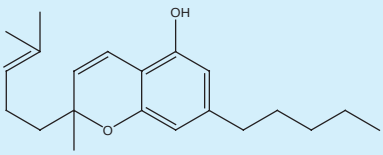
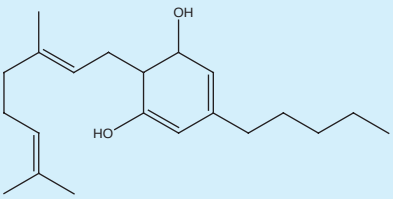
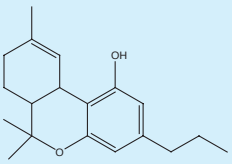
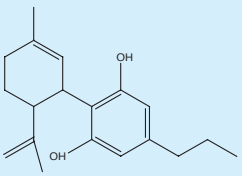
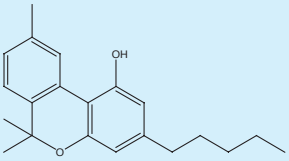
Phytocannabinoids, beyond THC: a brief survey

Phytocannabinoids are exclusively produced in cannabis (*vide infra* for exception), but their evolutionary and ecological *raisons d'être* were obscure until recently. THC production is maximized with increased light energy (Potter, 2009). It has been known for some time that CBG and CBC are mildly antifungal (ElSohly *et al.*, 1982), as are THC and CBD against a cannabis pathogen (McPartland, 1984). More pertinent, however, is the mechanical stickiness of the trichomes, capable of trapping insects with all six legs (Potter, 2009). Tetrahydrocannabinolic acid (THCA) and cannabichromenic acid (Morimoto *et al.*, 2007), as well as cannabidiolic acid and cannabigerolic acid (CBGA; Shoyama *et al.*, 2008) produce necrosis in plant cells. Normally, the cannabinoid acids are sequestered in trichomes away from the flower tissues. Any trichome breakage at senescence may contribute to natural pruning of lower fan leaves that otherwise utilize energy that the plant preferentially diverts to the flower, in continued efforts to affect fertilization, generally in vain when subject to human horticulture for pharmaceutical production. THCA and CBGA have also proven to be insecticidal in their own right (Sirikantaramas *et al.*, 2005).

Over 100 phytocannabinoids have been identified (Brenneisen, 2007; Mehmedic *et al.*, 2010), but many are artefacts of analysis or are produced in trace quantities that have not permitted thorough investigation. The pharmacology of the more accessible phytocannabinoids has received excellent recent reviews (Pertwee *et al.*, 2007; Izzo *et al.*, 2009; De Petrocellis and Di Marzo, 2010; De Petrocellis *et al.*, 2011), and will be summarized here, with emphasis on activities with particular synergistic potential.

Table 1

Phytocannabinoid activity table

Phytocannabinoid structure	Selected pharmacology (reference)	Synergistic terpenoids
 delta-9-tetrahydrocannabinol (THC)	Analgesic via CB_1 and CB_2 (Rahn and Hohmann, 2009)	Various
	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Bronchodilatory (Williams *et al.*, 1976)	Pinene
	↓ Sx. Alzheimer disease (Volicer *et al.*, 1997; Eubanks *et al.*, 2006)	Limonene, pinene, linalool
	Benefit on duodenal ulcers (Douthwaite, 1947)	Caryophyllene, limonene
	Muscle relaxant (Kavia *et al.*, 2010)	Linalool?
	Antipruritic, cholestatic jaundice (Neff *et al.*, 2002)	Caryophyllene?
 cannabidiol	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Anti-anxiety via 5-HT_{1A} (Russo *et al.*, 2005)	Linalool, limonene
	Anticonvulsant (Jones *et al.*, 2010)	Linalool
	Cytotoxic versus breast cancer (Ligresti *et al.*, 2006)	Limonene
	↑ adenosine A_{2A} signalling (Carrier *et al.*, 2006)	Linalool
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
	Decreases sebum/sebocytes (Biro *et al.*, 2009)	Pinene, limonene, linalool
	Treatment of addiction (see text)	Caryophyllene
 cannabichromene	Anti-inflammatory/analgesic (Davis and Hatoum, 1983)	Various
	Antifungal (ElSohly *et al.*, 1982)	Caryophyllene oxide
	AEA uptake inhibitor (De Petrocellis *et al.*, 2011)	–
	Antidepressant in rodent model (Deyo and Musty, 2003)	Limonene
 cannabigerol	TRPM8 antagonist prostate cancer (De Petrocellis *et al.*, 2011)	Cannabis terpenoids
	GABA uptake inhibitor (Banerjee *et al.*, 1975)	Phytol, linalool
	Anti-fungal (ElSohly *et al.*, 1982)	Caryophyllene oxide
	Antidepressant rodent model (Musty and Deyo, 2006); and via 5-HT_{1A} antagonism (Cascio *et al.*, 2010)	Limonene
	Analgesic, α-2 adrenergic blockade (Cascio *et al.*, 2010)	Various
	↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007)	adjunctive role?
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
 tetrahydrocannabivarin	AI/anti-hyperalgesic (Bolognini *et al.*, 2010)	Caryophyllene *et al.* . . .
	Treatment of metabolic syndrome (Cawthorne *et al.*, 2007)	–
	Anticonvulsant (Hill *et al.*, 2010)	Linalool
 cannabidivarin	Inhibits diacylglycerol lipase (De Petrocellis *et al.*, 2011)	–
	Anticonvulsant in hippocampus (Hill *et al.*, 2010)	Linalool
 cannabinol (CBN)	Sedative (Musty *et al.*, 1976)	Nerolidol, myrcene
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
	TRPV2 agonist for burns (Qin *et al.*, 2008)	Linalool
	↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007)	adjunctive role?
	↓ breast cancer resistance protein (Holland *et al.*, 2008)	Limonene

5-HT, 5-hydroxytryptamine (serotonin); AEA, arachidonoylethanolamide (anandamide); AI, anti-inflammatory; CB1/CB2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; TRPV, transient receptor potential vanilloid receptor; MRSA, methicillin-resistant *Staphylococcus aureus*; Sx, symptoms.

THC (Table 1) is the most common phytocannabinoid in cannabis drug chemotypes, and is produced in the plant via an allele co-dominant with CBD (de Meijer *et al.*, 2003). THC is a partial agonist at CB_1 and cannabinoid receptor 2 (CB_2) analogous to AEA, and underlying many of its activities as a psychoactive agent, analgesic, muscle relaxant and antispasmodic (Pacher *et al.*, 2006). Additionally, it is a bronchodilator (Williams *et al.*, 1976), neuroprotective antioxidant (Hampson *et al.*, 1998), antipruritic agent in cholestatic jaundice (Neff *et al.*, 2002) and has 20 times the anti-inflammatory power of aspirin and twice that of hydrocortisone (Evans, 1991). THC is likely to avoid potential pitfalls of either COX-1 or COX-2 inhibition, as such activity is only noted at concentrations far above those attained therapeutically (Stott *et al.*, 2005).

CBD is the most common phytocannabinoid in fibre (hemp) plants, and second most prevalent in some drug chemotypes. It has proven extremely versatile pharmacologically (Table 1) (Pertwee, 2004; Mechoulam *et al.*, 2007), displaying the unusual ability to antagonize CB_1 at a low nM level in the presence of THC, despite having little binding affinity (Thomas *et al.*, 2007), and supporting its modulatory effect on THC-associated adverse events such as anxiety, tachycardia, hunger and sedation in rats and humans (Nicholson *et al.*, 2004; Murillo-Rodriguez *et al.*, 2006; Russo and Guy, 2006). CBD is an analgesic (Costa *et al.*, 2007), is a neuroprotective antioxidant more potent than ascorbate or tocopherol (Hampson *et al.*, 1998), without COX inhibition (Stott *et al.*, 2005), acts as a TRPV1 agonist analogous to capsaicin but without noxious effect (Bisogno *et al.*, 2001), while also inhibiting uptake of AEA and weakly inhibiting its hydrolysis. CBD is an antagonist on GPR55, and also on GPR18, possibly supporting a therapeutic role in disorders of cell migration, notably endometriosis (McHugh *et al.*, 2010). CBD is anticonvulsant (Carlini and Cunha, 1981; Jones *et al.*, 2010), anti-nausea (Parker *et al.*, 2002), cytotoxic in breast cancer (Ligresti *et al.*, 2006) and many other cell lines while being cyto-preservative for normal cells (Parolaro and Massi, 2008), antagonizes tumour necrosis factor-alpha (TNF-α) in a rodent model of rheumatoid arthritis (Malfait *et al.*, 2000), enhances adenosine receptor A_{2A} signalling via inhibition of an adenosine transporter (Carrier *et al.*, 2006), and prevents prion accumulation and neuronal toxicity (Dirikoc *et al.*, 2007). A CBD extract showed greater anti-hyperalgesia over pure compound in a rat model with decreased allodynia, improved thermal perception and nerve growth factor levels and decreased oxidative damage (Comelli *et al.*, 2009). CBD also displayed powerful activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with a minimum inhibitory concentration (MIC) of 0.5–2 $\mu g \cdot mL^{-1}$ (Appendino *et al.*, 2008). In 2005, it was demonstrated that CBD has agonistic activity at 5-hydroxytryptamine $(5\text{-HT})_{1A}$ at 16 μM (Russo *et al.*, 2005), and that despite the high concentration, may underlie its anti-anxiety activity (Resstel *et al.*, 2009; Soares Vde *et al.*, 2010), reduction of stroke risk (Mishima *et al.*, 2005), anti-nausea effects (Rock *et al.*, 2009) and ability to affect improvement in cognition in a mouse model of hepatic encephalopathy (Magen *et al.*, 2009). A recent study has demonstrated that CBD 30 $mg \cdot kg^{-1}$ i.p. reduced immobility time in the forced swim test compared to imipramine ($P < 0.01$), an effect blocked by pre-treatment with the 5-HT_{1A} antagonist WAY100635 (Zanelati *et al.*, 2010), supporting a prospective role for CBD as an antidepressant. CBD also inhibits synthesis of lipids in sebocytes, and produces apoptosis at higher doses in a model of acne (*vide infra*). One example of CBD antagonism to THC would be the recent observation of lymphopenia in rats (CBD 5 $mg \cdot kg^{-1}$) mediated by possible CB_2 inverse agonism (Ignatowska-Jankowska *et al.*, 2009), an effect not reported in humans even at doses of pure CBD up to 800 mg (Crippa *et al.*, 2010), possibly due to marked interspecies differences in CB_2 sequences and signal transduction. CBD proved to be a critical factor in the ability of nabiximols oromucosal extract in successfully treating intractable cancer pain patients unresponsive to opioids (30% reduction in pain from baseline), as a high-THC extract devoid of CBD failed to distinguish from placebo (Johnson *et al.*, 2010). This may represent true synergy if the THC–CBD combination were shown to provide a larger effect than a summation of those from the compounds separately (Berenbaum, 1989).

CBC (Table 1) was inactive on adenylate cyclase inhibition (Howlett, 1987), but showed activity in the mouse cannabinoid tetrad, but only at 100 $mg \cdot kg^{-1}$, and at a fraction of THC activity, via a non-CB_1, non-CB_2 mechanism (Delong *et al.*, 2010). More pertinent are anti-inflammatory (Wirth *et al.*, 1980) and analgesic activity (Davis and Hatoum, 1983), its ability to reduce THC intoxication in mice (Hatoum *et al.*, 1981), antibiotic and antifungal effects (ElSohly *et al.*, 1982), and observed cytotoxicity in cancer cell lines (Ligresti *et al.*, 2006). A CBC-extract displayed pronounced antidepressant effect in rodent models (Deyo and Musty, 2003). Additionally, CBC was comparable to mustard oil in stimulating TRPA1-mediated Ca^{++} in human embryonic kidney 293 cells (50–60 nM) (De Petrocellis *et al.*, 2008). CBC recently proved to be a strong AEA uptake inhibitor (De Petrocellis *et al.*, 2011). CBC production is normally maximal, earlier in the plant's life cycle (de Meijer *et al.*, 2009a). An innovative technique employing cold water extraction of immature leaf matter from selectively bred cannabis chemotypes yields a high-CBC 'enriched trichome preparation' (Potter, 2009).

CBG (Table 1), the parent phytocannabinoid compound, has a relatively weak partial agonistic effect at CB_1 (K_i 440 nM) and CB_2 (K_i 337 nM) (Gauson *et al.*, 2007). Older work supports gamma aminobutyric acid (GABA) uptake inhibition greater than THC or CBD (Banerjee *et al.*, 1975) that could suggest muscle relaxant properties. Analgesic and anti-erythemic effects and the ability to block lipooxygenase were said to surpass those of THC (Evans, 1991). CBG demonstrated modest antifungal effects (ElSohly *et al.*, 1982). More recently, it proved to be an effective cytotoxic in high dosage on human epithelioid carcinoma (Baek *et al.*, 1998), is the next most effective phytocannabinoid against breast cancer after CBD (Ligresti *et al.*, 2006), is an antidepressant in the rodent tail suspension model (Musty and Deyo, 2006) and is a mildly anti-hypertensive agent (Maor *et al.*, 2006). Additionally, CBG inhibits keratinocyte proliferation suggesting utility in psoriasis (Wilkinson and Williamson, 2007), it is a relatively potent TRPM8 antagonist for possible application in prostate cancer (De Petrocellis and Di Marzo, 2010) and detrusor over-activity and bladder pain (Mukerji *et al.*, 2006). It is a strong AEA uptake inhibitor (De Petrocellis *et al.*, 2011) and a powerful agent against MRSA (Appendino *et al.*, 2008; *vide infra*). Finally, CBG behaves as a potent α-2 adrenorecep-

tor agonist, supporting analgesic effects previously noted (Formukong *et al.*, 1988), and moderate 5-HT_{1A} antagonist suggesting antidepressant properties (Cascio *et al.*, 2010). Normally, CBG appears as a relatively low concentration intermediate in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG (de Meijer and Hammond, 2005; de Meijer *et al.*, 2009a).

THCV (Table 1) is a propyl analogue of THC, and can modulate intoxication of the latter, displaying 25% of its potency in early testing (Gill *et al.*, 1970; Hollister, 1974). A recrudescence of interest accrues to this compound, which is a CB_1 antagonist at lower doses (Thomas *et al.*, 2005), but is a CB_1 agonist at higher doses (Pertwee, 2008). THCV produces weight loss, decreased body fat and serum leptin concentrations with increased energy expenditure in obese mice (Cawthorne *et al.*, 2007; Riedel *et al.*, 2009). THCV also demonstrates prominent anticonvulsant properties in rodent cerebellum and pyriform cortex (Hill *et al.*, 2010). THCV appears as a fractional component of many southern African cannabis chemotypes, although plants highly predominant in this agent have been produced (de Meijer, 2004). THCV recently demonstrated a CB_2-based ability to suppress carageenan-induced hyperalgesia and inflammation, and both phases of formalin-induced pain behaviour via CB_1 and CB_2 in mice (Bolognini *et al.*, 2010).

CBDV (Table 1), the propyl analogue of CBD, was first isolated in 1969 (Vollner *et al.*, 1969), but formerly received little investigation. Pure CBDV inhibits diacylglycerol lipase [50% inhibitory concentration (IC_{50}) 16.6 μM] and might decrease activity of its product, the endocannabinoid, 2-AG (De Petrocellis *et al.*, 2011). It is also anticonvulsant in rodent hippocampal brain slices, comparable to phenobarbitone and felbamate (Jones *et al.*, 2010).

Finally, CBN is a non-enzymatic oxidative by-product of THC, more prominent in aged cannabis samples (Merzouki and Mesa, 2002). It has a lower affinity for CB_1 (K_i 211.2 nM) and CB_2 (K_i 126.4 nM) (Rhee *et al.*, 1997); and was judged inactive when tested alone in human volunteers, but produced greater sedation combined with THC (Musty *et al.*, 1976). CBN demonstrated anticonvulsant (Turner *et al.*, 1980), anti-inflammatory (Evans, 1991) and potent effects against MRSA (MIC 1 $\mu g \cdot mL^{-1}$). CBN is a TRPV2 (high-threshold thermosensor) agonist (EC 77.7 μM) of possible interest in treatment of burns (Qin *et al.*, 2008). Like CBG, it inhibits keratinocyte proliferation (Wilkinson and Williamson, 2007), independently of cannabinoid receptor effects. CBN stimulates the recruitment of quiescent mesenchymal stem cells in marrow (10 μM), suggesting promotion of bone formation (Scutt and Williamson, 2007) and inhibits breast cancer resistance protein, albeit at a very high concentration (IC_{50} 145 μM) (Holland *et al.*, 2008).

Cannabis terpenoids: neglected entourage compounds?

Terpenoids are EO components, previously conceived as the quintessential fifth element, 'life force' or spirit (Schmidt, 2010), and form the largest group of plant chemicals, with 15–20 000 fully characterized (Langenheim, 1994). Terpenoids, not cannabinoids, are responsible for the aroma of cannabis. Over 200 have been reported in the plant (Hendriks *et al.*, 1975; 1977; Malingre *et al.*, 1975; Davalos *et al.*, 1977; Ross and ElSohly, 1996; Mediavilla and Steinemann, 1997; Rothschild *et al.*, 2005; Brenneisen, 2007), but only a few studies have concentrated on their pharmacology (McPartland and Pruitt, 1999; McPartland and Mediavilla, 2001a; McPartland and Russo, 2001b). Their yield is less than 1% in most cannabis assays, but they may represent 10% of trichome content (Potter, 2009). Monoterpenes usually predominate (limonene, myrcene, pinene), but these headspace volatiles (Hood *et al.*, 1973), while only lost at a rate of about 5% before processing (Gershenzon, 1994), do suffer diminished yields with drying and storage (Turner *et al.*, 1980; Ross and ElSohly, 1996), resulting in a higher relative proportion of sesquiterpenoids (especially caryophyllene), as also often occurs in extracts. A 'phytochemical polymorphism' seems operative in the plant (Franz and Novak, 2010), as production favours agents such as limonene and pinene in flowers that are repellent to insects (Nerio *et al.*, 2010), while lower fan leaves express higher concentrations of bitter sesquiterpenoids that act as anti-feedants for grazing animals (Potter, 2009). Evolutionarily, terpenoids seem to occur in complex and variable mixtures with marked structural diversity to serve various ecological roles. Terpenoid composition is under genetic control (Langenheim, 1994), and some enzymes produce multiple products, again supporting Mechoulam's 'Law of Stinginess'. The particular mixture of mono- and sesquiterpenoids will determine viscosity, and in cannabis, this certainly is leveraged to practical advantage as the notable stickiness of cannabis exudations traps insects (McPartland *et al.*, 2000), and thus, combined with the insecticidal phytocannabinoid acids (Sirikantaramas *et al.*, 2005), provides a synergistic mechano-chemical defensive strategy versus predators.

As observed for cannabinoids, terpenoid production increases with light exposure, but decreases with soil fertility (Langenheim, 1994), and this is supported by the glasshouse experience that demonstrates higher yields if plants experience relative nitrogen lack just prior to harvest (Potter, 2004), favouring floral over foliar growth. EO composition is much more genetically than environmentally determined, however (Franz and Novak, 2010), and while cannabis is allogamous and normally requires repeat selective breeding for maintenance of quality, this problem may be practically circumvented by vegetative propagation of high-performance plants under controlled environmental conditions (light, heat and humidity) (Potter, 2009), and such techniques have proven to provide notable consistency to tight tolerances as Good Manufacturing Practice for any pharmaceutical would require (Fischedick *et al.*, 2010).

The *European Pharmacopoeia*, Sixth Edition (2007), lists 28 EOs (Pauli and Schilcher, 2010). Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems and enzymes (Bowles, 2003; Buchbauer, 2010). All the terpenoids discussed herein are Generally Recognized as Safe, as attested by the US Food and Drug Admin-

istration as food additives, or by the Food and Extract Manufacturers Association and other world regulatory bodies. Germane is the observation (Adams and Taylor, 2010) (p. 193), 'With a high degree of confidence one may presume that EOs derived from food are likely to be safe'. Additionally, all the current entries are non-sensitizing to skin when fresh (Tisserand and Balacs, 1995; Adams and Taylor, 2010), but may cause allergic reactions at very low rates when oxidized (Matura *et al.*, 2005). For additional pharmacological data on other common cannabis terpenoids not discussed herein (1,8-cineole, also known as eucalyptol, pulegone, α-terpineol, terpineol-4-ol, ρ-cymene, borneol and Δ-3-carene), please see McPartland and Russo (2001b).

Are cannabis terpenoids actually relevant to the effects of cannabis? Terpenoid components in concentrations above 0.05% are considered of pharmacological interest (Adams and Taylor, 2010). Animal studies are certainly supportive (Buchbauer *et al.*, 1993). Mice exposed to terpenoid odours inhaled from ambient air for 1 h demonstrated profound effects on activity levels, suggesting a direct pharmacological effect on the brain, even at extremely low serum concentrations (examples: linalool with 73% reduction in motility at 4.22 ng·mL^{-1}, pinene 13.77% increase at trace concentration, terpineol 45% reduction at 4.7 ng·mL^{-1}). These levels are comparable to those of THC measured in humans receiving cannabis extracts yielding therapeutic effects in pain, or symptoms of multiple sclerosis in various randomized controlled trials (RCTs) (Russo, 2006; Huestis, 2007). Positive effects at undetectable serum concentrations with orange terpenes (primarily limonene, 35.25% increase in mouse activity), could be explainable on the basis of rapid redistribution and concentration in lipophilic cerebral structures. A similar rationale pertains to human studies (Komori *et al.*, 1995), subsequently discussed. Limonene is highly bioavailable with 70% human pulmonary uptake (Falk-Filipsson *et al.*, 1993), and a figure of 60% for pinene with rapid metabolism or redistribution (Falk *et al.*, 1990). Ingestion and percutaneous absorption is also well documented in humans (Jäger *et al.*, 1992): 1500 mg of lavender EO with 24.7% linalool (total 372 mg) was massaged into the skin of a 60 kg man for 10 min, resulting in a peak plasma concentration of 100 ng·mL^{-1} at 19 min, and a half-life of 13.76 min in serum (Jäger *et al.*, 1992). EO mixtures (including limonene and pinene) also increase permeation of estradiol through mouse skin (Monti *et al.*, 2002).

Government-approved cannabis supplied to patients in national programmes in the Netherlands and Canada is gamma-irradiated to sterilize coliform bacteria, but the safety of this technique for a smoked and inhaled product has never been specifically tested. Gamma-radiation significantly reduced linalool titres in fresh cilantro (Fan and Sokorai, 2002), and myrcene and linalool in orange juice (Fan and Gates, 2001).

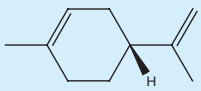
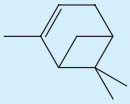
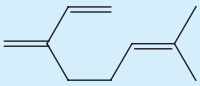
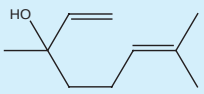
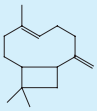
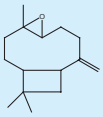
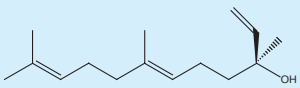
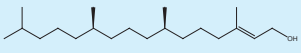
D-limonene, common to the lemon and other citrus EOs (Table 2), is the second most widely distributed terpenoid in nature (Noma and Asakawa, 2010), and is the precursor to other monoterpenoids (Figure 2) through species-specific synthetic schemes. Unfortunately, these pathways have not yet been investigated in cannabis. The ubiquity of limonene serves, perhaps, as a demonstration of convergent evolution that supports an important ecological role for this monoterpene. Studies with varying methodology and dosing in citrus oils in mice suggest it to be a powerful anxiolytic agent (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006), with one EO increasing serotonin in the prefrontal cortex, and dopamine (DA) in hippocampus mediated via 5-HT$_{1A}$ (Komiya *et al.*, 2006). Compelling confirmatory evidence in humans was provided in a clinical study (Komori *et al.*, 1995), in which hospitalized depressed patients were exposed to citrus fragrance in ambient air, with subsequent normalization of Hamilton Depression Scores, successful discontinuation of antidepressant medication in 9/12 patients and serum evidence of immune stimulation (CD4/8 ratio normalization). Limonene also produces apoptosis of breast cancer cells, and was employed at high doses in Phase II RCTs (Vigushin *et al.*, 1998). Subsequent investigation in cancer treatment has centred on its immediate hepatic metabolite, perillic acid, which demonstrates anti-stress effects in rat brain (Fukumoto *et al.*, 2008). A patent has been submitted, claiming that limonene effectively treats gastro-oesophageal reflux (Harris, 2010). Citrus EOs containing limonene proved effective against dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010), and citrus EOs with terpenoid profiles resembling those in cannabis demonstrated strong radical scavenging properties (Choi *et al.*, 2000). As noted above, limonene is highly bioavailable (Falk-Filipsson *et al.*, 1993), and rapidly metabolized, but with indications of accumulation and retention in adipose tissues (e.g. brain). It is highly non-toxic (estimated human lethal dose 0.5–5 g·kg^{-1}) and non-sensitizing (Von Burg, 1995)

β-Myrcene is another common monoterpenoid in cannabis (Table 2) with myriad activities: diminishing inflammation via prostaglandin E-2 (PGE-2) (Lorenzetti *et al.*, 1991), and blocking hepatic carcinogenesis by aflatoxin (De-Oliveira *et al.*, 1997). Interestingly, myrcene is analgesic in mice, but this action can be blocked by naloxone, perhaps via the α-2 adrenoreceptor (Rao *et al.*, 1990). It is non-mutagenic in the Ames test (Gomes-Carneiro *et al.*, 2005). Myrcene is a recognized sedative as part of hops preparations (*Humulus lupulus*), employed to aid sleep in Germany (Bisset and Wichtl, 2004). Furthermore, myrcene acted as a muscle relaxant in mice, and potentiated barbiturate sleep time at high doses (do Vale *et al.*, 2002). Together, these data would support the hypothesis that myrcene is a prominent sedative terpenoid in cannabis, and combined with THC, may produce the 'couch-lock' phenomenon of certain chemotypes that is alternatively decried or appreciated by recreational cannabis consumers.

α-Pinene is a bicyclic monoterpene (Table 2), and the most widely encountered terpenoid in nature (Noma and Asakawa, 2010). It appears in conifers and innumerable plant EOs, with an insect-repellent role. It is anti-inflammatory via PGE-1 (Gil *et al.*, 1989), and is a bronchodilator in humans at low exposure levels (Falk *et al.*, 1990). Pinene is a major component of *Sideritis* spp. (Kose *et al.*, 2010) and *Salvia* spp. EOs (Ozek *et al.*, 2010), both with prominent activity against MRSA (*vide infra*). Beyond this, it seems to be a broad-spectrum antibiotic (Nissen *et al.*, 2010). α-Pinene forms the biosynthetic base for CB_2 ligands, such as HU-308 (Hanus *et al.*, 1999). Perhaps most compelling, however, is its activity as an acetylcholinesterase inhibitor aiding memory (Perry *et al.*, 2000), with an observed IC_{50} of 0.44 mM (Miyazawa

Table 2

Cannabis Terpenoid Activity Table

Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT_{1A} (Komiya *et al.*, 2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-oesophageal reflux (Harris, 2010)	THC
α-Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)	CBD
			Bronchodilatory in humans (Falk *et al.*, 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THC?, CBD
β-Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001)	CBD, CBG?
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine A_{2A} (Peana *et al.*, 2006)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
			Potent anti-leishmanial (do Socorro *et al.*, 2003)	?
β-Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988)	CBD
			Gastric cytoprotective (Tambe *et al.*, 1996)	THC
			Anti-malarial (Campbell *et al.*, 1997)	?
			Selective CB_2 agonist (100 nM) (Gertsch *et al.*, 2008)	THC
			Treatment of pruritus? (Karsak *et al.*, 2007)	THC
			Treatment of addiction? (Xi *et al.*, 2010)	CBD
Caryophyllene Oxide		 Lemon balm	Decreases platelet aggregation (Lin *et al.*, 2003)	THC
			Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole (Yang *et al.*, 1999)	CBC,CBG
			Insecticidal/anti-feedant (Bettarini *et al.*, 1993)	THCA, CBGA
Nerolidol		 Orange	Sedative (Binet *et al.*, 1972)	THC, CBN
			Skin penetrant (Cornwell and Barry, 1994)	–
			Potent antimalarial (Lopes *et al.*, 1999, Rodrigues Goulart *et al.*, 2004)	?
			Anti-leishmanial activity (Arruda *et al.*, 2005)	?
Phytol		 Green tea	Breakdown product of chlorophyll	–
			Prevents Vitamin A teratogenesis (Arnhold *et al.*, 2002)	–
			↑GABA via SSADH inhibition (Bang *et al.*, 2002)	CBG

Representative plants containing each terpenoid are displayed as examples to promote recognition, but many species contain them in varying concentrations. 5-HT, 5-hydroxytryptamine (serotonin); AD, antidepressant; AI, anti-inflammatory; CB_1/CB_2, cannabinoid receptor 1 or 2; GABA, gamma aminobutyric acid; PGE-1/PGE-2, prostaglandin E-1/prostaglandin E-2; SSADH, succinic semialdehyde dehydrogenase.

and Yamafuji, 2005). This feature could counteract short-term memory deficits induced by THC intoxication (*vide infra*).

D-Linalool is a monoterpenoid alcohol (Table 2), common to lavender (*Lavandula angustifolia*), whose psychotropic anxiolytic activity has been reviewed in detail (Russo, 2001). Interestingly, linalyl acetate, the other primary terpenoid in lavender, hydrolyses to linalool in gastric secretions (Bickers *et al.*, 2003). Linalool proved sedating to mouse activity on inhalation (Buchbauer *et al.*, 1991; Jirovetz *et al.*, 1992). In traditional aromatherapy, linalool is the likely suspect in the remarkable therapeutic capabilities of lavender EO to alleviate skin burns without scarring (Gattefosse, 1993). Pertinent to this, the local anaesthetic effects of linalool (Re *et al.*, 2000) are equal to those of procaine and menthol (Ghelardini *et al.*, 1999). Another explanation would be its ability to produce hot-plate analgesia in mice ($P < 0.001$) that was reduced by administration of an adenosine A_{2A} antagonist (Peana *et al.*, 2006). It is also anti-nociceptive at high doses in mice via ionotropic glutamate receptors (Batista *et al.*, 2008). Linalool demonstrated anticonvulsant and antiglutamatergic activity (Elisabetsky *et al.*, 1995), and reduced seizures as part of *Ocimum basilicum* EO after exposure to pentylenetetrazole, picrotoxin and strychnine (Ismail, 2006). Furthermore, linalool decreased K^+-stimulated glutamate release and uptake in mouse synaptosomes (Silva Brum *et al.*, 2001). These effects were summarized (Nunes *et al.*, 2010, p. 303): 'Overall, it seems reasonable to argue that the modulation of glutamate and GABA neurotransmitter systems are likely to be the critical mechanism responsible for the sedative, anxiolytic and anticonvulsant properties of linalool and EOs containing linalool in significant proportions'. Linalool also proved to be a powerful anti-leishmanial agent (do Socorro *et al.*, 2003), and as a presumed lavender EO component, decreased morphine opioid usage after inhalation versus placebo ($P = 0.04$) in gastric banding in morbidly obese surgical patients (Kim *et al.*, 2007).

β-Caryophyllene (Table 2) is generally the most common sesquiterpenoid encountered in cannabis (Mediavilla and Steinemann, 1997), wherein its evolutionary function may be due to its ability to attract insect predatory green lacewings, while simultaneously inhibiting insect herbivory (Langenheim, 1994). It is frequently the predominant terpenoid overall in cannabis extracts, particularly if they have been processed under heat for decarboxylation (Guy and Stott, 2005). Caryophyllene is common to black pepper (*Piper nigrum*) and Copaiba balsam (*Copaifera officinalis*) (Lawless, 1995). It is anti-inflammatory via PGE-1, comparable in potency to the toxic phenylbutazone (Basile *et al.*, 1988), and an EO containing it was on par with etodolac and indomethacin (Ozturk and Ozbek, 2005). In contrast to the latter agents, however, caryophyllene was a gastric cytoprotective (Tambe *et al.*, 1996), much as had been claimed in the past in treating duodenal ulcers in the UK with cannabis extract (Douthwaite, 1947). Caryophyllene may have contributed to antimalarial effects as an EO component (Campbell *et al.*, 1997). Perhaps the greatest revelation regarding caryophyllene has been its demonstration as a selective full agonist at CB_2 (100 nM), the first proven phytocannabinoid beyond the cannabis genus (Gertsch *et al.*, 2008). Subsequent work has demonstrated that this dietary component produced anti-inflammatory analgesic activity at the lowest dose of 5 $mg \cdot kg^{-1}$ in wild-type, but not CB_2 knockout mice (Gertsch, 2008). Given the lack of attributed psychoactivity of CB_2 agonists, caryophyllene offers great promise as a therapeutic compound, whether systemically, or in dermatological applications such as contact dermatitis (Karsak *et al.*, 2007). Sensitization reactions are quite rare, and probably due to oxidized product (Skold *et al.*, 2006).

Nerolidol is a sesquiterpene alcohol with sedative properties (Binet *et al.*, 1972), present as a low-level component in orange and other citrus peels (Table 2). It diminished experimentally induced formation of colon adenomas in rats (Wattenberg, 1991). It was an effective agent for enhancing skin penetration of 5-fluorouracil (Cornwell and Barry, 1994). This could be a helpful property in treating fungal growth, where it is also an inhibitor (Langenheim, 1994). It seems to have anti-protozoal parasite control benefits, as a potent antimalarial (Lopes *et al.*, 1999; Rodrigues Goulart *et al.*, 2004) and anti-leishmanial agent (Arruda *et al.*, 2005). Nerolidol is non-toxic and non-sensitizing (Lapczynski *et al.*, 2008).

Caryophyllene oxide (Table 2) is a sesquiterpenoid oxide common to lemon balm (*Melissa officinalis*), and to the eucalyptus, *Melaleuca stypheloides*, whose EO contains 43.8% (Farag *et al.*, 2004). In the plant, it serves as an insecticidal/anti-feedant (Bettarini *et al.*, 1993) and as broad-spectrum antifungal in plant defence (Langenheim, 1994). Analogously, the latter properties may prove therapeutic, as caryophyllene oxide demonstrated antifungal efficacy in a model of clinical onychomycosis comparable to ciclopiroxalamine and sulconazole, with an 8% concentration affecting eradication in 15 days (Yang *et al.*, 1999). Caryophyllene oxide is non-toxic and non-sensitizing (Opdyke, 1983). This agent also demonstrates anti-platelet aggregation properties *in vitro* (Lin *et al.*, 2003). Caryophyllene oxide has the distinction of being the component responsible for cannabis identification by drug-sniffing dogs (Stahl and Kunde, 1973).

Phytol (Table 2) is a diterpene (McGinty *et al.*, 2010), present in cannabis extracts, as a breakdown product of chlorophyll and tocopherol. Phytol prevented vitamin A-induced teratogenesis by inhibiting conversion of retinol to a harmful metabolite, all-*trans*-retinoic acid (Arnhold *et al.*, 2002). Phytol increased GABA expression via inhibition of succinic semialdehyde dehydrogenase, one of its degradative enzymes (Bang *et al.*, 2002). Thus, the presence of phytol could account for the alleged relaxing effect of wild lettuce (*Lactuca sativa*), or green tea (*Camellia sinensis*), despite the latter's caffeine content.

Selected possibilities for phytocannabinoid-terpenoid synergy

Cannabis and acne

AEA simulates lipid production in human sebocytes of sebaceous glands at low concentrations, but induces apoptosis at higher levels, suggesting that this system is under ECS control (Dobrosi *et al.*, 2008). CBD 10–20 μM did not affect basal lipid synthesis in SZ95 sebocytes, but did block such stimulation by AEA and arachidonate (Biro *et al.*, 2009). Higher doses of CBD (30–50 μM) induced sebocyte apoptosis, which was augmented in the presence of AEA. The effect of CBD to increase

Ca^{++} was blocked by ruthenium red, a TRP-inhibitor. RNA-mediated silencing of TRPV1 and TRPV3 failed to attenuate CBD effects, but experiments did support the aetiological role of TRPV4, a putative regulator of systemic osmotic pressure (T. Bíró, 2010, pers. comm.). Given the observed ability of CBD to be absorbed transcutaneously, it offers great promise to attenuate the increased sebum production at the pathological root of acne.

Cannabis terpenoids could offer complementary activity. Two citrus EOs primarily composed of limonene inhibited *Propionibacterium acnes*, the key pathogen in acne (MIC 0.31 $\mu L \cdot mL^{-1}$), more potently than triclosan (Kim *et al.*, 2008). Linalool alone demonstrated an MIC of 0.625 $\mu L \cdot mL^{-1}$. Both EOs inhibited *P. acnes*-induced TNF-α production, suggesting an adjunctive anti-inflammatory effect. In a similar manner, pinene was the most potent component of a tea-tree eucalyptus EO in suppression of *P. acnes* and *Staph* spp. in another report (Raman *et al.*, 1995).

Considering the known minimal toxicities of CBD and these terpenoids and the above findings, new acne therapies utilizing whole CBD-predominant extracts, via multi-targeting (Wagner and Ulrich-Merzenich, 2009), may present a novel and promising therapeutic approach that poses minimal risks in comparison to isotretinoin.

MRSA

MRSA accounted for 10% of cases of septicaemia and 18 650 deaths in the USA in 2005, a number greater than that attributable to human immunodeficiency virus/acquired immunodeficiency syndrome (Bancroft, 2007). Pure CBD and CBG powerfully inhibit MRSA (MIC 0.5–2 $\mu g \cdot mL^{-1}$) (Appendino *et al.*, 2008).

Amongst terpenoids, pinene was a major component of *Sideritis erythrantha* EO that was as effective against MRSA and other antibiotic-resistant bacterial strains as vancomycin and other agents (Kose *et al.*, 2010). A *Salvia rosifolia* EO with 34.8% pinene was also effective against MRSA (MIC 125 $\mu g \cdot mL^{-1}$). The ability of monoterpenoids to enhance skin permeability and entry of other drugs may further enhance antibiotic benefits (Wagner and Ulrich-Merzenich, 2009).

Given that CBG can be produced in selected cannabis chemotypes (de Meijer and Hammond, 2005; de Meijer *et al.*, 2009a), with no residual THC as a possible drug abuse liability risk, a whole plant extract of a CBG-chemotype also expressing pinene would seem to offer an excellent, safe new antiseptic agent.

Psychopharmacological applications: depression, anxiety, insomnia, dementia and addiction

Scientific investigation of the therapeutic application of terpenoids in psychiatry has been hampered by methodological concerns, subjective variability of results and a genuine dearth of appropriate randomized controlled studies of high quality (Russo, 2001; Bowles, 2003; Lis-Balchin, 2010). The same is true of phytocannabinoids (Fride and Russo, 2006). Abundant evidence supports the key role of the ECS in mediating depression (Hill and Gorzalka, 2005a,b), as well as anxiety, whether induced by aversive stimuli, such as post-traumatic stress disorder (Marsicano *et al.*, 2002) or pain (Hohmann *et al.*, 2005), and psychosis (Giuffrida *et al.*, 2004). With respect to the latter risk, the presence of CBD in smoked cannabis based on hair analysis seems to be a mitigating factor reducing its observed incidence (Morgan and Curran, 2008). A thorough review of cannabis and psychiatry is beyond the scope of this article, but several suggestions are offered with respect to possible therapeutic synergies operative with phytocannabinoids-terpenoid combinations. While the possible benefits of THC on depression remain controversial (Denson and Earleywine, 2006), much less worrisome would be CBD- or CBG-predominant preparations. Certainly the results obtained in human depression solely with a citrus scent (Komori *et al.*, 1995), strongly suggest the possibility of synergistic benefit of a phytocannabinoid-terpenoid preparation. Enriched odour exposure in adult mice induced olfactory system neurogenesis (Rochefort *et al.*, 2002), an intriguing result that could hypothetically support plasticity mechanisms in depression (Delgado and Moreno, 1999), and similar hypotheses with respect to the ECS in addiction treatment (Gerdeman and Lovinger, 2003). Phytocannabinoid-terpenoid synergy might theoretically apply.

The myriad effects of CBD on 5-HT_{1A} activity provide a strong rationale for this and other phytocannabinoids as base compounds for treatment of anxiety. Newer findings, particularly imaging studies of CBD in normal individuals in anxiety models (Fusar-Poli *et al.*, 2009; 2010; Crippa *et al.*, 2010) support this hypothesis. Even more compelling is a recent randomized control trial of pure CBD in patients with social anxiety disorder with highly statistical improvements over placebo in anxiety and cognitive impairment (Crippa *et al.*, 2011). Addition of anxiolytic limonene and linalool could contribute to the clinical efficacy of a CBD extract.

THC was demonstrated effective in a small crossover clinical trial versus placebo in 11 agitated dementia patients with Alzheimer's disease (Volicer *et al.*, 1997). THC was also observed to be an acetylcholinesterase inhibitor in its own right, as well as preventing amyloid β-peptide aggregation in that disorder (Eubanks *et al.*, 2006). Certainly, the anti-anxiety and anti-psychotic effects of CBD may be of additional benefit (Zuardi *et al.*, 1991; 2006; Zuardi and Guimaraes, 1997). A recent study supports the concept that CBD, when present in significant proportion to THC, is capable of eliminating induced cognitive and memory deficits in normal subjects smoking cannabis (Morgan *et al.*, 2010b). Furthermore, CBD may also have primary benefits on reduction of β-amyloid in Alzheimer's disease (Iuvone *et al.*, 2004; Esposito *et al.*, 2006a,b). Psychopharmacological effects of limonene, pinene and linalool could putatively extend benefits in mood in such patients.

The effects of cannabis on sleep have been reviewed (Russo *et al.*, 2007), and highlight the benefits that can accrue in this regard, particularly with respect to symptom reduction permitting better sleep, as opposed to a mere hypnotic effect. Certainly, terpenoids with pain-relieving, anti-anxiety or sedative effects may supplement such activity, notably, caryophyllene, linalool and myrcene.

The issue of cannabis addiction remains controversial. Some benefit of oral THC has been noted in cannabis withdrawal (Hart *et al.*, 2002; Haney *et al.*, 2004). More intriguing, perhaps, are claims of improvement on other substance dependencies, particularly cocaine (Labigalini *et al.*, 1999; Dreher, 2002). The situation with CBD is yet more promising. CBD and THC at doses of 4 $mg \cdot kg^{-1}$ i.p. potentiated extinction of cocaine- and amphetamine-induced conditioned place preference in rats, and CBD produced no hedonic effects of its own (Parker *et al.*, 2004). CBD 5 $mg \cdot kg^{-1} \cdot d^{-1}$ in rats attenuated heroin-seeking behaviour by conditioned stimuli, even after a lapse of 2 weeks (Ren *et al.*, 2009). A suggested mechanism of CBD relates to its ability to reverse changes in α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate glutamate and CB_1 receptor expression in the nucleus accumbens induced by heroin. The authors proposed CBD as a treatment for heroin craving and addiction relapse. A recent study demonstrated the fascinating result that patients with damage to the insula due to cerebrovascular accident were able to quit tobacco smoking without relapse or urges (Naqvi *et al.*, 2007), highlighting this structure as a critical neural centre mediating addiction to nicotine. Further study has confirmed the role of the insula in cocaine, alcohol and heroin addiction (Naqvi and Bechara, 2009; Naqvi and Bechara, 2010). In a provocative parallel, CBD 600 mg p.o. was demonstrated to deactivate functional magnetic resonance imaging (fMRI) activity in human volunteers in the left insula versus placebo ($P < 0.01$) without accompanying sedation or psychoactive changes (Borgwardt *et al.*, 2008), suggesting the possibility that CBD could act as a pharmaceutical surrogate for insular damage in exerting an anti-addiction therapeutic benefit. Human studies have recently demonstrated that human volunteers smoking cannabis with higher CBD content reduced their liking for drug-related stimuli, including food (Morgan *et al.*, 2010a). The authors posited that CBD can modulate reinforcing properties of drugs of abuse, and help in training to reduce relapse to alcoholism. A single case report of a successful withdrawal from cannabis dependency utilizing pure CBD treatment was recently published (Crippa *et al.*, 2010).

Perhaps terpenoids can provide adjunctive support. In a clinical trial, 48 cigarette smokers inhaling vapour from an EO of black pepper (*Piper nigrum*), a mint-menthol mixture or placebo (Rose and Behm, 1994). Black pepper EO reduced nicotine craving significantly ($P < 0.01$), an effect attributed to irritation of the bronchial tree, simulating the act of cigarette smoking, but without nicotine or actual burning of material. Rather, might not the effect have been pharmacological? The terpenoid profile of black pepper suggests possible candidates: myrcene via sedation, pinene via increased alertness, or especially caryophyllene via CB_2 agonism and a newly discovered putative mechanism of action in addiction treatment.

CB_2 is expressed in dopaminergic neurones in the ventral tegmental area and nucleus accumbens, areas mediating addictive phenomena (Xi *et al.*, 2010). Activation of CB_2 by the synthetic agonist JWH144 administered systemically, intranasally, or by microinjection into the nucleus accumbens in rats inhibited DA release and cocaine self-administration. Caryophyllene, as a high-potency selective CB_2 agonist (Gertsch *et al.*, 2008), would likely produce similar effects, and have the advantage of being a non-toxic dietary component. All factors considered, CBD, with caryophyllene, and possibly other adjunctive terpenoids in the extract, offers significant promise in future addiction treatment.

Taming THC: cannabis entourage compounds as antidotes to intoxication

Various sources highlight the limited therapeutic index of pure THC, when given intravenously (D'Souza *et al.*, 2004) or orally (Favrat *et al.*, 2005), especially in people previously naïve to its effects. Acute overdose incidents involving THC or THC-predominant cannabis usually consist of self-limited panic reactions or toxic psychoses, for which no pharmacological intervention is generally necessary, and supportive counselling (reassurance or 'talking down') is sufficient to allow resolution without sequelae. CBD modulates the psychoactivity of THC and reduces its adverse event profile (Russo and Guy, 2006), highlighted by recent results above described. Could it be, however, that other cannabis components offer additional attenuation of the less undesirable effects of THC? History provides some clues.

In 10th century Persia, Al-Razi offered a prescription in his *Manafi al-agdhiya wa-daf madarri-ha* (p. 248), rendered (Lozano, 1993, p. 124; translation EBR) ' – and to avoid these harms {from ingestion of cannabis seeds or hashish}, one should drink fresh water and ice or eat any acid fruits'. This concept was repeated in various forms by various authorities through the ages, including ibn Sina (ibn Sina (Avicenna), 1294), and Ibn al-Baytar (ibn al-Baytar, 1291), until O'Shaughnessy brought Indian hemp to Britain in 1843 (O'Shaughnessy, 1843). Robert Christison subsequently cited lemon (Figure 3A) as an antidote to acute intoxication in numerous cases (Christison, 1851) and this excerpt regarding morning-after residua (Christison, 1848) (p. 973):

> Next morning there was an ordinary appetite, much torpidity, great defect and shortness of memory, extreme apparent protraction of time, but no peculiarity of articulation or other effect; and these symptoms lasted until 2 P.M., when they ceased entirely in a few minutes after taking lemonade.

Literary icons on both sides of the Atlantic espoused similar support for the citrus cure in the 19th century, notably Bayard Taylor after travels in Syria (Taylor, 1855), and Fitzhugh Ludlow after his voluntary experiments with ever higher cannabis extract doses in the USA (Ludlow, 1857). The sentiment was repeated by Calkins (1871), who noted the suggestion of a friend in Tunis that lemon retained the confidence of cure of overdoses by cannabis users in that region. This is supported by the observation that lemon juice, which normally contains small terpenoid titres, is traditionally enhanced in North Africa by the inclusion in drinks of the limonene-rich rind, as evidenced by the recipe for *Agua Limón* from modern Morocco (Morse and Mamane, 2001). In his comprehensive review of cannabis in the first half of the 20th century, Walton once more supported its prescription (Walton, 1938).

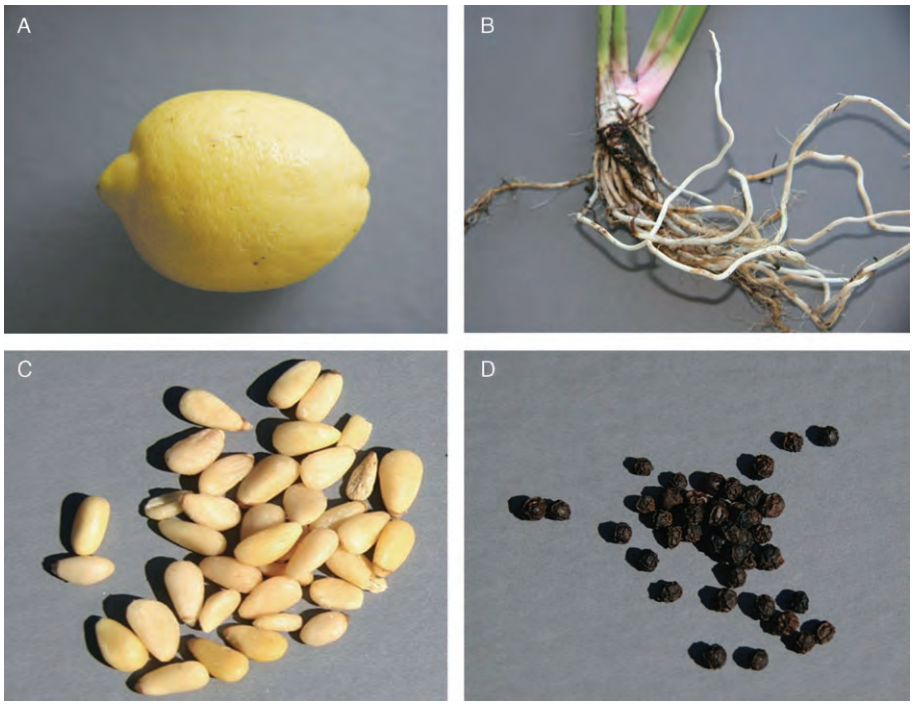


Figure 3

Ancient cannabis antidotes. (A) Lemon (*Citrus limon*). (B) Calamus plant roots (*Acorus calamus*). (C) Pine nuts (*Pinus* spp.). (D) Black pepper (*Piper nigrum*).

Another traditional antidote to cannabis employing *Acorus calamus* (Figure 3B) is evident from the Ayurvedic tradition of India (Lad, 1990, p. 131):

> Calamus root is the best antidote for the ill effects of marijuana. . . . if one smokes a pinch of calamus root powder with the marijuana, this herb will completely neutralize the toxic side effects of the drug.

This claim has gained credence, not only through force of anecdotal accounts that abound on the Internet, but with formal scientific case reports and scientific analysis (McPartland *et al.*, 2008) documenting clearer thinking and improved memory with the cannabis–calamus combination, and with provision of a scientific rationale: calamus contains beta-asarone, an acetylcholinesterase inhibitor with 10% of the potency of physotigmine (Mukherjee *et al.*, 2007). Interestingly, the cannabis terpenoid, α-pinene, also has been characterized as a potent inhibitor of that enzyme (Miyazawa and Yamafuji, 2005), bolstering the hypothesis of a second antidote to THC contained in cannabis itself. Historical precedents also support pinene in this pharmacological role.

In the firstt century, Pliny wrote of cannabis in his *Natural History, Book XXIV* (Pliny, 1980, p. 164):

> The gelotophyllis ['leaves of laughter' = cannabis] grows in Bactria and along the Borysthenes. If this be taken in myrrh and wine all kinds of phantoms beset the mind, causing laughter which persists until the kernels of pine-nuts are taken with pepper and honey in palm wine.

Of the components, palm wine is perhaps the most mysterious. Ethanol does not reduce cannabis intoxication (Mello and Mendelson, 1978). However, ancient wines were stored in clay pots or goatskins, and required preservation, usually with addition of pine tar or terebinth resin (from *Pistacia* spp.; McGovern *et al.*, 2009). Pine tar is rich in pinene, as is terebinth resin (from *Pistacia terebinthus*; Tsokou *et al.*, 2007), while the latter also contains limonene (Duru *et al.*, 2003). Likewise, the pine nuts (Figure 3C) prescribed by Pliny the Elder harbour pinene, along with additional limonene (Salvadeo *et al.*, 2007). Al-Ukbari also suggested pistachio nuts as a cannabis antidote in the 13th century (Lozano, 1993), and the ripe fruits of *Pistacia terebinthus* similarly contain pinene (Couladis *et al.*, 2003). The black pepper (Figure 3D), might offer the mental clarity afforded by pinene, sedation via myrcene and helpful contributions by β-caryophyllene. The historical suggestions for cannabis antidotes are thus supported by modern scientific rationales for the claims, and if proven experimentally would provide additional evidence of synergy (Berenbaum, 1989; Wagner and Ulrich-Merzenich, 2009).

Conclusions and suggestions for future study

Considered ensemble, the preceding body of information supports the concept that selective breeding of cannabis chemotypes rich in ameliorative phytocannabinoid and terpenoid content offer complementary pharmacological activities that may strengthen and broaden clinical applications and improve the therapeutic index of cannabis extracts containing THC, or other base phytocannabinoids. Psychopharmacological and dermatological indications show the greatest promise.

One important remaining order of business is the elucidation of mono- and sesquiterpenoid biosynthetic pathways in cannabis, as has been achieved previously in other species of plants (Croteau, 1987; Gershenzon and Croteau, 1993; Bohlmann *et al.*, 1998; Turner *et al.*, 1999; Trapp and Croteau, 2001).

Various cannabis component combinations or cannabis extracts should be examined via high throughput pharmacological screening where not previously accomplished. Another goal is the investigation of the biochemical targets of the cannabis terpenoids, along with their mechanisms of action, particularly in the central nervous system. Possible techniques for such research include radio-labelling of select agents in animals with subsequent necropsy. On a molecular level, investigation of terpenoid changes to phytocannabinoid signal transduction and trafficking may prove illuminating. While it is known that terpenoids bind to odorant receptors in the nasal mucosa (Friedrich, 2004) and proximal olfactory structures (Barnea *et al.*, 2004), it would be essential to ascertain if direct effects in limbic or other cerebral structures are operative. Given that farnesyl pyrophosphate is a sesquiterpenoid precursor and the most potent endogenous agonist yet discovered for GPR92 (McHugh *et al.*, 2010), *in silico* studies attempting to match minor cannabinoids and terpenoids to orphan GPCRs may prove fruitful. Behavioural assays of agents in animal models may also provide clues. Simple combinations of phytocannabinoids and terpenoids may demonstrate synergy as antibiotics if MICs are appreciable lowered (Wagner and Ulrich-Merzenich, 2009). Ultimately, fMRI and single photon emission computed tomography studies in humans, with simultaneous drug reaction questionnaires and psychometric testing employing individual agents and phytocannabinoid-terpenoid pairings via vaporization or oromucosal application, would likely offer safe and effective methods to investigate possible interactions and synergy.

Should positive outcomes result from such studies, phytopharmaceutical development may follow. The development of zero-cannabinoid cannabis chemotypes (de Meijer *et al.*, 2009b) has provided extracts that will facilitate discernment of the pharmacological effects and contributions of different fractions. Breeding work has already resulted in chemotypes that produce 97% of monoterpenoid content as myrcene, or 77% as limonene (E. de Meijer, pers. comm.). Selective cross-breeding of high-terpenoid- and high-phytocannabinoid-specific chemotypes has thus become a rational target that may lead to novel approaches to such disorders as treatment-resistant depression, anxiety, drug dependency, dementia and a panoply of dermatological disorders, as well as industrial applications as safer pesticides and antiseptics. A better future via cannabis phytochemistry may be an achievable goal through further research of the entourage effect in this versatile plant that may help it fulfil its promise as a pharmacological treasure trove.

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Conflict of Interest

The author is a Senior Medical Advisor to GW Pharmaceuticals and serves as a consultant.

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Patient-Reported Symptom Relief Following Medical Cannabis Consumption

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Background: The Releaf App™ mobile software application (app) data was used to measure self-reported effectiveness and side effects of medical cannabis used under naturalistic conditions.

Methods: Between 5/03/2016 and 12/16/2017, 2,830 Releaf App™ users completed 13,638 individual sessions self-administering medical cannabis and indicated their primary health symptom severity rating on an 11-point (0–10) visual analog scale in real-time prior to and following cannabis consumption, along with experienced side effects.

Results: Releaf App™ responders used cannabis to treat myriad health symptoms, the most frequent relating to pain, anxiety, and depressive conditions. Significant symptom severity reductions were reported for all the symptom categories, with mean reductions between 2.8 and 4.6 points (ds ranged from 1.29–2.39, *p*s < 0.001). On average, higher pre-dosing symptom levels were associated with greater reported symptom relief, and users treating anxiety or depression-related symptoms reported significantly more relief (ps < 0.001) than users with pain symptoms. Of the 42 possible side effects, users were more likely to indicate and showed a stronger correlation between symptom relief and experiences of positive (94% of sessions) or a context-specific side effects (76%), whereas negative side effects (60%) were associated with lessened, yet still significant symptom relief and were more common among patients treating a depressive symptom relative to patients treating anxiety and pain-related conditions.

Conclusion: Patient-managed cannabis use is associated with clinically significant improvements in self-reported symptom relief for treating a wide range of health conditions, along with frequent positive and negative side effects.

Keywords: pain, anxiety, depression, cannabis, marijuana, quality of life, symptom management, side effects

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INTRODUCTION

Medicinal cannabis use is expanding rapidly in the United States, with thousands of new users daily, particularly older patients and people with significant health concerns, treating many different symptoms (Centers for Disease Control and Prevention, 2016; Han et al., 2016). Most patients have a wide variety of medicinal cannabis products available to them, ranging from traditional flower to edibles and tinctures. Naturalistic observational studies are generally well-suited for capturing how patients manage their treatment decisions in real-life, and how patient-managed cannabis therapies may contribute to symptom relief and potential side effects from use. Observational research designs allow patients to use the myriad *Cannabis* strains and cannabis-derived formulations (e.g., concentrates, tinctures, edibles, topicals, suppositories, toothpaste) made at home and/or commercially available and widely used in society, and can incorporate the breadth of health conditions for which medical cannabis has been sanctioned for use at the state-level. Lastly, observational studies also circumvent research barriers associated with cannabis' Schedule I status under United States federal law, which makes randomized controlled trials (RCTs) challenging to conduct (Stith and Vigil, 2016; National Academies of Sciences, Engineering, and Medicine, 2017).

Since its release in 2016, the commercially developed Releaf App^{TM} application (app; Releaf App, 2018) has been the only publically available, incentive-free patient educational software program designed for recording how individual cannabis usage sessions may correspond to immediate changes in primary symptom intensity levels and experienced side effects. This electronic assessment tool enables patients to monitor and manage their cannabis consumption decisions under naturalistic conditions while avoiding the limitations of retrospective survey collection methods (e.g., memory bias, social desirability effects). We used the Releaf App^{TM} repository of over 2,830 patients and 13,368 individual cannabis administration sessions to examine two research questions: How does cannabis used under naturalistic conditions affect user-experienced symptom relief and side effects? Does the magnitude of experienced symptom relief and the prevalence of side effects vary across symptom categories? The results have clinical relevance for understanding how patient-managed medical cannabis therapies may correspond to changes in symptom intensity and potential side effects among people using cannabis for treating distinct health conditions (Hill and Weiss, 2016; Rubin, 2017).

MATERIALS AND METHODS

Study Design

A naturalistic observational research design, approved by the Institutional Review Board at the University of New Mexico, was used to analyze the Releaf App^{TM} user-submitted data recorded between 5/03/2016 and 12/16/2017. Releaf App^{TM} is a cross-platform (iOS and Android) mobile and tablet app backed by a secure cloud programming interface for capturing, processing, and storing anonymized user data. Out of 4,369 total users and 23,373 user interactions, we included only cannabis consumption sessions with reported starting symptom levels greater than 0 (on a 0–10, 11-point scale) and ending symptom levels reported within 90 min of the start of the session, resulting in a final sample of 2,830 users and 13,638 individual sessions for analysis. The Releaf App^{TM} measures 27 possible negative symptom categories and 42 possible side effects. Symptoms were ultimately derived from qualifying conditions across medical cannabis programs in the United States, along with a few suggested by dispensaries and patients. The side effects (called "feelings" within the app) were crowd-sourced among Releaf App^{TM} developers, beta testers, dispensaries, and patients, and included 19 positive, 12 negative, and 11 context-specific side effects available for selection. **Supplementary Tables S1, S2** in the **Supplemental Appendix** provide descriptive statistics for all symptoms and side effects.

User sessions consist of a series of electronic instructions for recording characteristics of the cannabis medication (e.g., strain, potency, formulation), pre-dosing symptom severity rating along an 11-point visual analog facial pain scale from 0 (no detectable symptom level) to10 (severe), the timing of cannabis consumption, a post-dosing symptom severity rating, and the option to indicate any of the 42 listed side effects at any time during the session. Among our primary sample of users, 2,332 users reported side effects during 10,535 sessions.

Study Outcomes

Our goal was to calculate changes in patient-perceived symptom severity, the prevalence of positive and negative side effects associated with cannabis consumption, and whether the reported-effects differs depending on the symptom for which users were seeking treatment. We measured changes in symptom relief by subtracting the ending symptom level from the beginning symptom (possible range from −10 to 10). (**Supplementary Figure S1** in the **Supplemental Appendix** provides a frequency table for each level of symptom relief.) Side effects were recorded as {0,1} variables for whether the user selected that side effect from the menu. We categorize the side effects as positive, negative, or context-specific and then convert these categories of side effects into {0,1} outcomes, count outcomes and outcomes measuring the portion of total available side effects in that category a user selected.

Statistical Analysis

We use means comparisons and least squares regression models to estimate the absolute and relative symptom changes and side effect profiles resulting from the cannabis user sessions. We also created an *adjusted symptom relief profile score*, the mean change in symptom levels plus the absolute number of listed negative side effects, to provide a relative metric of cost-benefit tradeoffs associated with cannabis use. Due to the small user counts for some of the reported symptoms, the large number of possible symptoms, and to facilitate interpretation in our regression analysis, we aggregate the most commonly reported symptoms across three broad symptom categories that included: Anxiety Symptoms (agitation/irritability, anxiety, insomnia, stress, and muscle spasms), Pain Symptoms (ten pain categories), and

Depression Symptoms (depression). The remaining types of symptoms are less frequently reported or not clearly categorized. We also report the full regression results for the three categories of side effects (positive, negative, and context-specific) and the sign for regressions of symptom relief on the full range of 42 side effects. Standard errors are clustered at the user level to control for heteroskedasticity and arbitrary correlation.

RESULTS

Figure 1 shows the starting and ending symptom severity levels, the change in levels, the Cohen's d of the difference, and the adjusted symptom relief profile score for each of the 27 discrete symptom categories. For all symptoms, the null hypothesis that the starting symptom severity level is less than or equal to the ending symptom severity can be rejected at the $p < 0.001$ level. Using the adjusted symptom relief measure (symptom relief plus negative side effects), all but users with convulsions, dizziness, excessive appetite, or tremors experienced a net improvement in their symptom severity levels. Even for these symptoms, the adjusted mean symptom relief score still indicates a net benefit from use and the lack of a statistically significant change likely relates more to the small number of observations rather than the lack of an effect, given that these symptoms together constituted less than 3% of users and less than 1% of our sample. For all other symptoms, the null hypothesis of an increase or no change in the adjusted symptom relief score can be rejected at the $p < 0.001$ level.

Table 1 provides additional information on starting and ending symptom severity levels, mean symptom relief, and the prevalence of positive, negative, and context-specific side effects by the aggregated symptom categories (anxiety, pain, and depression symptoms). For completeness, we include a fifth column including the remaining discrete symptom categories which did not fall under the three aggregated symptom categories. Little variation exists in starting and ending symptom levels and the symptom relief experienced, with the average user reporting a symptom decrease of 3.7. With regards to side effects, those with depression have a higher probability of reporting negative or context-specific side effects. The most common positive side effects are "relaxed" (64%), "peaceful" (54%), and "comfy" (38%), the most common negative side effects are "dry mouth" (23%), "foggy" (22%), and "forgetful" (13%) and the most common context-specific side effects are "high" (32%), "sleepy" (27%), and "thirsty" (27%).

Table 2 examines how symptom relief varies across the broader symptom categories, with the constant representing the mean adjusted symptom change for the omitted category, (patients with pain-related symptoms). The first two regressions shown in **Table 2** indicate that people with anxiety and depression report greater relief from using cannabis than people with chronic pain, and users with higher starting symptom levels report greater symptom relief. (The effects of cannabis on anxiety and depression symptoms are not statistically different from each other, although they are both greater than the effect of cannabis on pain-related symptoms). Negative responses or increases in symptom severity do occur, but the intercept in combination with the starting symptom level predicts that increases in symptom severity levels predominantly occur among users with starting symptoms equal to one. The third column in **Table 2** shows that cannabis is more effective for anxiety and depression symptoms than for pain-related symptoms among patients reporting higher

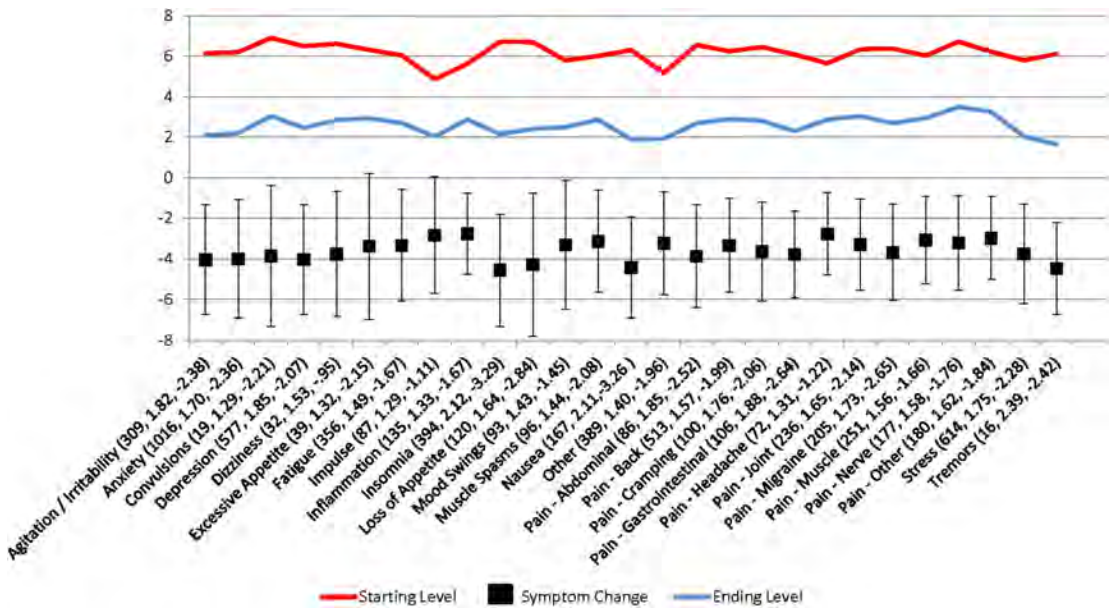

FIGURE 1 | Patient-reported symptom relief following medical cannabis consumption. Values in parantheses are the symptom category sample size, Cohen's d, and adjusted symptom relief score (symptom relief + number of negative side effects), respectively.

TABLE 1 | Descriptive statistics – symptom levels and experienced side effects.

	Overall	Anxiety symptoms	Pain symptoms	Depression symptoms	Other
N Sessions	13638	5343	4267	1440	2588
N Users	2830	1679	1223	577	1026
Starting symptom level	6.2 ± 2.2	6.2 ± 2.3	6.3 ± 2.0	6.5 ± 2.2	5.8 ± 2.4
Ending symptom level	2.5 ± 2.2	2.2 ± 2.2	3.0 ± 2.1	2.5 ± 2.2	2.4 ± 2.3
Symptom relief	−3.7 ± 2.6	−4.0 ± 2.8	−3.3 ± 2.3	−4.0 ± 2.7	−3.4 ± 2.8
Better	94.2%	94.8%	94.7%	95.4%	91.6%
Same	2.7%	2.4%	2.8%	2.4%	3.2%
Worse	3.1%	2.8%	2.5%	2.2%	5.2%
Any positive side effect	94.4%	94.7%	94.5%	93.9%	94.2%
Any negative side effect	60.0%	60.0%	58.9%	65.5%	58.8%
Any context-specific side effect	76.2%	75.2%	75.9%	80.1%	76.6%
# of positive side effects	4.6 ± 3.2	4.6 ± 3.2	4.4 ± 3.1	4.8 ± 3.4	4.8 ± 3.4
# of negative side effects	1.4 ± 1.7	1.4 ± 1.7	1.3 ± 1.6	1.6 ± 1.9	1.3 ± 1.7
# of context-specific side effects	2.0 ± 1.9	2.0 ± 1.9	1.9 ± 1.9	2.1 ± 1.9	2.0 ± 1.9
% of positive side effects	24%	24%	23%	26%	25%
% of negative side effects	11%	11%	10%	13%	10%
% of context-specific side effects	20%	20%	19%	21%	20%

Symptoms designated as treatable with benzodiazepines (Anxiety Symptoms) include agitation/irritability, anxiety, insomnia, muscle spasms, and stress. Symptoms associated with Opioid treatment (Pain Symptoms) include all ten pain conditions. Depression is the only symptom designated as treatable with antidepressants.

TABLE 2 | Reported symptom relief for users treating anxiety, pain, and depression.

	Outcome = symptom relief		
	(1)	(2)	(3)
Constant (opioid mean)	−3.309***	1.120***	0.355**
	(−3.459 to −3.160)	(0.804 to 1.436)	(0.034 to 0.675)
Anxiety symptoms	−0.704***	−0.763***	0.365*
	(−0.944 to −0.465)	(−0.953 to −0.574)	(−0.062 to 0.792)
Depression symptoms	−0.723***	−0.563***	0.643*
	(−1.060 to −0.385)	(−0.817 to −0.310)	(−0.021 to 1.308)
Starting symptom level (1–10)		−0.706***	−0.582***
		(−0.757 to −0.656)	(−0.639 to −0.525)
Anxiety*start			−0.181***
			(−0.259 to −0.102)
Depression*start			−0.189***
			(−0.305 to −0.074)
Observations	11,050	11,050	11,050
R^2	0.018	0.372	0.377

*Each column represents a separate regression. The omitted category is symptoms treatable with an opioid medication. Robust standard errors are clustered at the user level. The coefficients are reported in line with the variable names with confidence intervals below. Coefficients are reported with 95% Confidence Intervals below. ***$p < 0.01$, **$p < 0.05$, *$p < 0.10$.*

symptom severity levels (A graphical representation of this relationship is presented in **Supplementary Figure S2** in the **Supplemental Appendix**).

In order to take advantage of the full range of symptom categories available to Releaf App™ users, we also ran regressions including dummy variables for each of the symptoms, using back pain as the omitted category. After controlling for starting symptom level, clustering the standard errors at the user level, and using a statistical significance threshold of $p < 0.05$, our results indicate that patients report greater symptom relief for treating agitation/irritability, anxiety, depression, excessive appetite, insomnia, loss of appetite, nausea, gastrointestinal pain, stress, and tremors than they do for treating back pain. Patients reported less symptom relief for treating impulsivity, headache, and nerve pain as compared to relief for treating back pain. The symptom relief for the other discrete symptom categories was indistinguishable from the reported symptom relief associated with back pain.

Table 3 explores whether patients using cannabis to treat pain, anxiety, or depressive symptoms differ in their experiences of positive, negative, or context-specific side effects. Chows tests (Chow, 1960) showed that users with anxiety-related symptoms

TABLE 3 | Differences in side effect profiles across symptom categories.

	Outcome = side effect type		
	Positive	**Negative**	**Context-specific**
		Any	
Constant (opioid mean)	0.966***	0.496***	0.695***
	(0.942 to 0.989)	(0.428 to 0.565)	(0.637 to 0.753)
Anxiety symptoms	0.001	0.013	−0.006
	(−0.012 to 0.015)	(−0.033 to 0.059)	(−0.049 to 0.037)
Depression symptoms	−0.006	0.066**	0.042*
	(−0.029 to 0.017)	(0.002 to 0.131)	(−0.005 to 0.090)
Starting symptom level	−0.003*	0.015***	0.010**
	(−0.007 to 0.000)	(0.007 to 0.024)	(0.002 to 0.019)
		Number	
Constant (opioid mean)	4.583***	1.081***	1.652***
	(4.013 to 5.154)	(0.768 to 1.395)	(1.356 to 1.947)
Anxiety symptoms	0.182	0.077	0.077
	(−0.100 to 0.465)	(−0.104 to 0.257)	(−0.113 to 0.268)
Depression symptoms	0.476*	0.324**	0.134
	(−0.010 to 0.962)	(0.053 to 0.596)	(−0.187 to 0.454)
Starting symptom level	−0.035	0.036**	0.044**
	(−0.142 to 0.072)	(0.000 to 0.072)	(0.003 to 0.085)
		Percent of possible	
Constant (opioid mean)	0.241***	0.083***	0.165***
	(0.211 to 0.271)	(0.059 to 0.107)	(0.136 to 0.195)
Anxiety symptoms	0.01	0.006	0.008
	(−0.005 to 0.024)	(−0.008 to 0.020)	(−0.011 to 0.027)
Depression symptoms	0.025*	0.025**	0.013
	(−0.001 to 0.051)	(0.004 to 0.046)	(−0.019 to 0.045)
Starting symptom level	−0.002	0.003**	0.004**
	(−0.007 to 0.004)	(0.000 to 0.006)	(0.000 to 0.009)

*The first panel uses {0,1} outcomes for the presence of side effects in each category, the second uses the count of side effects reported by category, and the third uses the number of reported side effects for each category divided by the total number of possible side effects a user could select in that category. Robust standard errors are clustered at the user level. Coefficients are reported with 95% Confidence Intervals below. ***p < 0.01, **p < 0.05, *p < 0.10.*

are no more or less likely than those with pain symptoms to report any of the three categories of side effects. Individuals with depression, however, are more likely to report negative and context-specific side effects than positive side effects. Higher starting symptom levels are also associated with more negative or context-specific side effect reporting and this relationship persists whether the side effect profile is defined as any of the side effects from that category of side effects, the number of side effects by category, or the percent of possible side effects in a category.

Table 4 tests whether different types of side effects are associated with differences in symptom relief. The results are robust across specifications; reporting positive or context-specific side effects is associated with greater symptom relief, while reporting negative side effects is associated with less symptom relief. For example, based on Column (4), a person with a starting symptom level of 5 who reports 100% of negative side effects would experience a 0.5 point increase in symptom severity on a 1–10 scale, whereas a similar user who does not report any negative side effects would experience 2.2 points of symptom relief, highlighting the importance of adjusting for starting symptom severity level and side effect profiles when evaluating the overall effectiveness of cannabis as a treatment modality.

DISCUSSION

This is the largest observational study to measure immediate changes in patient-reported symptom severity ratings and experienced side effects in real-time from using cannabis under naturalistic conditions. Building on previous research showing that cannabis may be an effective substitute for opioids (Hurd, 2016; Vigil et al., 2017) and other classes of prescription medications (e.g., sedatives; Piper et al., 2017; Stith et al., 2017), we provide evidence that cannabis is used to treat many different types of symptoms for which conventional pharmaceutical medications are typically prescribed, and that the magnitude of reported symptom relief and side effect profiles from using cannabis varies for people with different symptoms.

TABLE 4 | Association of positive, negative, and context-specific side effects with symptom relief.

	Outcome = symptom relief			
	(1)	(2)	(3)	(4)
	Any {0,1}		Percent of possible in category	
Positive	−1.100***	−1.344***	−2.345***	−2.899***
	(−1.360 to −0.841)	(−1.578 to −1.111)	(−3.046 to −1.643)	(−3.653 to −2.145)
Negative	0.174**	0.336***	2.311***	2.772***
	(0.015 to 0.334)	(0.192 to 0.480)	(1.461 to 3.161)	(2.045 to 3.498)
Context-specific	−0.339***	−0.239***	−0.781**	−0.417
	(−0.540 to −0.138)	(−0.413 to −0.065)	(−1.495 to −0.068)	(−0.931 to 0.096)
Starting symptom level		−0.660***		−0.666***
		(−0.710 to −0.610)		(−0.724 to −0.608)
Constant	−2.307***	1.894***	−3.098***	1.100***
	(−2.625 to −1.989)	(1.441 to 2.348)	(−3.372 to −2.824)	(0.818 to 1.382)
Observations	10,535	10,535	10,535	10,535
R^2	0.015	0.349	0.036	0.376

*The first two columns measure use the existence of each category of side effect as independent variables, while the second two columns use the percent of possible in each category of side effects. The second and fourth columns include the starting symptom level. In all four regressions, the outcome is the change in symptom severity. Robust standard errors are clustered at the user level. Coefficients are reported with 95% Confidence Intervals below. ***p < 0.01, **p < 0.05, *p < 0.10.*

The Releaf App™ users consumed cannabis to treat a wide range of health symptoms, the most frequent relating to pain, anxiety, or depression. Clinically and statistically significant reductions in patient-reported symptom severity levels existed in every single symptom category, suggesting that cannabis may be an effective substitute for several classes of medications with potentially dangerous and uncomfortable side effects and risky polypharmaceutical interactions, including opioids, benzodiazepines, and antidepressants (Weich et al., 2014; Centers for Disease Control and Prevention, 2016; Fontanella et al., 2016; Rudd et al., 2016; Sharma et al., 2016). Higher pre-dosing symptom levels were generally associated with greater post-dosing symptom relief and users treating an anxiety-related symptom or depression showed stronger symptom relief than users treating a pain symptom, even though depression is not a condition approved for medical cannabis use in most states.

Similar to clinical reviews showing that cannabis is associated with numerous, yet generally non-serious side effects (Wang et al., 2008; Whiting et al., 2016), positive and context-specific side effects were more commonly reported than negative side effects by the Releaf App™ users, with the most frequent reported side effects being positive (relaxed, peaceful, comfy) and the least frequent side effects being negative (paranoid, confused, headache). Positive side effect reporting was associated with the greatest reported symptom relief, followed by context-specific side effects, while negative side effects were associated with lower reported symptom relief. In general, patients treating depression were more likely to indicate a negative side effect than patients treating anxiety- or pain-related symptoms, though even users who reported only negative side effects reported significant decreases in moderate to severe symptom intensity levels after using cannabis.

One of the most striking patterns in the current results was the breadth of symptoms that appeared to improve following cannabis consumption. This pattern of responses could have been a function of characteristics of the software user interface (e.g., symptom intensity scale range), manner in which responders interacted with their mobile device (e.g., visual attention to common symptom severity levels), or with the systemic nature by which phytocannabinoids may affect the human mind and body. According to the endocannabinoid deficiency theory, many mental and physical health disturbances result from the dysregulation of the body's innate endocannabinoid system (ECS; Smith and Wagner, 2014; Di Marzo et al., 2015; Karhson et al., 2016; Russo, 2018), often described as a master network of chemical signals that promote somatic and psychological homeostasis, or psychobiological state-efficiency (Bermudez-Silva et al., 2010; Silvestri and Di Marzo, 2013; Acharya et al., 2017). The ECS consists of natural ligands (e.g., anandamide and 2-AG) and receptors (CB1 and CB2) that appear to play a major role in efficient regulation of a wide range of systems that include sleep, feeding (e.g., gut permeability and adipogenesis), libido and fertility, pain perception, motivation, happiness, anxiety, learning and memory, social functioning, autoimmune responses, cellular redox, and cancer pathophysiology (Valvassori et al., 2009; Muccioli et al., 2010; Abdel-Salam et al., 2012; Cani, 2012; Burstein, 2015; Du Plessis et al., 2015; McPartland et al., 2015; Karhson et al., 2016; Pava et al., 2016; Tegeder, 2016; Turcotte et al., 2016; Androvicova et al., 2017; Sierra et al., 2018). In other words, unlike conventional pharmaceutical approaches, which largely target specific neurotransmitter sites (e.g., monoamine neurotransmitter hypothesis; Delgado, 2000; Ng et al., 2015), cannabis may act to improve a broad spectrum of symptoms by regulating homeostatic functioning, perhaps best described as a system-modulating rather than symptom-modulating form of therapy.

Notwithstanding the strengths of the naturalistic research design and the potential implications of the study's findings,

the study was limited primarily by the lack of a control group, e.g., non-cannabis users with the same symptom using a mobile device to indicate their immediate symptom intensity levels. There is also the potential confound of user-selection bias and exclusion of users that failed to complete sessions or even use the Releaf App^{TM} due to a lack of symptom relief or negative side effects. (It is possible that selection bias could have worked in the opposite way, excluding patients that are already satisfied with their cannabis choices and therefore choose not to use the software app). This study chose to focus on the existence of symptom relief and side effects rather than offer clinical guidance as to which cannabis products offer preferential symptom relief and side effects profiles. As such we did not include product characteristics, e.g., routes of administration, quantity and method of ingestion, and cannabinoid content, all of which are likely crucial for understanding how cannabis affects symptom relief and side effect manifestation. We only show that, on average, most cannabis users experience symptom relief. Future research will benefit by incorporating these contextual factors into measurements of patient decisions and by dissecting how fundamental characteristics of the cannabis products themselves affect immediate and longer term changes in symptom relief and potential adverse consequences.

Patients with certain health conditions such as neurological disorders (e.g., multiple sclerosis, seizures, epilepsy, headache) may face differential risks for experiencing adverse effects or exacerbating their symptoms, for instance, depending on the amount of delta-9-tetrahydrocannabinol they consume, and caution should be used for patients considering using highly potent cannabis products (Solimini et al., 2017). Complicating matters are the allogamous (variable) and unstable nature of the *Cannabis* plant and the inherent inconsistencies in the chemical contents across plant batches and derived formulations, which are affected by genetic characteristics, but also environmental, cultivation, and storage conditions (Thomas and Pollard, 2016; Pacifici et al., 2017, 2018). These factors present challenges for both medical cannabis consumers and researchers as patients never have continuous access to cannabis products with precisely consistent chemotypes. Cannabis-based products (e.g., dried flower vs. oils) can differ in their dose reliability, and researchers have offered guidelines for dosing titration and experimental usage (Kahan et al., 2014; Pichini et al., 2018). However, until federal laws currently restricting pharmacodynamics research in the United States are reformed (Stith and Vigil, 2016) investigators still have tremendous opportunities to develop and incorporate innovative assessment tools, like the Releaf App^{TM}, into observational research designs for measuring how patients experience self-directed cannabis treatment in their normal everyday lives outside of clinical settings.

AUTHOR CONTRIBUTIONS

JV and SS conceived the study. FB, KK, and BH independently designed and developed the Releaf App^{TM} and server infrastructure as part of their effort to help create an education tool for medical cannabis patients. SS conducted the analyses. JV and SS drafted the manuscript. All authors contributed substantially to its intellectual content and revision.

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All authors had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2018.00916/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.