Medical Marijuana Qualifying Condition Summary and Decision

Condition to be added: Bipolar Disorder, ICD-10 Code F 31

Date received: February 5th, 2018

End of public comment period: April 16th 2018, 12:00 p.m.

End of 120 days from date of receipt: June 5th 2018

Petition decision: Approved_____ Denied X

Comments:

I have reviewed the public comments and the recommendations of Chief Medical Officer Dr. Gary Wheeler, as well as comments by Dr. Richard Smith at UAMS. I have also reviewed the key articles myself.

Signature

5-23-18

Date

To: Arkansas Department of Health
Date: 5/7/18
RE: Bipolar disorder as a Qualifying Medical Condition for medical marijuana use.

I do not recommend adding bipolar disorder to the list of Qualifying Medical Conditions specific to medical marijuana use.
The depressive effects of THC cause and prolong depression and THC's frontal lobe release function impairs the judgement needed to manage a severe disease like bipolar disorder.

Regards,

G. Richard Smith, M.D.
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Medical Marijuana addition of Bipolar Disorder as a qualifying condition

JG Wheeler, MD 5/2/18

I have reviewed the packet including the articles and public comments and reviewed clinicaltrials.gov website.

The PLOS article by Sagaret al is the most scientific of the submitted articles based on its design and methods. It has limitations largely due to the small numbers of subjects in the four groups associated with the conclusion that no group differed from the others in terms of negative consequences of marijuana use. This is notable since other studies have found that bipolar subjects had higher rates of negative consequences if they used marijuana as well. This article does not resolve the issue but is a start in addressing it. In separate assessments the study does use ecological momentary assessments to determine if marijuana use improved symptoms in users. While this was a very select group of heavy users, there was evidence of benefits.

The rest of the articles are unhelpful reviews largely of the basic science of why THC/CBD might work or series of anecdotal reports.

Clinicaltrials.gov only listed two studies in bipolar disorders, one pre-recruitment and another just recruiting looking at THC or CBD.

My assessment is that the science at this time is inadequate to endorse medical marijuana for bipolar disease, but the pilot information to date suggests that it might prove to have benefit, particularly CBD which is now a FDA approved product, although not indicated for BPD.

The medical standards for approval for the medical marijuana indications have not been established for Arkansas and none were used in the initial listing of syndromes currently in the statute.

The closest medical corollary for this situation is "compassionate use". Bipolar disorder is a devastating disease and if CBD were available and was overseen in an individual trial by a knowledgeable physician, it would be reasonable to make available.

However, with no requirements for physician oversight in the statute and the likelihood that the bipolar community would widely use this option, my concern would be that there would be more harm than good.

The reality is that BPD patients use marijuana at high rates and probably have access. For physicians who care for these patients, the new science and availability of pharmacologic grade CBD products may add to their arsenal without using medical marijuana. Since none of the latter product is available, it may be prudent to simply hold on adding this indication to the list until medical marijuana is available in Arkansas. At that time if the FDA approved product has shown efficacy by the medical community, the product could be held off the list. If not yet adequately studied, BPD could be added as a compassionate addition.

U.S. National Library of Medicine

ClinicalTrials.gov

Modify Search Start Over

8 Studies found for: **bipolar disorder marijuana**

Also searched for **Diseases** and **Cannabis**. See Search Details

List **By Topic** **On Map** **Search Details**

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Recruitment Status

Clinical Study :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access :

Eligibility Criteria

Age :

years OR

Age Group :

Row	Saved	Status	Study Title	Conditions	Interve
1		Withdrawn	**Cannabinoids** in **Bipolar Affective Disorder**	• **Bipolar Affective Disorder**	• Drug: Synth **cann** (1:1 r THC
2		Completed Has Results	Efficacy Study of Quetiapine Plus Topiramate for Reducing **Cannabis** Consumption and **Bipolar** Mania	• **Bipolar Disorder** • **Cannabis**-Related **Disorder**	• Drug: Queti and p • Drug: Queti and Topira
3		Completed Has Results	Study of Icariin for **Bipolar Disorder** and Co-Occurring Substance Use **Disorders**	• **Bipolar Disorder** • Substance Use **Disorder**	• Drug:

Child (birth–17)
Adult (18–65)
Senior (66+)

Sex :
- All
- Female
- Male

Accepts Healthy Volunteers

Study Type

Study Results

Study Phase

Funder Type

Clear

Row	Saved	Status	Study Title	Conditions	Interve
4		Not yet recruiting	Cognitive and Psychophysiological Effects of Delta-9-Tetrahydrocannabinol in **Bipolar Disorder**	• Delta-9-Tetrahydroncannabinol • **Bipolar Disorder** • Healthy Controls	• Drug: Delta- • Drug: • Drug: Delta-
5		Recruiting	Gabapentin for **Bipolar** & **Cannabis** Use **Disorders**	• **Bipolar** I **Disorder** • **Bipolar** II **Disorder** • **Cannabis** Use **Disorder** • Substance Use **Disorders**	• Drug: Gaba • Drug: Oral (
6		Completed	Combination Therapy in Dual Diagnosis **Bipolar** Rapid Cycling	• **Bipolar Disorder**	• Drug: Dival • Drug: Lamo • Drug:
7		Recruiting	Cannabidiol as an Adjunctive Treatment for **Bipolar** Depression	• **Bipolar Disorder** • **Bipolar** Depression • **Bipolar Affective Disorder**	• Drug: Cann. • Drug:
8		Completed Has Results	Lithium and Divalproex for the Treatment of Comorbid Rapid Cycling **Bipolar Disorder** and Substance Abuse **Disorder**	• **Bipolar Disorder**	• Drug: • Drug: Dival • Drug:

Arkansas Department of Health
Petition to Add a Debilitating Medical Condition

Complete each section of this petition. Attach supportive documents. Attachments must include a title page which identifies the specific section to which it corresponds (section A, B, C...). Incomplete petitions will be returned. **Petitions must be sent by U.S. mail to:** Arkansas Department of Health 4815 West Markham Slot 50 Little Rock, AR 72205. For questions: toll free 1-833-214-8619 or 501-682-4982

Petitioner Information	First	Middle	Last
	Home Address (including Apartment or Suite#)		
	City:	State: AR	Zip Code:
	Phone:	Email Address:	

A	Name the medical condition, medical treatment or disease. Provide the ICD-10 code(s). Bipolar Affective Disorder. ICD-10 code: F31
B	Describe the extent to which the debilitating medical condition or disease itself and/or the treatments, cause severe suffering and impair a person's daily life. See attached
C	Describe conventional medical therapies, to alleviate suffering caused by the condition or the treatment thereof. See attached
D	Describe proposed benefits from the medical use of cannabis, for the named medical condition or disease. See attached
E	Provide evidence generally accepted by the medical community and other experts, that the use of medical cannabis alleviates suffering caused by the named condition or disease. Supporting evidence includes full text peer reviewed journal articles and/or complete medical studies. See attached
F	Attach letters of support for the use of medical cannabis from physicians and or other licensed health care providers knowledgeable about the named condition or disease. This may include a letter from the physician with whom the petitioner has a bona-fide physician patient relationship. And any additional medical testimonial or scientific documentation. See attached

I attest the information provided in this petition is true and that the attached documents are authentic.

Signature	Date (mm/dd/yyyy)
	01/30/2018

20171101

Petition to Add a Debilitating Medical Condition

Attachments to Application, Sections B-F.

Section B

Description of the extent to which Bipolar Affective Disorder causes suffering and impairs a person's daily life.

Bipolar affective disorder is the condition that used to be called manic-depressive illness. It is a serious disturbance of the emotions, in which the affected person will show an abnormal degree of elation at one stage in the disease and at another will show clinical depression. These episodes are commonly widely separated in time.

Mood is a continuum capable of extending a long way in both directions. But there are limits beyond which excessive elation or excessive sadness, however induced, must be considered abnormal. At the extremes are clinical depression at one end and mania at the other. Mania is an abnormal state of severely elevated mood. In mania there is also a qualitative difference from normal. It features hyperactivity, both of body and mind, and sometimes, delusional ideas. When this is of moderate degree the condition is called hypomania. Most of the people who experience mania at least once in their lives will at some other time have a depressive disorder. The combination of the two episodes, which are at the opposite poles of the range of mood, is called bipolar disorder or bipolar affective disorder. Rarely, some people show features of both mania and depression at the same time. They are hyperactive while experiencing depressive mood. Such patients are said to have a mixed affective disorder. The term 'affect' means mood.

<u>Symptoms In the depressive (low) phase symptoms may include</u>:

Mental and physical slowing
Loss of interest and energy
Loss of concentration
Loss of motivation for everyday activities
Feeling of emptiness or worthlessness
Sadness
Pessimism
Feel very sad, down, empty, or hopeless
Have very little energy
Have trouble sleeping, they may sleep too little or too much
Feel like they can't enjoy anything
Have trouble concentrating
Forget things a lot
Eat too much or too little
Think about death or suicide

<u>Symptoms in the manic phase may include:</u>

Have increased activity levels

Decreased perceived need for sleep
Feel "jumpy" or "wired"
Have trouble sleeping
Become more active than usual
Talk really fast about a lot of different things
Be agitated, irritable, or "touchy"
Feel like their thoughts are going very fast
Think they can do a lot of things at once
Do risky things, like spend a lot of money or have reckless sex

Section C
Conventional Medical Therapies to Treat Bipolar Affective Disorder

Conventional medical therapies used to treat Bipolar Affective Disorder include, but are not limited to: mood stabilizers, atypical antipsychotics, antidepressants, anxiolytics, and electroconvulsive therapy.

Section D

Proposed benefits from the use of medical *Cannabis* to treat Bipolar Affective Disorder

The proposed benefit from the use of medical *Cannabis* to treat bipolar is mood stabilization.

Section E

Evidence of the use of medical *Cannabis* alleviates suffering caused by Bipolar Affective Disorder

PLOS | ONE

RESEARCH ARTICLE

Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood

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Abstract

Marijuana is the most widely used illicit substance in those diagnosed with bipolar I disorder. However, there is conflicting evidence as to whether marijuana may alleviate or exacerbate mood symptomatology. As bipolar disorder and marijuana use are individually associated with cognitive impairment, it also remains unclear whether there is an additive effect on cognition when bipolar patients use marijuana. The current study aimed to determine the impact of marijuana on mood in bipolar patients and to examine whether marijuana confers an additional negative impact on cognitive function. Twelve patients with bipolar disorder who smoke marijuana (MJBP), 18 bipolar patients who do not smoke (BP), 23 marijuana smokers without other Axis 1 pathology (MJ), and 21 healthy controls (HC) completed a neuropsychological battery. Further, using ecological momentary assessment, participants rated their mood three times daily as well as after each instance of marijuana use over a four-week period. Results revealed that although the MJ, BP, and MJBP groups each exhibited some degree of cognitive impairment relative to HCs, no significant differences between the BP and MJBP groups were apparent, providing no evidence of an additive negative impact of BPD and MJ use on cognition. Additionally, ecological momentary assessment analyses indicated alleviation of mood symptoms in the MJBP group after marijuana use. MJBP participants experienced a substantial decrease in a composite measure of mood symptoms. Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

power

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Bipolar disorder (BPD), considered one of the most debilitating mood disorders, is the sixth leading cause of disability in the world according the World Health Organization. In those affected, BPD is often a significant source of distress and burden on relatives and caregivers [1]. Further, among Axis I pathologies, BPD carries the highest risk of substance use comorbidity, which can complicate the course of illness and impact treatment outcomes. In fact, patients with co-occurring BPD and substance use often experience poor treatment response, relapse of mood symptoms, psychosocial difficulties, and reduced treatment compliance [2–4]. Despite evidence that suggests substance use is linked to poorer outcomes, some studies have also shown that BPD patients engage in substance use to improve clinical symptoms. Bolton and colleagues [5] found that almost a quarter of those with mood disorders used alcohol or drugs to relieve symptoms, with the highest rates of self-medication seen in bipolar I disorder. In another study, the authors found that specifically amongst BPD patients who use substances, 79% engaged in drug use *specifically* to improve mood symptoms [6].

Marijuana (MJ) is the most commonly used illicit substance in the US; this statistic also holds true among those diagnosed with BPD [7]. Moreover, rates of MJ use disorders in BPD patients have been found to equal or exceed those of alcohol abuse or dependence, particularly in younger patients [8]. Research has also shown that 20–50% of patients report some form of MJ-related problems [9]. In those who endorse MJ-related problems, 63.7% reported disability, as compared to only 44.5% of those not meeting criteria for MJ use disorders, supporting previous findings that patients with BPD who engage in MJ use exhibit reduced compliance, higher levels of illness severity, and increased likelihood to attempt suicide [4, 7–8, 10–12].

While these studies appear to suggest that MJ use *results* in negative outcomes, a specific cause-and-effect relationship has yet to be determined. Although many studies have reported that MJ use precedes the onset of BPD [13–16], it remains unclear whether MJ use contributes to the pathogenesis of the disorder, or if it is used to address symptomatology, perhaps as a form of premorbid self-medication [17–19], especially if traditional pharmacotherapeutic regimens are ineffective at symptom alleviation. Others have also reported that individuals with higher levels of illness severity may be at risk for MJ use *after* the onset of the disorder [20]. Further research is needed to clarify the relationship between MJ use and the manifestation of BPD symptoms. Despite claims of negative outcomes associated with MJ use, whether patients' view MJ use as successful in symptom improvement is rarely assessed. In a single study of BPD patients, Weiss et al. [21] reported that nearly all patients initiated substance use as the *result* of one bipolar symptom, and the majority of patients reported improvement that was attributable to substance use for at least one symptom. Further, in a review of anecdotal reports of MJ use among BPD patients, the authors concluded that MJ was not utilized for the "high" sought out by recreational users, which may suggest that the effects of MJ are unique in sub-euphoric doses [22]. Regardless of the motive for use, the fact remains that MJ use is common in patients with BPD. As noted above, patients with BPD who use MJ have been shown to have higher illness severity and poorer outcome, yet report subjective improvement in symptoms after using MJ, suggestive of a complex relationship between MJ and mood [23]. Taken together, these data provide evidence that some patients with BPD may derive a clinical benefit from using MJ and highlight the importance of understanding the effects of MJ on mood symptomatology in those diagnosed with affective disorders.

Ecological Momentary Assessment (EMA), utilized in the current study, allows for the investigation of real-time assessment of mood and related symptoms as well as repeated collection of real-time data in participants' natural environment [24–25]. While most symptom assessments and diagnostic tools in both research and clinical settings rely on retrospective

recall of emotions and symptomatology using interviews and self-report questionnaires, EMA data is collected in naturalistic, real-world contexts and therefore offers improved ecological validity over traditional, retrospective methods. In fact, retrospective reports of mood have been shown to have a bias towards negative mood states such as anxiety, depression, and helplessness [26]. Collecting data in real-time with EMA reduces error bias from retrospective assessment and limits the effects of recall bias and generalization of symptoms over a period of time (Shiffman et al., 2008). Additionally, in a review article assessing the contribution of EMA on psychopathology research, Myin-Germeys and colleagues [27] suggest that symptoms in psychiatric disorders are dynamic and can meaningfully fluctuate through the course of the day. Thus, the increased ecological validity of EMA tools can provide better insight into the phenomenology and etiology of psychopathology than retrospective techniques. Better understanding of the development, maintenance, and progression of symptoms may lead to improved models of these disorders and help inform future treatment strategies [27].

Given a growing body of research indicating cognitive deficits associated with MJ use, it is also important to explore the impact of MJ across various cognitive domains. Interestingly, MJ users (without Axis I pathology) and BPD patients (who do not necessarily smoke MJ) have been shown to exhibit similar cognitive deficits. MJ use has been linked to impairments across a wide range of areas, including attention [28], memory [29–31], IQ [32–34], and executive function [35–37]. Similarly, BPD patients often evidence cognitive deficits across multiple overlapping domains; in two meta-analyses of euthymic BPD patients [38–39], the authors note marked impairment relative to healthy controls on measures of executive function, verbal memory, and attention. Despite the fact that MJ use and a diagnosis of BPD are both individually related to cognitive deficits, two studies examining neurocognitive function in MJ-smoking patients with BPD report surprising outcomes. Both Ringen et al. [40] and Braga, Burdick, DeRosse, and Malhotra [41] reported a *positive* association between neuropsychological functioning and MJ use in BPD patients, perhaps suggestive of a unique relationship between BPD and MJ use. Specifically, Ringen and colleagues [40] examined a variety of cognitive domains, including psychomotor speed, attention, working memory, executive functioning, and verbal learning. Overall, BPD patients who used MJ demonstrated better performance than patients who did *not* use MJ, although statistically significant results were only observed on tests of executive function. Similarly, Braga et al. [41] reported neurocognitive advantages in MJ-smoking BPD patients, relative to a non-smoking BPD group, spanning several domains, including executive function (Trails B) as well as attention and working memory. These results suggest that despite a more severe clinical course, BPD patients who use MJ may demonstrate a cognitive advantage relative to patients without a history of MJ use, underscoring the need for additional investigation.

Through EMA and a comprehensive neuropsychological battery, the current study aimed to clarify the relationship between acute MJ use and mood symptoms as well as cognitive function in patients with BPD. In order to accurately assess the impact of MJ use, BPD diagnosis, and the additive effects of both MJ use and BPD, we utilized a four-group study design enrolling healthy control subjects without MJ use or Axis I disorders (HC), MJ smokers without other Axis I disorders (MJ), individuals diagnosed with BPD without a history of MJ use (BP), and those diagnosed with BPD who currently used MJ (MJBP). We expected, in line with previous research, that the BP and MJBP groups would have more severely affected mood overall relative to the HC group. However, we further hypothesized that the MJBP group would experience significant mood improvement secondary to MJ use. In addition, although previous studies have shown that MJ use is related to cognitive deficits, there is a relative paucity of literature focused on the association between MJ use and cognitive function in patients with BPD. Therefore, the current study also aimed to determine whether MJ use has a differential effect

on cognitive performance in pure MJ smokers, BPD patients who smoke MJ (MJBP), and BPD patients who do not use MJ (BP).

Materials and Methods

Prior to participation, study procedures were thoroughly explained. All participants were also required to read and sign an informed consent form, a document that describes the procedures, risks, benefits, and voluntary nature of the study. This study and all study procedures were approved by the McLean Hospital Institutional Review Board.

Participants

As part of a larger study conducted between 2008 and 2014, 21 healthy control subjects (HC), 23 MJ smokers without other Axis I pathology (MJ), 18 individuals with bipolar I disorder who do not smoke MJ (BP), and 12 individuals diagnosed with bipolar I disorder who smoke MJ (MJBP), were enrolled and completed neuropsychological assessments. A subset of these participants also completed daily EMA assessments over the course of four weeks to assess mood.

Participants were not enrolled in the current study if they met criteria for any *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) Axis I pathology (with the exception of bipolar I disorder in the BPD groups, and MJ abuse/dependence in the MJ-smoking groups), as assessed by the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P) [42]. Individuals were also excluded if they reported a neurological disorder or significant medical problems, significant head injury with loss of consciousness, or were non-native English speakers (as necessitated by the cognitive assessment battery). Further, no participant was enrolled if they reported more than 15 lifetime uses of any illicit drugs (except MJ for the smoking groups) or recreational use of prescription or over-the-counter (OTC) medications, or had received electroconvulsive therapy.

Subjects enrolled in the MJ and MJBP groups were all well-characterized as chronic MJ smokers who reported smoking a minimum of 2,500 times in their lives, used MJ at least four out of the last seven days and tested positive for urinary cannabinoids. In order to ensure that cognitive test results were not affected by acute intoxication, all participants were also required to abstain from MJ use for at least twelve hours prior to study visits. Upon arrival, all individuals were required to provide a urine sample and, to ensure adherence to the twelve-hour abstinence requirement, were led to believe that this sample could be used to detect use within this time frame. This method has previously been used by our laboratory with success [36, 43–44]. Subjects were assessed for most recent use and any who violated the abstinence schedule or who appeared even vaguely intoxicated were rescheduled for a later date. An aliquot of the urine sample was sent to an outside laboratory for quantification of urinary cannabinoid concentration via gas chromatography–mass spectrometry during the initial and final study visit. Urinary THC levels were averaged across the two study visits.

Study Design and Measures

After completing diagnostic assessments, subjects who met inclusion criteria were enrolled in the four-week study, which contained a baseline visit and four weekly check-in visits. This study employed a combination Time-Based EMA design and Event-Based Monitoring [24–25]. The Time-Based EMA employed an alarm schedule, which alerted participants to complete three rating sessions per day. Each subject pre-selected three times throughout the day (at least five hours apart), which were tailored to his/her typical daily schedules, to rate their mood. In Event-Based Monitoring, EMA measures are triggered by the occurrence of a specific

event. For this study, participants were instructed to complete rating scales as soon as possible after MJ use in order to assess the acute impact of MJ on mood.

At the end of their initial screening study visit, all enrolled participants were issued a Palm Pilot (Palm Tungsten T5 PalmOne PDA) and instructed to use the device to rate their mood three times daily over the course of the four-week study. All individuals rated their mood using a custom-designed application, which contained electronic versions of several clinical rating scales: the Profile of Mood States (POMS) [45], which yields subscores for vigor, anger, confusion, tension, fatigue, depression, and a composite score for total mood disturbance (TMD); the Hamilton Anxiety Rating Scale (HAM-A) [46]; Montgomery-Asberg Depression Rating Scale (MADRS) [47]; and the Young Mania Rating Scale (YMRS) [48]. Participants who smoked MJ were also asked to use the device to record episodes of MJ use to allow for the calculation of pre- and post-MJ use mood changes. More specifically, for each episode of MJ use, participants recorded the amount (in grams), frequency, and mode of MJ use (bong, bowl, joint, etc.). Date and time were automatically recorded at the completion of each scale in order to assist with accurate pre- and post-smoking determinations. However, participants were also given the option to adjust the time of last MJ use when completing post-use ratings. Only ratings identified as being completed within four hours of MJ use were categorized as post-MJ use and used for analysis. To ensure that participants were not arbitrarily answering clinical rating questions, "quality control" questions were interspersed throughout the scales, with such questions such as "who is the current US president?" and "how thoughtfully are you answering these questions?"

In order to establish an estimate of overall intellectual functioning, participants completed the Wechsler Abbreviated Scale of Intelligence (WASI) [49]. In addition, all individuals enrolled also completed a neuropsychological battery designed to assay a variety of cognitive domains. Neuropsychological assessments were typically completed by the end of the first check-in visit, and consisted of a number of measures including the Wisconsin Card Sorting Test (WCST), Trail Making Test, Stroop Color Word Test, the Controlled Oral Word Association Test (COWAT), and Digit Span, which served as direct measures of executive function. The WCST assesses the ability to form abstract concepts, shift and maintain set, and utilize feedback, and is considered a gold-standard measure of executive function [50–51]. The Trail Making Test is comprised of two parts; while Trails A measures visual scanning and psychomotor speed, Trails B serves as a measure of cognitive set-shifting and attention [51]. The Stroop measures the ability to establish competing response tendencies, inhibit inappropriate responses, and resist interference [52]. The COWAT consists of two parts and serves as a measure of phonemic verbal fluency and executive function (participants must generate words starting with the specific letters F, A, and S) as well as verbal memory function (participants are required to generate words from a specific semantic category, in this case "Animals") [53–54]. The Digit Span subtest from the Wechsler Adult Intelligence Scale—Revised (WAIS-R), requires subjects to recall increasingly longer strings of numbers in forward and then backward order, and reflects attention, working memory and executive functioning [55–56].

Study participants also completed additional cognitive measures, including the California Verbal Learning Test (CVLT), Rey-Osterrieth Complex Figure Test (ROCF), and Hooper Visual Organization Test (HVOT). The CVLT-II requires subjects to learn an orally presented list of words across five trials to assess verbal learning [57]. Errors and clustering strategies (i.e., grouping list items by category) are also documented to assess efficiency of learning. Further, the CVLT incorporates a delay trial, in which individuals are required to remember the list of words after a 20-minute delay in order to assess verbal memory. The ROCF assesses visual-spatial organization as well as visual memory and requires individuals to copy a complex figure and then draw it from memory both immediately and after a twenty-minute delay [51]. Finally,

the HVOT, a measure of visuoperception, requires participants to name objects in drawings that have been "cut" into pieces [58].

In addition, study participants completed the Fagerström Test for Nicotine Dependence (FTND) [59] in order to assess current level of nicotine use and level of dependence. The Addiction Severity Index (ASI) [60] was administered to calculate days of alcohol use within the past month. In order to assess average frequency and magnitude of MJ use, a modified timeline follow-back procedure [61] was utilized at weekly study visits, with a specific focus on the past week of use. Participants were asked to report the number of times they smoked MJ, the amount of MJ used (in grams) and the mode of use each time (i.e., joint, blunt, bong, etc.). Lifetime use was also assessed using the SCID-P and guided substance use interviews.

Statistical Analyses

In order to ensure that groups were well-matched, one-way analyses of variance (ANOVAs) with Scheffé all pairwise post hoc comparisons (two-tailed) were used to compare the four groups on all continuous demographic variables: age, IQ, ASI alcohol use (days/month), and FTND. As analyses identified age as a potential confounding variable, analyses of covariance (ANCOVAs) controlling for age were performed for all comparisons in which age was significantly different between the groups. In addition, chi-squared analyses were used to compare the sex frequencies between the four groups and to compare medication in the BP and MJBP groups. One-way ANOVAs (two-tailed) were conducted to compare age of BP onset in the BP and MJ BP groups, as well as MJ use variables in the MJ and MJBP groups, including age of MJ onset (defined as first *regular* use: a measurable, consistent pattern of use that occurred at least monthly); frequency of MJ use (average number of smoking episodes per week); magnitude of MJ use (average amount, in grams, used each week); duration of use (number of years since onset of regular MJ use); and urinary THC concentration (ng/mL).

EMA analyses

Average mood scores over the entire four-week EMA data collection period were calculated for all clinical rating scales for each individual. Additionally, for MJ-smoking participants (MJ & MJBP groups), clinical rating scales were coded to indicate whether each rating was collected before (pre) or after (post) MJ use and, with this information, "average pre-MJ use" and "average post-MJ use" ratings scales were calculated for each individual. As previously mentioned, a four-hour threshold was utilized, such that all scales completed within four hours of MJ use were coded as post-MJ use ratings. Ratings completed before MJ use each day, as well as those completed in excess of four hours after MJ use were labeled as pre-MJ use ratings. In an effort to obtain at least one daily baseline rating per day, participants were asked to complete their first set of clinical rating scales prior to smoking MJ. Obtaining overall mood rating averages for each individual, as well as pre- and post-MJ use ratings in the MJ and MJBP participants, provided the opportunity to conduct several levels of analyses in order to assess the unique effects of MJ and BPD on mood, as described below.

One-way ANCOVAs controlling for age were used to analyze differences between the four groups. In order to reduce the number of unnecessary pairwise comparisons, one-tailed Dunnett *t* post hoc comparisons were employed to compare each group to the HC control group. More specifically, to assess the effects of MJ use on both mood and cognition, the HC and MJ groups were directly compared. Similarly, the effect of BPD was examined by comparing the HC group to the "pure" BP group. The additive effect of MJ use and BPD was assessed by comparing the HC group to the MJBP group, and additional one-way ANCOVAs (one-tailed) were also conducted in order to compare the BP group to the MJBP group. These analyses were

performed on the overall average mood ratings from the EMA data and, to determine whether significant between-groups differences in overall mood were affected by MJ use, ANCOVAs were repeated using the pre-MJ use average mood ratings, and again using the post-MJ use average mood ratings from the MJ-using groups (MJ and MJBP). In addition, in order to investigate the acute effects of MJ on mood *within* both the MJ and MJBP groups, pre-MJ use average mood scores were compared to post-MJ use average mood scores using paired *t* tests (one-tailed) in each of these two groups separately.

EMA compliance analyses and controlling for missing data. Compliance checks were completed during weekly visits and involved saving the EMA data from the PDA to ensure that subjects were completing the majority of their scales. Subjects were informed of their level of compliance at each check-in visit and were encouraged to complete as many scales as possible during the following week. Overall compliance percentages were calculated for each subject. One-way ANOVAs with two-tailed Scheffé all pairwise post hoc comparisons were used to assess compliance percentage differences between the four groups. Additionally, two-tailed Pearson correlations between compliance percentage and EMA average rating scales were used to ensure that missing data did not significantly impact or skew the study findings.

Neuropsychological assessment statistical analyses. To examine the effect of BPD on cognition, regardless of MJ use status, one-way two-group ANCOVAs (2-tailed) controlling for age were performed to compare HC participants to participants with BPD (BP and MJBP groups combined). One-way, three-group ANCOVAs with Scheffé all-pairwise post hoc comparisons (2-tailed) were also conducted to compare the HC, BP, and MJBP participants. These three-group analyses assessed the impact of BPD on cognition *exclusive* of MJ use (HC vs BP), and addressed any potential additive effects of MJ use in BP patients (HC vs MJBP and BP vs MJBP).

Results

Demographics

Demographics are reported in Table 1. ANOVAs of demographic variables between the four groups revealed that the groups were well matched for IQ and alcohol use (days/month). Between-group differences were noted for age ($F(3,70) = 5.819$, $p = .001$); Scheffé post hoc comparisons indicated that the BP subjects were significantly older than both HC ($p = .029$), and MJ ($p = .002$) participants. Accordingly, age differences were controlled for by utilizing ANCOVAs in all analyses of mood and cognitive performance. Chi-squared analyses indicated that the groups were not well matched for sex ($X^2(3, N = 74) = 11.628$, $p = .009$) with the MJBP group having a significantly lower percentage of females than the HC ($X^2(1, N = 33) = 8.972$, $p = .003$) and BP groups ($X^2(1, N = 30) = 6.914$, $p = .009$). Average scores on the FTND reflected very low nicotine use across the groups. However, between-group differences were noted ($F(3,70) = 6.335$, $p = .001$); the MJBP group reported significantly more nicotine use relative to the HC ($p = .002$), MJ ($p = .019$) and BP ($p = .004$) groups. All of the other groups reported similar FTND scores to one another, and given such low use indicated by the total scores, even for the MJBP group ($M = 1.92$, $SD = 3.00$), it is unlikely that nicotine use was a confound for subsequent analyses.

Analyses of medication use revealed that the BP and MJBP groups reported similar medication regimens (Table 2). No significant differences were noted for the frequency of use of different classes of medications: mood stabilizers, antidepressants, antipsychotics, and benzodiazepines. There were also no significant differences between the BP and MJBP groups for the number of medicated vs unmedicated patients within each group. In addition, the BP and MJBP groups were well-matched for age of BPD onset. With regard to MJ use characteristics,

Table 1. ANOVAs for 4-group comparison of demographic data (2-tailed).

Variable	HC	MJ	BP	MJBP	ANOVA		Scheffé All Pairwise Post Hoc Comparisons					
					F	*p* (η^2)	HC v MJ	HC v BP	HC v MJBP	MJ v BP	MJ v MJBP	BP v MJBP
n Sex	21 (8M, 13F)	23 (16M, 7F)	18 (8M,10F)	12 (11M,1F)	-	-	-	-	-	-	-	-
Age	23.38 *(4.20)*	21.96 *(5.07)*	20.50 *(6.70)*	23.75 *(4.45)*	5.619	.001 (.200)	NS	.029	NS	.002	NS	NS
IQ	124.65 *(8.15)*	119.61 *(14.35)*	119.17 *(9.92)*	115.00 *(9.62)*	1.948	.130 (.079)	NS	NS	NS	NS	NS	NS
Alcohol Use (days/month)	5.24 *(5.44)*	7.18 *(6.05)*	3.94 *(5.71)*	5.17 *(4.71)*	1.133	.342 (.048)	NS	NS	NS	NS	NS	NS
BPD Age of Onset	-	-	18.06 *(4.53)*	15.21 *(3.17)*	3.556	.070 (.113)	-	-	-	-	-	-
MJ Age of Onset	-	16.35 *(2.31)*	-	16.92 *(2.61)*	0.438	.513 (.013)	-	-	-	-	-	-
MJ Smokes/ Week	-	15.99 *(7.39)*	-	15.55 *(13.63)*	0.015	.903 (<.001)	-	-	-	-	-	-
MJ Grams/Week	-	7.21 *(5.55)*	-	5.19 *(2.76)*	1.289	.265 (.039)	-	-	-	-	-	-
MJ Duration of Use (yrs)	-	5.61 *(3.99)*	-	6.83 *(2.76)*	0.901	.349 (.027)	-	-	-	-	-	-
Urinary THC (ng/mL)	-	617.53 *(873.71)*	-	443.13 *(528.43)*	0.370	.547 (.011)	-	-	-	-	-	-

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the MJ and MJBP groups were also well-matched for age of MJ onset (Table 1), as well as current levels of MJ use. In fact, no significant differences emerged between groups for frequency (smokes/week) and magnitude of MJ use (grams/week), duration of MJ use (years since onset of regular use), or urinary THC levels (ng/mL).

EMA Results

EMA compliance results and controlling for missing data. Across all groups, high levels of compliance were noted for rating scale completion, with the average overall number of completed rating scales at 88% of all possible rating opportunities. Within the HC group, EMA rating compliance indicated that they completed 94% of scales, while the BP completed 90%, and the MJ and MJBP groups each completed 84% of scales. Notably, the MJ and MJBP groups both were required to complete more rating scales than the non-smoking groups, as they rated their mood three times daily *in addition* to completing ratings after MJ use. Therefore, it is not

Table 2. Chi Squared Analyses of Medication Use in the BP and MJBP Groups.

Variable	BP	MJBP	Chi Squared	
			X^2	*p*
Mood Stabilizers	72.22%	75.00%	0.028	NS
Antidepressants	27.78%	16.67%	0.497	NS
Antipsychotics	55.56%	58.33%	0.023	NS
Benzodiazepines	16.67%	8.33%	0.433	NS
Unmedicated	16.67%	8.33%	0.433	NS

(df = 1, n = 30)

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surprising that ANOVA results indicated that despite very high levels of compliance across all groups, some differences in compliance levels were evident ($F(3,57) = 3.238$, $p = .029$). Two-tailed Scheffé all pairwise post hoc comparisons revealed that these differences were driven by a trend in which the MJ group exhibited lower percentages for completion of EMA ratings ($M = 83.71$, $SD = 9.81$) than the HC group ($M = 93.78$, $SD = 5.91$, $p = .055$). Compliance percentages for the BP ($M = 90.08$, $SD = 9.90$) and MJBP groups ($M = 84.20$, $SD = 19.29$) were not significantly different from the other groups. However, due to the significant between-group differences, EMA analyses were re-run with compliance percentage as a covariate, and results remained unchanged. Further, in order to determine the nature of missing EMA data, correlation analyses were also conducted to assess the association between compliance percentage and EMA clinical ratings. Compliance percentage did not significantly correlate with any clinical rating scale ($r(59) \leq .203$, $p \geq .12$), suggesting that ratings were missing at random, and therefore missing EMA data did not unduly influence clinical mood ratings results.

Between-group analyses. Overall average mood ratings from across the 4-week data collection period are presented in Table 3. As expected, compared to the HC group, BP and MJBP participants reported higher levels of anger, confusion, tension, fatigue, depression, and total mood disturbance (TMD) as measured by the POMS, as well as increased anxiety (HAM-A), depression (MADRS), and mania (YMRS). Among patients, those in the BP group reported similar overall mood to MJBP participants, with no significant differences observed on any rating scale, with the exception of higher MADRS scores in the MJBP group. Despite this difference, depression ratings on the POMS were similar between groups, and actually were slightly (albeit not significantly) lower in the MJBP group relative to the BP group. With regard to the MJ group, no significant differences were noted between MJ smokers and HCs for average mood ratings.

Analyses of average *pre*-MJ use mood data in the MJ and MJBP group compared to overall average mood in the HC and BP group are presented in Table 4 (top portion of table); analyses of average *post*-MJ mood data in the MJ and MJBP group compared to overall average mood in the HC and BP group are presented in Table 4 (bottom half of table). *Prior to* smoking MJ, the MJBP participants reported higher levels of anger, confusion, tension, depression, and TMD on the POMS, as well as greater anxiety, depression, and mania as measured by the HAM-A, MADRS, and YMRS, relative to the average mood ratings of the HC participants. *After* smoking MJ, while some significant differences remained between the MJBP and HC groups, the MJBP group no longer endorsed significantly higher anger, tension, or TMD on the POMS relative to the HCs. Notably, the MJ participants did not report significantly different mood ratings compared to the HC participants either pre- or post-MJ use.

Two-group ANCOVAs directly comparing the BPD patient groups (BP vs MJBP; Table 4) revealed that *prior to MJ* use, MJBP participants exhibited higher depression (MADRS) scores and a trend for higher mania (YMRS) ratings relative to the BP group. Interestingly, *after smoking MJ*, the MJBP group reported decreased levels of depression and mania; MADRS scores fell to a level no longer significantly different from ratings in the BP group, and the trend for higher mania ratings on the YMRS was no longer observed in MJBP participants relative to BP participants. In addition, the MJBP group reported a trend for lower levels of tension on the POMS after MJ use compared to BP patients. Together, these decreases in clinical symptoms led to far lower TMD scores in the MJBP group *after* MJ use, relative to the BP group's average TMD score (MJBP: 11.15 vs BP: 22.53); however, this difference was not statistically significant.

Within-group analyses. Paired *t* tests investigating within-group mood changes pre- and post MJ use suggest that *after* smoking MJ, the MJ smokers experienced slightly worse mood overall. As a group, they reported significantly increased confusion and fatigue, and decreased

Table 3. ANCOVAs (controlling for age differences) of the 4-group (HC, MJ, BP, MJBP with Dunnett *t* post hoc comparisons) and 2-group (BP v MJBP) comparisons of overall 4-week average mood EMA ratings (1-tailed).

Variable	HC	MJ	BP	MJBP	4-group ANCOVA		4-group Dunnett *t* Post Hoc Comparisons			2-group BP v MJBP ANCOVA	
					F	*p* (η^2)	HC v MJ	HC v BP	HC v MJBP	*F*	*p* (η^2)
n	18	21	12	10	-	-	-	-	-	-	-
POMS											
Vigor	11.13 *(3.77)*	12.92 *(4.73)*	9.71 *(3.67)*	9.39 *(3.23)*	2.039	.060 (.098)	NS	NS	NS	0.357	.279 (.018)
Anger	0.86 *(0.76)*	1.31 *(1.71)*	4.24 *(3.41)*	4.14 *(2.59)*	7.616	<.001 (.290)	NS	<.001	<.001	0.355	.279 (.018)
Confusion	3.48 *(1.44)*	3.51 *(1.81)*	7.06 *(3.39)*	5.76 *(2.69)*	5.951	<.001 (.242)	NS	<.001	.019	0.022	.442 (.001)
Tension	3.27 *(1.30)*	2.71 *(1.61)*	6.92 *(3.37)*	6.48 *(3.94)*	7.851	<.001 (.296)	NS	<.001	.003	0.187	.335 (.010)
Fatigue	3.07 *(1.86)*	2.00 *(1.65)*	7.06 *(3.48)*	5.08 *(2.99)*	8.843	<.001 (.321)	NS	<.001	.050	0.219	.323 (.011)
Depression	1.31 *(1.37)*	1.06 *(2.07)*	6.95 *(7.04)*	6.61 *(5.17)*	6.462	.001 (.257)	NS	<.001	.002	0.570	.230 (.029)
TMD	0.86 *(7.58)*	-2.33 *(9.52)*	22.53 *(21.17)*	18.68 *(17.41)*	8.686	<.001 (.318)	NS	<.001	.002	0.196	.332 (.010)
HAMA	0.68 *(0.65)*	0.86 *(1.23)*	4.43 *(3.44)*	4.82 *(3.92)*	9.904	<.001 (.347)	NS	<.001	<.001	0.771	.120 (.039)
MADRS	1.52 *(1.37)*	1.57 *(2.00)*	7.21 *(5.43)*	10.60 *(7.01)*	14.832	<.001 (.443)	NS	<.001	<.001	3.183	.045 (.143)
YMRS	1.56 *(0.84)*	1.50 *(1.42)*	3.99 *(3.23)*	5.64 *(2.83)*	8.193	<.001 (.305)	NS	.008	<.001	1.693	.105 (.082)

POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

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vigor on the POMS, resulting in higher TMD scores relative to pre-smoking levels. It is of note, however, that their average TMD scores still fell below zero, reflecting very low levels of mood-related symptomatology overall. MJ smokers also reported higher levels of anxiety (HAM-A) *after* MJ use (Fig 1A). In contrast, the MJBP participants reported *positive* changes in mood *after* MJ use. Paired *t* tests comparing pre- and post-MJ use mood ratings within the MJBP group indicated significantly decreased ratings of anger, tension, depression, and TMD scores on the POMS as well as lower levels of depression on the MADRS. In addition, MJBP participants reported increased vigor on the POMS after MJ use (Fig 1B).

Neuropsychological Assessment

HC vs All BP: Effects of BPD on cognition (regardless of MJ use status). When all BPD patients (BP and MJBP combined) were compared to the HC group, they generally demonstrated poorer performance on tasks of executive function. Specifically, as noted in Table 5, 2-way ANCOVAS revealed that patients with BPD achieved fewer categories, made more perseveration errors and had more losses of set on the WCST. Patients with BPD had significantly longer completion times and made more errors on the Stroop during the Color Naming and Word Reading condition. They also demonstrated slightly slower completion times on the Stroop Interference condition relative to the HCs, although this did not reach statistical significance. Similarly, BPD patients also performed Trails B significantly more slowly and exhibited

Table 4. Pre- vs Post-MJ Use Mood in MJ and MJBP Participants: ANCOVAs (controlling for age differences) of the 4-group (HC, MJ, BP, MJBP with Dunnett *t* post hoc comparisons) and 2-group (BP v MJBP) comparisons of overall 4-week average mood in the HC and BP participants to average pre- and post-MJ use mood in the MJ and MJBP participants (1-tailed).

Variable	HC (avg)	MJ (pre)	BP (avg)	MJBP (pre)	4-group ANCOVA		4-group Dunnett *t* Post Hoc Comparisons			2-group ANCOVA BP v MJBP	
					F	*p* (η^2)	HC v MJ	HC v BP	HC v MJBP	*F*	*p* (η^2)
n	18	21	12	10	-	-	-	-	-	-	-
		PRE MJ USE									
POMS											
Vigor	11.13 *(3.77)*	13.67 *(5.50)*	9.71 *(3.67)*	9.26 *(2.96)*	**2.792**	**.025 (.130)**	NS	NS	NS	0.672	.211 (.034)
Anger	0.86 *(0.76)*	1.29 *(1.84)*	4.24 *(3.41)*	4.52 *(3.14)*	**7.604**	**<.001 (.289)**	NS	**<.001**	**<.001**	0.728	.202 (.037)
Confusion	3.48 *(1.44)*	3.00 *(1.64)*	7.06 *(3.39)*	6.43 *(2.96)*	**8.455**	**<.001 (.312)**	NS	**<.001**	**.003**	0.133	.360 (.007)
Tension	3.27 *(1.30)*	2.69 *(2.12)*	6.92 *(3.37)*	7.53 *(4.41)*	**8.933**	**<.001 (.324)**	NS	**.001**	**<.001**	1.166	.147 (.058)
Fatigue	3.07 *(1.86)*	1.68 *(1.70)*	7.06 *(3.48)*	4.77 *(3.05)*	**9.290**	**<.001 (.332)**	NS	**<.001**	NS	0.464	.252 (.024)
Depression	1.31 *(1.37)*	0.71 *(1.11)*	6.95 *(7.04)*	7.40 *(6.06)*	**8.086**	**<.001 (.302)**	NS	**<.001**	**<.001**	0.904	.177 (.045)
TMD	0.86 *(7.58)*	-4.30 *(8.86)*	22.53 *(21.17)*	21.39 *(19.68)*	**10.608**	**<.001 (.362)**	NS	**<.001**	**<.001**	0.590	.226 (.030)
HAMA	0.68 *(0.65)*	0.61 *(1.13)*	4.43 *(3.44)*	5.06 *(4.15)*	**10.997**	**<.001 (.371)**	NS	**<.001**	**<.001**	0.980	.168 (.049)
MADRS	1.52 *(1.37)*	1.41 *(1.63)*	7.21 *(5.43)*	11.91 *(7.53)*	**18.538**	**<.001 (.498)**	NS	**<.001**	**<.001**	5.317	**.017 (.219)**
YMRS	1.56 *(0.84)*	1.90 *(2.44)*	3.99 *(3.23)*	6.10 *(3.89)*	**7.762**	**<.001 (.294)**	NS	**.020**	**<.001**	2.084	.083 (.009)
		POST MJ USE									
POMS											
Vigor	11.13 *(3.77)*	12.02 *(4.65)*	9.71 *(3.67)*	10.78 *(3.52)*	0.656	.292 (.034)	NS	NS	NS	0.095	.381 (.005)
Anger	0.86 *(0.76)*	1.43 *(1.78)*	4.24 *(3.41)*	2.35 *(2.54)*	**4.840**	**.003 (.206)**	NS	**<.001**	NS	0.953	.171 (.048)
Confusion	3.48 *(1.44)*	3.63 *(1.68)*	7.06 *(3.39)*	5.85 *(3.11)*	**5.771**	**.001 (.236)**	NS	**<.001**	**.017**	0.021	.443 (.001)
Tension	3.27 *(1.30)*	2.54 *(1.66)*	6.92 *(3.37)*	4.15 *(2.62)*	**7.707**	**<.001 (.292)**	NS	**<.001**	NS	2.473	.066 (.115)
Fatigue	3.07 *(1.86)*	2.77 *(2.72)*	7.06 *(3.48)*	4.88 *(3.24)*	**5.186**	**.002 (.217)**	NS	**<.001**	NS	0.430	.260 (.022)
Depression	1.31 *(1.37)*	0.77 *(1.23)*	6.95 *(7.04)*	4.69 *(3.64)*	**6.073**	**.001 (.245)**	NS	**<.001**	**.026**	0.030	.433 (.002)
TMD	0.86 *(7.58)*	-0.87 *(10.32)*	22.53 *(21.17)*	11.15 *(13.69)*	**6.626**	**.001 (.262)**	NS	**<.001**	NS	0.511	.242 (.026)
HAMA	0.68 *(0.65)*	0.82 *(1.08)*	4.43 *(3.44)*	4.23 *(4.12)*	**8.315**	**<.001 (.308)**	NS	**<.001**	**<.001**	0.065	.401 (.003)
MADRS	1.52 (1.37)	1.46 (1.71)	7.21 (5.43)	9.35 (6.89)	**12.229**	**<.001 (.397)**	NS	**<.001**	**<.001**	1.341	.131 (.066)
YMRS	1.56 *(0.84)*	2.30 *(1.96)*	3.99 *(3.23)*	5.61 *(3.81)*	**6.856**	**.001 (.269)**	NS	**.013**	**<.001**	1.091	.155 (.054)

POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

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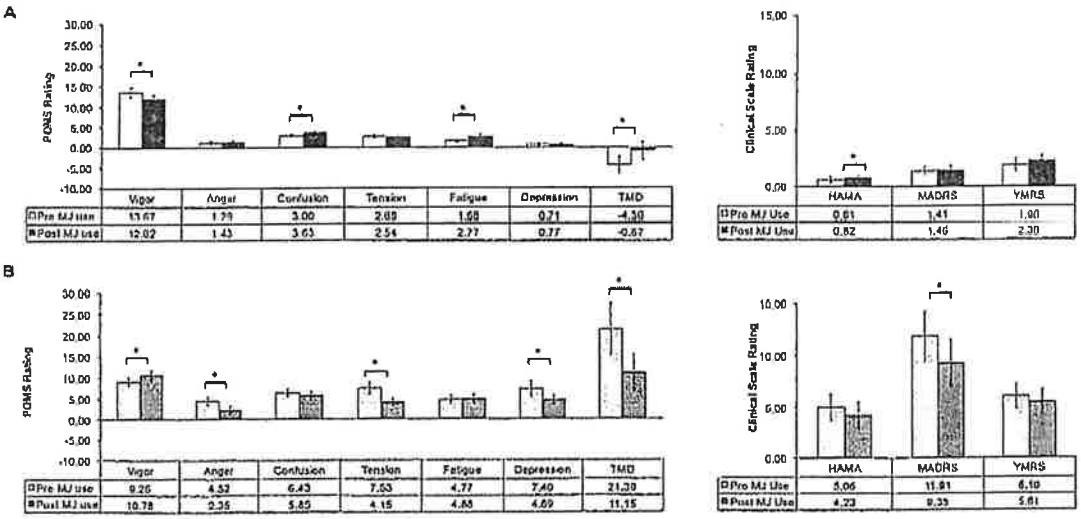

Fig 1. Paired *t*-Test EMA Analyses of Clinical State Pre- versus Post-MJ Use. EMA analyses of clinical state (POMS, HAMA, MADRS, YRMS) changes pre- versus post-MJ use in the (A) MJ group and (B) MJBP group revealed a slight worsening of symptoms in the MJ group after smoking MJ but a significant mood improvement in the MJBP group after smoking MJ, $*t(\geq 9) \geq 1.942, p \leq .042$, 1-tailed. *POMS = Profile of Mood States, TMD = Total Mood Disturbance, HAM-A = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale*

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a trend for more errors on Trails A relative to HCs. BPD patients achieved lower total scores across the three trials of the COWAT in which they had to generate words starting with a given letter (F, A, S); during the semantic category trial (animals) a trend was also observed for fewer words generated among BPD patients. In addition, BPD patients recalled fewer digits on Digit Span overall, including recollection of digits in forward order (Forward) and in reverse order (Backward), which led to lower Total Digit Span scores.

On the remaining measures, BPD patients also tended to demonstrate reduced performance. Despite similar scores on the copy condition of the ROCF, they exhibited slightly lower scores on the immediate recall condition, and achieved significantly lower scores on delayed recall relative to the HCs. On the CVLT, BPD patients recalled fewer words during the initial learning trial (Trial 1), as well as across all five trials (Trial 1–5 Total Correct), and after the Long Delay. They also used less semantic clustering on the CVLT across the five trials (Trial 1–5 Total Semantic Clusters). No significant differences in performance were apparent on the HVOT.

HC vs BP: Effects of BPD on cognition (exclusive of MJ use). Post hoc analyses from a three-way ANCOVA comparing HC, BP and MJBP patients revealed that, relative to HCs, the non-MJ smoking BP participants (BP group only) demonstrated similar deficits when examined separate from the MJBP group as when grouped with MJBP participants (see Table 5). The BP group exhibited poorer performance across the majority of assessment measures. Non-MJ smoking BP patients achieved significantly fewer categories on the WCST; they also made more perseverative errors, and had more losses of set, although this did not reach the threshold for significance. Participants in the BP group also made more errors on the Stroop Color Naming and Word Reading subtests. They took significantly longer to complete Trails B, and exhibited a trend for more Trails B errors. Further, they recalled slightly fewer digits across on Digit Span Backwards, which contributed to significantly lower scores on the Total Digit Span scores among BPD patients relative to HCs. On the CVLT, the BP group recalled fewer words than

Table 5. Neuropsychology Data and Between-Groups Comparisons: ANCOVAs (controlling for age) of the 2-group (HC v All BP) and 3-group (HC, BP, and MJBP) comparisons (2-tailed).

Variable	HC	All BP	BP	MJBP	2-group ANCOVA HC v All BP		3-group ANCOVA HC v BP v MJBP		Scheffé All Pairwise Post Hoc Comparisons		
					F	*p* (η^2)	*F*	*p* (η^2)	HC vs BP	HC vs MJBP	BP vs MJBP
n	21	30	18	12	-	-	-	-	-	-	-
WCST											
Total Categories	9.30 *(0.98)*	8.21 *(1.26)*	8.29 *(1.31)*	8.08 *(1.24)*	**9.598**	**.003 (.173)**	**4.858**	**.012 (.178)**	**.041**	**.023**	NS
Total Perseverations	6.40 *(4.44)*	10.72 *(7.30)*	10.00 *(7.16)*	11.75 *(7.69)*	**5.718**	**.021 (.111)**	2.996	.060 (.118)	NS	.080	NS
Total Losses of Set	0.15 *(0.37)*	0.59 *(0.87)*	0.59 *(0.87)*	0.58 *(0.90)*	**4.694**	**.035 (.093)**	2.318	.110 (.093)	NS	NS	NS
Stroop											
Color Naming Time (sec)	49.60 *(7.47)*	54.33 *(9.01)*	52.17 *(7.29)*	57.58 *(10.61)*	**4.148**	**.047 (.081)**	**3.444**	**.040 (.130)**	NS	**.038**	NS
Color Naming Errors	0.55 *(1.00)*	1.37 *(1.33)*	1.67 *(1.50)*	0.92 *(0.90)*	**5.495**	**.023 (.105)**	**4.811**	**.013 (.173)**	**.021**	NS	NS
Word Reading Time (sec)	38.95 *(4.39)*	42.10 *(5.82)*	41.56 *(5.95)*	42.92 *(5.78)*	**6.539**	**.014 (.122)**	**3.201**	**.050 (.122)**	NS	NS	NS
Word Reading Errors	0.35 *(0.59)*	0.93 *(1.05)*	1.11 *(1.08)*	0.67 *(0.98)*	**5.041**	**.029 (.097)**	**3.781**	**.030 (.141)**	**.039**	NS	NS
Interference Time (sec)	85.75 *(15.60)*	91.63 *(15.94)*	89.56 *(16.13)*	94.75 *(15.82)*	2.763	.103 (.056)	1.435	.248 (.059)	NS	NS	NS
Interference Errors	2.10 *(1.94)*	2.03 *(2.11)*	2.33 *(2.35)*	1.58 *(1.68)*	0.046	.831 (.001)	1.172	.319 (.048)	NS	NS	NS
Trail Making Test											
A Time (sec)	20.85 *(6.29)*	24.07 *(8.55)*	23.33 *(6.45)*	25.17 *(11.24)*	1.919	.173 (.039)	1.160	.322 (.048)	NS	NS	NS
A Errors	0.10 *(0.31)*	0.30 *(0.53)*	0.39 *(0.61)*	0.17 *(0.39)*	3.351	.074 (.067)	**3.655**	**.034 (.137)**	NS	NS	NS
B Time (sec)	38.85 *(11.21)*	54.23 *(19.86)*	55.50 *(21.75)*	52.33 *(17.38)*	**7.670**	**.008 (.140)**	**3.770**	**.030 (.141)**	**.016**	NS	NS
B Errors	0.15 *(0.49)*	0.40 *(0.62)*	0.56 *(0.70)*	0.17 *(0.39)*	0.992	.663 (.004)	1.356	.268 (.056)	.093	NS	NS
COWAT											
Total (FAS)	47.65 *(8.78)*	39.14 *(11.58)*	38.25 *(11.69)*	40.20 *(11.98)*	**7.318**	**.010 (.158)**	**3.835**	**.030 (.168)**	.060	NS	NS
Semantic Category	26.45 *(5.42)*	22.59 *(4.82)*	22.25 *(5.67)*	23.00 *(3.80)*	3.146	.084 (.075)	1.552	.225 (.076)	NS	NS	NS
Digit Span											
Forward	9.80 *(2.09)*	8.50 *(2.35)*	8.24 *(2.54)*	8.91 *(2.07)*	**4.262**	**.045 (.087)**	2.681	.080 (.109)	NS	NS	NS
Backward	8.85 *(2.50)*	7.18 *(1.87)*	7.18 *(2.24)*	7.18 *(1.17)*	**9.792**	**.003 (.179)**	**5.063**	**.010 (.187)**	.077	NS	NS
Total	18.65 *(4.06)*	15.68 *(3.58)*	15.41 *(4.06)*	16.09 *(2.81)*	**8.993**	**.004 (.167)**	**5.009**	**.001 (.185)**	**.046**	NS	NS
ROCF											
Copy	33.00 *(2.92)*	30.93 *(3.71)*	31.04 *(4.45)*	30.80 *(2.79)*	2.491	.123 (.063)	1.325	.278 (.069)	NS	NS	NS
Immediate	22.69 *(7.55)*	16.93 *(7.30)*	16.83 *(8.26)*	17.05 *(6.41)*	3.019	.091 (.075)	1.778	.184 (.090)	NS	NS	NS

(Continued)

Table 5. (*Continued*)

Variable	HC	All BP	BP	MJBP	2-group ANCOVA HC v All BP		3-group ANCOVA HC v BP v MJBP		Scheffé All Pairwise Post Hoc Comparisons		
					F	*p* (η^2)	*F*	*p* (η^2)	HC vs BP	HC vs MJBP	BP vs MJBP
n	21	30	18	12	-	-	-	-	-	-	-
Delay	22.81 *(6.82)*	16.68 *(6.58)*	16.63 *(6.91)*	16.75 *(6.54)*	**4.957**	**.031 (.118)**	2.660	.084 (.129)	.062	.091	NS
CVLT											
Trial 1 Correct	8.25 *(1.89)*	6.46 *(1.91)*	6.88 *(1.83)*	5.82 *(1.94)*	**8.997**	**.004 (.167)**	**6.005**	**.005 (.214)**	NS	**.005**	NS
Total Correct	61.10 *(8.14)*	51.18 *(10.53)*	53.35 *(11.75)*	47.82 *(7.61)*	**10.182**	**.003 (.185)**	**7.192**	**.002 (.246)**	.057	**.002**	NS
Total Perseverations	4.75 *(5.44)*	5.57 *(4.76)*	5.29 *(4.78)*	6.00 *(4.94)*	0.331	.568 (.007)	0.212	.810 (.010)	NS	NS	NS
Total Intrusions	1.60 *(2.14)*	1.11 *(2.74)*	0.53 *(1.23)*	2.00 *(4.05)*	0.669	.418 (.015)	2.130	.131 (.086)	NS	NS	NS
Total Semantic Clusters	27.10 *(11.09)*	18.57 *(13.01)*	21.47 *(14.82)*	14.09 *(8.34)*	**4.393**	**.042 (.089)**	**4.262**	**.020 (.162)**	NS	**.023**	NS
Long Delay Correct	13.90 *(1.68)*	10.64 *(3.68)*	10.65 *(4.14)*	10.64 *(3.04)*	**10.328**	**.002 (.187)**	**5.239**	**.009 (.192)**	**.009**	**.024**	NS
HVOT											
Total	26.56 *(1.76)*	26.41 *(1.88)*	25.71 *(2.03)*	27.25 *(1.34)*	0.016	.901 (<.001)	2.063	.142 (.103)	NS	NS	NS

WCST = Wisconsin Card Sorting Test, ROCF = Rey-Osterrieth Complex Figure, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, HVOT = Hooper Visual Organization Test.

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HCs on the CVLT across all five trials and after a delay. On the COWAT and ROCF, although results were not significant, the BP group demonstrated several trends for worse performance, as noted in Table 5. No deficits were noted the HVOT between HCs and the BP group.

HC vs MJ: Effects of MJ use on cognition (exclusive of BPD diagnosis). Similar to our previous report of MJ smokers [43], two-way ANCOVAs directly comparing MJ smokers to HCs demonstrated that pure MJ smokers exhibited impairment on a number of tasks relative to HCs, including the WCST, Trail Making Test, COWAT, and CVLT (See Table 6). Specifically, as noted in the BPD patients, MJ smokers demonstrated poorer executive functioning relative to controls. They achieved fewer categories and made more perseverative errors on the WCST, and took longer to complete Trails B of the Trail Making Test. MJ smokers generated fewer words than HCs on the COWAT when asked to provide words in a given semantic category. On the CVLT, although MJ smokers recalled a similar number of correct words, they had more Intrusions (incorrect responses) and utilized less semantic clustering across trials (Total Semantic Clusters). HC and MJ participants did not differ significantly with regard to their performance of the Stroop Color Word Test, Digit Span, ROCF, or HVOT.

HC vs MJBP and BP vs MJBP: Potential additive effects of BPD and MJ use. Post hoc analyses from three-way ANCOVAs (HC vs BP vs MJBP) designed to detect potential additive effects of BPD and MJ use revealed that MJBP patients demonstrated some areas of poorer cognitive performance relative to HCs (see Table 5, HC vs MJBP). They achieved fewer categories on the WCST and their performance suggests a trend for making more perseverative errors on this task. On the Stroop, significantly slower times were noted relative to HCs on the Color Naming subtest, while on the CVLT, MJBP participants recalled significantly fewer words

Table 6. Neuropsychology Data and Between-Groups Comparisons: ANCOVAs (controlling for age differences) of the 2-group (HC v MJ) comparisons (1-tailed).

Variable	HC	MJ	2-group ANCOVA	
			F	*p* (η^2)
n	20	23		
WCST				
Total Categories	9.30 (0.98)	8.73 (1.55)	6.746	.007 (.147)
Total Perseverations	6.40 (4.44)	10.50 (8.55)	12.680	.001 (.245)
Total Losses of Set	0.15 (0.37)	0.36 (0.73)	2.502	.061 (.060)
Stroop Color Word Test				
Color Naming Time (sec)	49.60 (7.47)	52.26 (8.43)	1.449	.118 (.035)
Color Naming Errors	0.55 (1.00)	1.09 (1.12)	2.281	.070 (.054)
Word Reading Time (sec)	38.95 (4.39)	39.65 (4.51)	0.256	.308 (.006)
Word Reading Errors	0.35 (0.59)	0.43 (0.59)	0.248	.311 (.006)
Interference Time (sec)	85.75 (15.60)	86.96 (14.50)	0.273	.302 (.007)
Interference Errors	2.10 (1.94)	2.65 (2.25)	0.802	.188 (.020)
Trail Making Test				
A Time (sec)	20.85 (6.29)	20.95 (4.53)	0.122	.365 (.003)
A Errors	0.10 (0.31)	0.18 (0.39)	0.231	.317 (.006)
B Time (sec)	38.85 (11.21)	50.50 (22.65)	**4.784**	**.018 (.109)**
B Errors	0.15 (0.49)	0.32 (0.48)	0.863	.180 (.022)
COWAT				
Total (FAS)	47.65 (8.78)	48.45 (11.43)	0.035	.426 (.001)
Semantic Category	26.45 (6.42)	21.86 (5.59)	**7.134**	**.006 (.155)**
Digit Span				
Forward	9.80 (2.09)	9.78 (2.39)	0.010	.462 (<.001)
Backward	8.85 (2.50)	8.70 (2.24)	0.113	.370 (.003)
Total	18.65 (4.06)	18.48 (3.82)	0.021	.443 (.001)
ROCF				
Copy	33.00 (2.92)	32.72 (3.33)	0.206	.327 (.005)
Immediate	22.69 (7.55)	22.42 (7.01)	0.078	.391 (.002)
Delayed	22.81 (6.82)	22.07 (6.65)	0.239	.314 (.006)
CVLT				
Trial 1 Correct	8.25 (1.89)	7.39 (2.41)	2.381	.065 (.056)
Total Correct	61.10 (8.14)	57.52 (8.95)	2.717	.054 (.064)
Total Perseverations	4.75 (5.44)	5.57 (5.47)	0.155	.348 (.004)
Total Intrusions	1.60 (2.14)	0.57 (0.90)	**3.637**	**.032 (.083)**
Total Semantic Clusters	27.10 (11.09)	21.61 (8.52)	**4.347**	**.022 (.098)**
Long Delay Correct	13.90 (1.68)	13.09 (3.13)	2.596	.058 (.061)
HVOT	26.56 (1.76)	26.80 (2.18)	0.133	.359 (.004)

WCST = Wisconsin Card Sorting Test, ROCF = Rey Osterrieth Complex Figure, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, HVOT = Hooper Visual Organization Test

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during Trial 1, throughout all five learning trials, and after a 20-minute delay. MJBP participants also had fewer semantic clusters on the CVLT. On the ROCF, like the pure BP group, MJBP participants exhibited a trend for lower scores on the Delayed Recall; however, they did not exhibit impairment on the remaining conditions of the task, nor did they demonstrate impaired performance on the Trail making Test, Digit Span, or HVOT relative to HCs.

Although BPD patients and MJ smokers each demonstrated impairment on several measures of cognitive performance relative to HCs, *no differences emerged* when directly comparing the BP and MJBP groups (see Table 5, BP vs MJBP). In fact, Scheffé all pairwise post hoc comparisons revealed no significant between-group differences for BP vs MJBP participants for any task: WCST, Stroop, Trail Making Test, COWAT, CVLT, ROCF, Digit Span, or HVOT.

Discussion

The current investigation, to our knowledge, marks the first study to examine the effects of MJ on both mood and neuropsychological performance in BPD patients. As the nation explores indications for medical MJ (MMJ), it is imperative to determine how MJ use might affect clinical symptoms in those diagnosed with mood disorders, such as BPD. In addition, given the fact that cognitive decrements are well-documented in both MJ smokers [43, 62–64] and those with BPD [39, 65], it is critical to examine whether these impairments may be exacerbated or possibly ameliorated by the combination of a BPD diagnosis and regular MJ use. Through the utilization of proper control groups (achieved by including four discrete groups: healthy controls, MJ smokers with no Axis I pathology, non-MJ smoking BP patients, and MJ-smoking BP patients), the current study was able to begin to clarify both the individual effects and potential for additive effects of MJ use and BPD on mood and cognition.

As hypothesized, our findings suggest that after smoking MJ, BPD patients experienced improvement in several aspects of clinical state secondary to MJ use. In fact, direct analyses of the MJ-smoking BPD patients (MJBP) *before* and *after* MJ use revealed notable symptom alleviation within four hours of smoking. After smoking MJ, the MJBP group reported significantly lower scores of anger, tension, depression (POMS and MADRS), as well as higher levels of vigor, which led to a marked decrease in TMD scores (22.39 to 11.15), a composite measure of overall mood on the POMS. Further, prior to smoking MJ, the MJBP participants reported slightly worse levels of symptomatology relative to the pure BP group, with higher levels of depressive and manic symptoms. In contrast, after MJ use, the MJBP group demonstrated considerably *lower* levels of tension and lower TMD scores relative to the BP group. In addition, although depression (MADRS) and mania scores were still slightly higher in the MJBP group after MJ use relative to the BP group, scores dropped to levels that were no longer significant or approaching significance between the two groups, highlighting positive changes in mood-related symptoms. In addition, average mood ratings across the course of the study showed that overall mood was comparable between MJBP and BP subjects. Although MADRS scores were generally elevated in MJBP patients, POMS scores for depression were similar between groups (and were actually marginally lower within MJBP participants). As the MADRS reflects specific depressive symptoms, as compared to the POMS which measures self-perceived mood, results may indicate that while certain depressive symptoms were more evident in MJBP participants relative to BP participants, a *self-perceived* mood of depression (i.e., feeling sad, lonely, blue) was not more prevalent in MJBP participants.

To some extent, these findings support recent work, which found that MJ use was correlated with increased positive affect in BPD patients [66]. However, the authors also observed a relationship between MJ use and increased manic and depressive symptoms. Although the authors of this study report both positive and negative fluctuations in clinical symptoms, they posit that bidirectional effects of MJ use, outlined by Ashton and colleagues [22], are likely impacted by a range of factors, including dose, mode of use, and personality differences. In addition, as we learn more about the differential effects of individual constituents of MJ, (i.e., THC vs cannabidiol [CBD]), it is possible that strains higher in certain constituents are at least partially

responsible for the moderation of specific dimensions of clinical symptoms. Some research suggests that CBD may be beneficial in alleviating, anxiety, psychosis, and other psychological symptoms [67–70] and may have a pharmacological profile similar to that of antipsychotic medications [69], which are often prescribed to patients with bipolar I disorder. Further, CBD has been shown to be an effective anticonvulsant treatment for those with pediatric seizure disorders [70], another class of drugs frequently prescribed for mood stabilization in patients with BPD.

Interestingly, among pure MJ smokers (those not diagnosed with BPD), beneficial effects on mood were *not* observed in the current study. MJ smokers reported decreases in vigor, as well as higher levels of confusion, fatigue and TMD after smoking, consistent with effects commonly reported in the general population after MJ use. It is of note, however, that MJ smokers continued to exhibit very low levels of mood-related symptoms even after MJ use, suggesting that while their mood did appear to worsen slightly after using MJ, these changes remained far below clinical thresholds. Overall, results may indicate that MJ use may have unique effects in BPD patients, effects which are not necessarily observed in those without Axis I pathology.

With regard to cognitive performance, MJ smokers and BPD patients performed more poorly than HCs overall. However, within the BPD patients, impairment was observed *regardless* of MJ use status; deficits were apparent when the non-smoking BP patients were analyzed as a whole group (BP and MJBP) as well as separately (BP vs MJBP). Overall, patients in both BPD groups demonstrated poorer performance on tasks of executive function. They also exhibited less efficient learning and recall strategies during a serial list-learning task, reduced verbal fluency, inferior attention and working memory, and poorer visuospatial organization. Interestingly, when the non-smoking BP group was compared to the MJBP group, no significant differences across any measure were noted. Taken together, study findings suggest that MJ use may result in at least short-term mood term stabilization for a subset of BPD patients, and further, that MJ use does not have an additive, negative impact on cognitive performance in BPD patients.

These findings provide a valuable contribution to the field, which has only begun to clarify the effects of MJ on mood and cognition in psychiatric populations. While many would posit that the individual relationships between cognitive impairment and both MJ use and BPD would collectively result in a *more severe impact* on cognitive function, some studies have actually reported a cognitive advantage in BPD patients who use MJ regularly [40–41]. In addition, a recent study of MJ-smoking patients diagnosed with schizophrenia found no evidence for an additive effect of MJ use and schizophrenia diagnosis on cognitive dysfunction [71]. In combination, these studies provide evidence that cognitive deficits associated with certain Axis I pathologies may not be worsened by MJ use. In fact, improved cognitive performance may be related to the potential anxiolytic effects of MJ. Anxiety, common in BPD patients [72], often interferes with attention and the ability to encode information, suggesting that if MJ acts as an anxiolytic in at least a subset of patients, this may result in better concentration and enhanced cognitive performance.

Despite these positive changes, one previous study also observed that patients tended to experience improved cognitive performance at the expense of a more severe clinical course [41]. While the current study did not examine long-term treatment outcomes, our preliminary findings provide evidence that BPD patients who smoke MJ may derive at least a short-term clinical benefit. MJBP participants reported improvements in mood within four hours of smoking MJ, did not have elevated average mood ratings (with the exception of the MADRS) relative to the BPD group across the four-week study, and did not experience additional cognitive deficits when compared to the non-smoking BP group. Future studies will need to be conducted in order to investigate the effect of MJ use on clinical course over longer durations of time.

Limitations

Data from the current study provide critical information about MJ use in psychiatric populations, as guidelines regarding indications for medical MJ are considered; however, these findings must be interpreted in light of several limitations. First, although this study served as a pilot investigation, it is important to acknowledge that the overall sample is moderate in size, with a modest number of patients completing EMA ratings, which may limit the generalizability of findings. For example, only participants who were well characterized as chronic, heavy MJ smokers were enrolled in the current study; participants with less frequent use (i.e., casual MJ smokers) may not experience the same effects of MJ on mood and cognition as observed in this sample of participants. Further, rather stringent enrollment criteria were employed, which excluded participants who reported comorbid diagnoses (via phone interview or through the clinical interview). In addition, participants were required to be predominantly euthymic throughout the course of the study. Although these criteria limited the effects of extraneous variables, the impact of MJ on mood and cognition may differ in those who have been diagnosed with comorbid disorders (i.e., ADHD, PTSD, polysubstance use, etc.) or who may be experiencing more acute clinical symptomatology. Finally, likely related to the geographic region from which patients were recruited (the Greater Boston area is home to many universities, hospitals, and research institutions), participants generally demonstrated higher than average IQs. This may limit generalizability to populations with average to below average cognitive abilities. It will be important for future studies to recruit larger numbers of research participants to further investigate the impact of MJ on mood and cognition in BPD, as well as to examine additional factors that were not explored in the current pilot investigation.

Additionally, although the four groups were not statistically matched for sex (more males were enrolled than females in the MJ and MJBP groups), it is likely that the sex distribution of this sample is actually representative of the larger population. In fact, national surveys of substance-using populations have revealed that males engage in the use of illicit substances, including MJ, more frequently than females [73–74].

Regarding the EMA study design, overall compliance was very high among all study groups with an overall completion rate of 88% of all possible scheduled ratings. Several measures were also put in place to encourage completion of ratings after MJ use, including comparing reported frequency of MJ use during interim visits to the frequency of EMA ratings. However, given the nature of EMA data, it is not possible to guarantee that all participants completed mood ratings immediately after MJ use. In an attempt to address this issue, all participants were asked to adjust the time of last use if necessary, and any ratings reported more than four hours after MJ use were not coded as post-use data. While this four-hour window was selected to capture the acute effects of MJ use on mood, the duration of MJ effects are likely related to a range of factors including, but not limited to the specific product used (i.e. high THC/low THC), amount and frequency of use, mode of use, and metabolism. It may therefore be an important consideration for future studies to explore whether the duration of MJ intoxication is related to the duration of reported symptom improvement by BPD participants.

Further, although this investigation examined the *acute* effects of MJ use in BPD patients, additional investigations should explore the potential long-term impact of MJ use on clinical state. It is of note that over the duration of the study, the overall average mood ratings for the MJBP and BP were not significantly different across any measure (except for the MADRS), which provides preliminary evidence that MJ use may not *directly* result in poorer clinical course. Higher levels of clinical severity previously reported in MJ-smoking BPD patients [4, 8, 11] may be a result of several factors, including a failure to inform clinicians of MJ use. As MJ may partially address mood-related symptoms, the pharmacotherapeutic regimen prescribed

by physicians may, as a result, be different from what would normally be prescribed. Additionally, any short-term improvement following MJ use may result in non-adherence with patients' prescribed medications, which could ultimately result in poorer long-term outcomes.

Due to the preliminary nature of the current study, the relationship between specific patterns or levels of MJ use and symptom improvement were not thoroughly investigated. In addition, all MJ using participants in the current study were chronic MJ users and results may therefore not be generalizable to more casual MJ users. Future investigations should consider the impact of frequency and amount of MJ smoked, as well as mode of use, and strain of MJ used on both cognition and symptomotology. In fact, several studies have shown promise for the alleviation of anxiety using MJ products that contain high levels of CBD [67–68]. Given that CBD is a non-psychoactive phytocannabinoid that has shown promise as an anxiolytic and anticonvulsant (often used to stabilize mood in patients with BPD), high CBD-containing products may afford more viable options than other cannabinoid-based treatments. Therefore, future studies should also aim to explore whether high-CBD relative to low-CBD strains have differential effects in BPD patients as well as other clinical populations.

Finally, it should be noted the current study design does not imply cause and effect, but rather shows a *relationship* between MJ use and mood improvement. Clinical trials will be needed in order to further investigate the potential for MJ and cannabinoid-containing products as a potential treatment for patients with BPD.

Conclusions

New legislation across the nation has increased the overall accessibility of MJ to the general public for both recreational and medical use. To date, 24 states and the District of Columbia have fully legalized medical marijuana and another 18 states have allowed the use of CBD-based products for medical use. Each state individually regulates the use of MMJ, and perhaps not surprisingly, a wide range of acceptable conditions are often listed as eligible for MMJ certification. While some states include a "catchall" category, allowing physicians to certify conditions at their discretion, other states employ a restrictive list of indications suitable for MMJ. Additional studies are needed to help shape public policy regarding conditions that may be amenable to MMJ treatment, especially with regard to psychiatric illnesses. The current study highlights preliminary evidence that patients with BPD who regularly smoked MJ reported at least short-term clinical symptom alleviation following MJ use, indicating potential mood-stabilizing properties of MJ in at least a subset of patients with BPD. Furthermore, despite previous research showing that MJ use and BPD individually can have a negative impact on cognition, MJ use in BPD patients may *not* result in additional impairment. Further research is warranted to explore the impact of MJ on mood in clinical and non-clinical populations.

Supporting Information

S1 File. Manuscript Database. Demographic, cognitive, and EMA raw data, which were analyzed for the current manuscript, are available and arranged by group (HC, MJ, BP, and MJBP).
(XLSX)

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Author Contributions

Conceived and designed the experiments: SG DO. Performed the experiments: SG MKD KS MD MR. Analyzed the data: SG MKD KS. Wrote the paper: KS SG MKD.

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Clinical overview

Endocannabinoid system dysfunction in mood and related disorders

Ashton CH, Moore PB. Endocannabinoid system dysfunction in mood and related disorders.

Objective: The endocannabinoid (EC) system is widely distributed throughout the brain and modulates many functions. It is involved in mood and related disorders, and its activity may be modified by exogenous cannabinoids. This article examines the therapeutic potential of cannabinoids in psychiatric disorders.
Method: An overview is presented of the literature focussed on the functions of the EC system, its dysfunction in mood disorders and the therapeutic potential of exogenous cannabinoids.
Results: We propose (hypothesize) that the EC system, which is homoeostatic in cortical excitation and inhibition, is dysfunctional in mood and related disorders. Anandamide, tetrahydrocannabinol (THC) and cannabidiol (CBD) variously combine antidepressant, antipsychotic, anxiolytic, analgesic, anticonvulsant actions, suggesting a therapeutic potential in mood and related disorders. Currently, cannabinoids find a role in pain control. Post mortem and other studies report EC system abnormalities in depression, schizophrenia and suicide. Abnormalities in the cannabinoid-1 receptor (CNR1) gene that codes for cannabinoid-1(CB1) receptors are reported in psychiatric disorders. However, efficacy trials of cannabinoids in psychiatric disorders are limited but offer some encouragement.
Conclusion: Research is needed to elucidate the role of the EC system in psychiatric disorders and for clinical trials with THC, CBD and synthetic cannabinoids to assess their therapeutic potential.

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Key words: cannabis; endocannabinoid system; anandamide; mood and related disorders

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Clinical recommendations

Laboratory studies

- Laboratory and *post mortem* investigations are required to determine the blood concentrations of anandamide and other endocannabinoids in mood and related disorders.
- Cannabinoid 1 (CB_1) receptor density and distribution in key brain areas should be examined in mood and related disorders.
- Polymorphism of the CB_1 gene should be determined in mood and related disorders.

Clinical studies

- Clinical trials of cannabinoids such as tetrahydrocannabinol (THC), cannabidiol (CBC) and synthetic cannabinoids should be instigated in mood and related disorders. For some applications, cannabinoids may be used individually; for others, the ratio of THC : CBD may need to be optimized.

Additional comments

- Many other neurotransmitters are known to be dysfunctional in mood and related disorders. Manipulation of these has led to important therapeutic advances.
- However, the endocannabinoid (EC) system interacts with and modulates the actions of many of these systems.
- Endocannabinoid dysfunction would cause secondary changes in the activity of other neurotransmitters, including monoamines, serotonin, opioids and other excitatory and inhibitory neurotransmitters, and may link changes in these systems.

Introduction

Numerous neurotransmitter systems operate in the human brain, some of which are primarily executive (glutamate, gamma aminobutyric acid, GABA), whereas others are mainly modulatory. Several modulatory systems are located in specific pathways (e.g. the monoamine systems) but others are distributed more diffusely throughout the brain. The cannabinoid system in the brain (the endocannabinoid system) is one such system. Its functions are becoming increasingly understood.

In this paper, we offer an overview of current knowledge of the endocannabinoid system comprising specific Cannabinoid 1 and 2 receptors (CB_1, CB_2), natural ligands (anandamide and others) and enzymes for their biosynthesis and inactivation. We discuss how endocannabinoids act as a homoeostatic mechanism preventing extremes of cortical excitation or inhibition. Knowledge of the principal plant cannabinoids (THC and CBD) is summarized.

In addition, we evaluate the preclinical and clinical evidence of endocannabinoid involvement in psychiatric and related disorders and present a hypothesis that this system is dysfunctional in a range of psychiatric disorders. Finally, we suggest that plant or synthetic cannabinoids may have a therapeutic value in these conditions.

Aims of study

The aim of this study was to provide an overview of the actions of the EC system and evidence of its dysfunction in mood and related disorders. A hypothesis is offered to explain the role of the EC system in psychiatric disorders. We examine the therapeutic potential of these agents in psychiatric disorders.

Material and methods

An overview of the current literature on the function of the endocannabinoid system, its dysfunction in mood and related disorders and the action of exogenous cannabinoids was undertaken. The potential therapeutic action of these agents in treating mood and related disorders was explored.

Results

The endocannabinoid system

As described by Perry and Young (1), the general level of cortical excitability is determined by the 'chief executive' neurotransmitters GABA (gamma aminobutyric acid) and glutamate. Interacting with this primary control mechanism is a series of modulatory systems mediated by acetylcholine, monoamines, serotonin, histamine and others. Many of these originate in discrete subcortical nuclei but have widespread cortical connections. A further series of diffusely distributed linked interacting modulatory systems include neuropeptides such as endorphins, adenosine, nitric oxide and the endocannabinoid system.

Of the modulator systems that influence every conscious thought and feeling, possibly the most powerful is the endocannabinoid system. This system, which has been fully described by many authors (2–4), consists of specific cannabinoid receptors (CB_1, CB_2 and probably others), their natural ligands (anandamides and others) and specific enzymes for their biosynthesis and inactivation. In humans, this system modulates many vital functions including those associated with consciousness (cognition, learning, memory, perception, mood, sleep, pain, appetite, reward, motivation) and many that do not normally reach consciousness (motor control, cardiovascular regulation, endocrine activity, metabolism, immune reactions) (3, 5, 6). The system interacts closely with other modulators, particularly endogenous opioids, and influences the activity of most neurotransmitters including GABA and glutamate. It is tonically active and important in the control of neuronal excitability and in maintaining the balance between excitation and inhibition in the brain (7). The endocannabinoid system probably operates mainly as an undercurrent of brain activity below the level of consciousness but the tone of the system, 'endocannabinoid tone', influences con-

scious perceptions and affects mood and behaviour and their physical accompaniments (8).

Mechanisms of action. The underlying mechanism of endocannabinoid action consists of the interaction of specific cannabinoid receptors (CB_1, CB_2) with their endogenous ligands such as anandamide (N-arachydonyl-ethanolamine) and 2AG (2-arachydonyl-glycerol) (9, 10). The main cannabinoid receptor in the brain is the CB_1 receptor. This receptor is widely distributed including cerebral cortex especially frontal cortex, limbic system including hippocampus and amygdala, sensory and motor areas and hypothalamus, pons and medulla (11). There are more CB_1 receptors in the brain than all the dopamine, noradrenaline and serotonin receptors combined and ten times more than opioid receptors (12). Anandamide and 2-AG, the natural ligands, are present in the same areas as CB_1 receptors (13). Unlike monoamine neurotransmitters, they are not stored in vesicles but are synthesized through various enzymatic pathways (13) in postsynaptic neural membranes and released at discrete loci 'on demand' following physiological stimuli such as neuronal depolarisation. After release from the postsynaptic membrane, they act retrogradely as agonists on CB_1 and CB_2 receptors and are then rapidly inactivated by enzymatic hydrolysis and neuronal reuptake (14, 15).

Cannabinoid 1 receptors are presynaptic metabotropic receptors coupled to a G-protein. Signal transduction through these receptors is shown in Fig. 1. The final result of their activation is the inhibition of neuronal depolarisation, decreased action potential generation, decreased release of neurotransmitters, either excitatory or inhibitory, and hence reduced impulse propagation. Other receptors, including those for monoamines or opioids, located on the same neurones as CB_1 receptors (Fig. 1), may share common mechanisms, thus setting the scene for interactions between the different modulator systems.

Cannabinoid 2 receptors are mainly distributed in immune tissues and inflammatory cells including spleen, tonsils, thymus, lymphocytes and macrophages (16), although some are present in the brain. They are metabotropic receptors similar to CB_1 receptors and are also activated by anandamide and 2-AG. CB_2 receptors play an important part in pain and inflammation and are dramatically up-regulated in inflamed tissues (17), modulating pain by decreasing the release of nociceptive agents such as substance P and histamine.

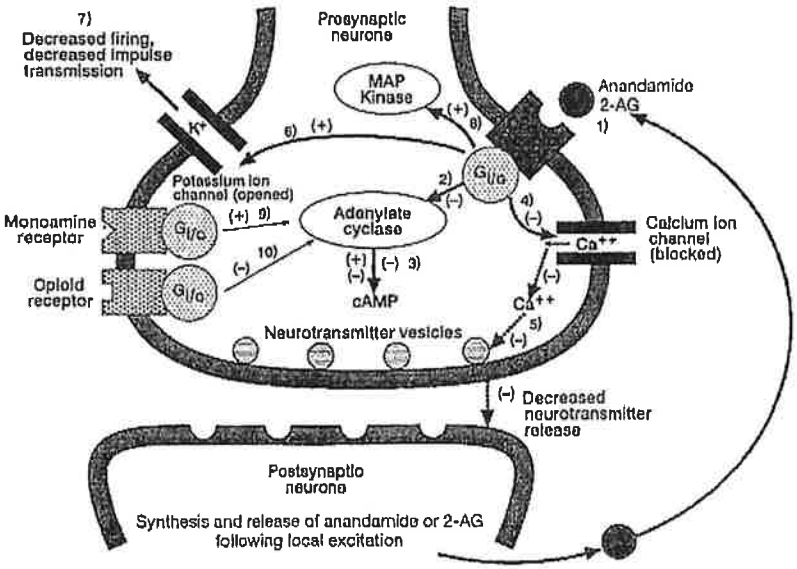

Fig. 1. Signal transduction mechanisms mediated by CB_1 receptors. Local excitation of a postsynaptic neurone triggers the synthesis of anandamide or 2-arachydonyl-glycerol which are released into the extracellular space and act retrogradely as agonists on presynaptic CB_1 receptors, which also may be activated by exogenous cannabinoids. The principal pathway is highlighted in red: the CB_1 receptor 1) is coupled to a second messenger $G_{i/o}$ protein. Via this protein, activation of the receptor inhibits the enzyme adenylate cyclase 2) and decreases the production of cAMP 3). Via the G-protein, the inward flow of calcium ions is blocked 4), decreasing the release of neurotransmitters 5). Also via the G-protein, the outward flow of potassium ions is enhanced 6), resulting in decreased neuronal firing and decreased impulse transmission 7). Stimulation of the G-protein also activates MAP kinase 8), affecting intracellular gene expression. Other receptors on the same neurone (for monoamines and/or opioids) may activate their own G-proteins but share a common adenylate cyclase, which they may stimulate 9) or inhibit 10). (Christie and Vaughan, 2001; Alger, 2004) (14, 15).

Other cannabinoid receptors include the transient receptor potential vanilloid-1 ($TRPV_1$) receptor that is involved in pain and inflammation and is activated by capsaicin and also by anandamide (18) and the recently cloned (19) G-protein-coupled receptor-55 (GPR55), which may be involved in anxiety modulation (20).

In many ways, the endocannabinoid system acts as a kind of 'dimmer switch' which protects the brain from being overwhelmed by excessive excitatory or inhibitory activity. If this system is dysfunctional, extremes of cortical excitation or inhibition may occur leading to neuropsychological states such as mania or hyperarousal at one extreme and depression, anhedonia or apathy on the other. The particular state or combination of states that occur may depend on individual differences in the activity of other receptors or neurotransmitters, for example, decreased brain density of GABA/benzodiazepine receptors has been demonstrated in subjects with anxiety disorders (21) and decreased serotonergic activity may account for some depressive disorders. The intrinsic tone of the endocannabinoid system may also be a major contributor to the spectrum of personality characteristics in normal individuals and their vulnerability to mood disorders.

Cannabis

At least two constituents of the cannabis plant (*cannabis sativa*) activate the endocannabinoid system. Δ^9-Tetrahydrocannabinol (THC) is a direct agonist of CB_1 and CB_2 receptors, while cannabidiol (CBD) inhibits the inactivation and reuptake of anandamide (22, 23) but antagonizes CB_1 and CB_2 receptor agonists and has several other actions described later (24). When cannabis is smoked or ingested, both THC and CBD are widely distributed, stimulating simultaneously cannabinoid receptors in all areas. In addition, both are very slowly eliminated over several days (25–28). This wide distribution and slow elimination is in sharp contrast to the physiological localized release and rapid inactivation of anandamide and 2-AG. The effects of cannabis, especially in high doses, override the delicate balance within the endocannabinoid system and can lead to adverse effects. Yet many individuals take cannabis in moderate doses to alleviate symptoms such as depression and mania in bipolar disorder (11) and pain and spasticity in multiple sclerosis (29).

Actions of THC. The effects of cannabis, mainly ascribed to THC, have been described by many authors (11, 30) and are summarized by Ashton et al. (11). Many of these effects are biphasic and bidirectional depending on dose, mode of administration, environment, expectation, personality, degree of tolerance, time after dose and other individual factors. Small to moderate doses produce euphoria, anxiolytic, sedative/hypnotic, myorelaxant and analgesic effects. In healthy subjects, THC, 5 and 10 mg smoked in herbal cigarettes under placebo-controlled conditions, produced relaxation and decreased subjective ratings of anxiety, tension and depression (31). Patients using cannabis or synthetic THC compounds (dronabinol, nabilone) for chronic pain conditions or multiple sclerosis report improvement of mood and increased general wellbeing and mental health as well as improved sleep, relief of pain and spasticity and anxiolytic effects (32–38). Many anecdotal reports attest to the calming and antidepressant effects of cannabis in bipolar affective disorder (11, 39, 40).

Many of the adverse effects of cannabis result from high doses or rapid administration of THC or chronic cannabis use. Intravenous infusion of THC in normal subjects can induce transient psychotic symptoms, anxiety, detachment, perceptual distortion and cognitive impairment (41, 42). Smoked cannabis, especially varieties with high concentrations of THC, such as 'skunk', can cause acute psychosis, sometimes with hypomanic features, in previously normal individuals and may precipitate schizophrenia in genetically predisposed individuals (43). Chronic or repeated use of cannabis is associated with tolerance, dependence, a withdrawal syndrome (44) and possibly long-term cognitive impairment (45).

Actions of CBD. Cannabidiol has many actions, recently reviewed by Zuardi (24). These include anxiolytic, sedative/hypnotic, antipsychotic and anticonvulsant effects, and it antagonizes the intoxicant and psychomimetic actions of THC. Anxiolytic effects of CBD have been demonstrated in animal models utilizing the elevated plus maze (46). In humans, it has anxiolytic effects similar to diazepam in a simulated public speaking task (47) and decreases anxiety scores in other experimental studies reviewed by Crippa et al. (48). As with THC, biphasic sedative/hypnotic effects have been demonstrated in rodents (49–51). In humans, high doses of CBD (160–600 mg) increase sleep in insomniacs and healthy volunteers, but low doses (15 mg) have an alerting effect, increasing wakefulness during sleep and counteracting residual sedative effects of 15 mg THC (52).

Antipsychotic actions of CBD similar to the effects of haloperidol (53, 54) and of the atypical

antipsychotic clozapine (55) have been demonstrated in rodents. Antipsychotic effects are also suggested in human volunteers in experiments in which cannabis resin attenuated psychotic symptoms induced by nabilone (a synthetic THC analogue) (56) and ketamine (57). Recent studies (58) in normal subjects have shown that CBD and THC have opposite effects on regional cerebral blood flow, as measured by functional magnetic resonance imaging (fMRI) during several cognitive tasks, and that CBD blocks the induction of psychiatric symptoms induced by intravenous THC. In a few small studies, cannabis resin had a partial therapeutic effect in patients with schizophrenia (54, 59, 60). A preliminary report from a double-blind trial comparing CBD with amisulpiride in acute schizophrenic psychosis showed that both drugs were equally effective in reducing symptoms (56). CBD also significantly reduced psychotic symptoms evaluated by the Brief Psychiatric Rating Scale (BPRS) in six patients with psychosis and Parkinson's disease (61) and also reduced anxious-depression scores in these patients.

Cannabidiol has potent anticonvulsant effects in rodents, controlling pilocarpine and kainic acid–induced seizures (7, 62, 63). One small trial of CBD in epileptic patients with a temporal lobe focus gave promising results (64), but the clinical efficacy of CBD in epilepsy remains uncertain (24). Other actions of CBD discussed by Zuardi (24) include anti-inflammatory, anti-ischaemic, antiemetic, anticancer and immunosuppressive effects.

The mechanisms of action of CBD are also diverse. CBD antagonizes CB1 and CB2 receptor agonists at low concentrations, probably by a non-competitive action (24). CBD also antagonizes the activation of the GPR55 receptors (19). In addition, CBD is an agonist of the human 5-HT_{1A} receptor (65), an action that may be involved in its anxiolytic effects. Mechanisms of the other actions of CBD, mentioned elsewhere, are discussed by Zuardi (24).

A hypothesis

As described earlier, the endocannabinoid system is one of several neuromodulatory systems that closely interact at the cellular level (see Fig. 1). Changes in the functional activity of the endocannabinoid system can cause altered activity in the other neuromodulatory systems as well as imbalance in the primary GABA/glutamate control system. We hypothesize that dysfunction of the endocannabinoid system may result in neuropsychological disturbances leading to psychiatric disorders such as depression, anxiety states and psychosis. We discuss the evidence for this hypothesis later.

The endocannabinoid system in mood and related disorders

In psychiatry, mood disorders are generally classified separately as, for instance, 'depression' or 'anxiety disorder'. But there is a high degree of overlap or comorbidity in these states (66). Anxiety commonly accompanies depression and many people with anxiety states are also depressed; mixed states of depression and mania exist. Many people with schizophrenia have high anxiety levels, but many are depressed while others are overactive. Clearly, emotions are not separate, nor are they necessarily divisible.

The runner's high. An example of how the endocannabinoid system can simultaneously affect many different emotions is provided by the 'runner's high' (67, 68). This sensation is described by athletes, including runners, cyclists and marathon runners. Its components include 'pure happiness', elation, a sense of wellbeing, 'endless peacefulness', boundless energy, decreased anxiety, sedation (postexercise calm) and reduction in pain sensation. This experience has previously been ascribed to release of endorphins by exercise, but endorphins depress respiration and cause pinpoint pupils, reactions that are not seen in exercising individuals. Moreover, the evidence is derived from the measures of endorphins in peripheral blood, and endorphins do not readily cross the blood–brain barrier.

However, exercise (running or cycling for one hour at moderate intensity) causes a significant rise in the blood levels of anandamide, which does cross the blood–brain barrier, compared with non-exercising controls (67). Exercise makes 'demands' on many systems and presumably causes widespread, but specific, peripheral and central release of anandamide. The emotions experienced in the 'runner's high' are similar to those induced by cannabis and CB_1 receptor agonists such as THC (67, 68). These authors suggest that endocannabinoids, rather than endorphins, are important mediators of the 'runner's high'.

Yet, as described previously (Fig. 1), there is a close interaction between the endocannabinoid and endogenous opioid systems. Both cannabinoid and opioid receptors are present in the major reward pathways in the brain, and both increase dopamine release in the nucleus accumbens, an action common to all rewarding and addictive drugs (69). It is possible that their combined action may

not only account for the 'runner's high' but also for the addictive quality of regular exercise (and cannabis) and the withdrawal symptoms when regular exercise (or cannabis) is stopped.

Nevertheless, there is increasing evidence that dysfunction of the endocannabinoid system – which affects many mood states – may contribute to the psychopathology of psychiatric disorders and that cannabinoid receptor agonists may be of value in the treatment of such disorders.

Depression. A body of preclinical evidence, reviewed by Serra and Fratta (70), indicates that cannabinoid receptor agonists have antidepressant activity. For example, Hill and Gorzalka (71) showed that pharmacological stimulation of CB_1 receptors elicits antidepressant-like effects in the rat forced swimming test and that such stimulation also has similar effects to antidepressants on the rat Hypothalamic Pituitary Adrenal Axis (HPA) (72). Similar effects on the rat forced swimming test and the mouse tail suspension test are shown by [3-(3 carbanoylphenyl)phenyl]N-cyclohexylcarbamate (URB597) that inhibits the hydrolysis of anandamide (73). These effects are all blocked by CB_1 receptor antagonists. Furthermore, blockade of CB_1 receptors *per se* induces a state analogous to depression in the rat, including reduced food intake, heightened anxiety, increased wakefulness, deficits in the extinction of aversive memories and supersensitivity to stress (74). All the aforementioned authors propose that an endocannabinoid deficiency may underlie some of the symptoms of depression in humans.

Decreased endocannabinoid activity could account for the anhedonia, anxiety, decreased pain tolerance, chronic pain conditions and decreased serotonergic activity that often accompanies human depression, as well as the observation that the CB_1 receptor antagonist, rimonabant, causes depression and anxiety in a significant proportion of psychiatrically normal subjects (75). Conversely, cannabis is taken recreationally for pleasure. THC is euphorigenic in some doses (76) and improves mood in multiple sclerosis and chronic pain conditions (35–42). Euphoria and elation are also components of the 'runner's high' (67, 68), and exercise is known to lessen depression (77, 78).

There have been few direct investigations into endocannabinoid activity in depressed patients. However, Serra and Fratta (70) cite some preliminary suggestive evidence that serum concentrations of 2-AG and of anandamide are reduced in some patients with major depression, a decrease that correlates with duration of the depressive episode (73, 74, 79), and Koethe et al. (80) found a decrease in CB_1 receptor density in grey matter glial cells in the *post mortem* brains of patients with major depression. However, there appear to have been no formal clinical trials of cannabinoids in depression.

Pain. Chronic pain in humans is frequently associated with depression (81), and Beutler et al. (82) suggested that chronic pain patients and depressed patients share the characteristic of being unable to modulate intense feelings. An elaborate endocannabinoid system modulates pain responses at all levels of the nervous system from the periphery to the brain (83) (Fig. 2). The system involves CB_1 and CB_2 and other cannabinoid receptors and interacts with endogenous opioid systems and descending pain suppressant pathways mediated by monoaminergic and opioid neurotransmitters. The endocannabinoid system appears to be tonically active, while the endogenous opioid system is activated by intense or prolonged pain, although both systems become more active as pain intensity increases (84).

In rodents, microinjection of CB_1 agonists into pain processing areas in the brain suppresses pain responses, and electrical stimulation of periaqueductal grey causes a marked increase in the release of anandamides. Systemically administered CB_1 agonists inhibit activity in spinal dorsal horn neurones and decrease the release of pain-stimulating agents such as substance P

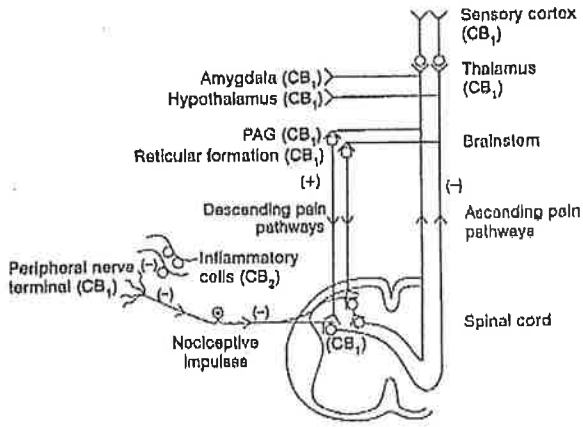

Fig. 2. Cannabinoid receptors in pain processing pathways. Cannabinoid CB_1 receptors are present on peripheral nerve terminals, dorsal horn spinal cord and pain processing pathways in the brain. Their activation inhibits activity in excitatory ascending pain pathways and stimulates activity in descending pain pathways. CB_2 receptors are present in blood cells associated with inflammation and may modulate pain initiation at site of tissue injury. (PAG = periaqueductal grey matter).

and glutamate. At peripheral nerve terminals, CB_1 receptors interact with CB_2 receptors where they modulate inflammation and pain responses (18, 85).

In humans, there is considerable evidence that cannabinoids alleviate many types of chronic intractable pain. These are reviewed by the British Medical Association (29), Russo (86) and Guindon and Hohmann (87) and are supported by many clinical studies in multiple sclerosis, chronic pain conditions and others (35–38, 88). The analgesic effect is separate from that of endogenous opioid systems, as exemplified by Hamann and diVadi (89) who described a patient with neuropathic pain that was controlled by the CB_1 receptor agonist nabilone but not by opioids, and the analgesic effect of nabilone was not reversed by the opioid antagonist naloxone.

Anxiety. Cannabinoid receptors are densely located in brain areas involved in emotional states, including amygdala, hypocampus and other limbic sites. Effects on anxiety are thought to be mediated mainly by CB_1 receptors but possibly also by CB_2 and GPR55 receptors. Recently, the CB_1 receptor has been shown to have a pivotal role in the anxiolytic actions of benzodiazepines in CB_1 knockout mice (90). In rodents, the levels of anandamide in the amygdala increase in a conditioned fear response (electric footshock) (91) and cannabinoid receptor activation decreases anxiety in a variety of rodent tests such as the elevated plus maze and others reviewed by Degroot (20), while cannabinoid receptor inactivation is anxiogenic. However, the latter effects are inconsistent and may depend on regional endogenous tone, species differences, type of test, dosage of cannabinoid receptor agonists and antagonists, and other factors (20). Endocannabinoids also exert an amnesic effect and are crucial for the extinction (forgetting) of aversive memories (91, 92), while blockade of the CB_1 receptor induces deficits on the extinction of aversive memories and supersensitivity to stress (74).

The preclinical evidence is borne out by human experience. Cannabis and THC have biphasic effects on anxiety, depending on dose, environment, personality and other factors, and can have anxiolytic or anxiogenic actions (11). In relation to anxiety states in humans, particularly in the recreational users of cannabis or in those who apparently take it as self-medication, the relation between cannabis use and anxiety is complex (reviewed by Crippa et al. 48). The many clinical reports of anxiolytic effects of cannabis are mentioned earlier (under *Actions of THC*) as well as the anxiolytic effects of CBD (under *Actions of CBD*). It has also been mentioned that decreased anxiety is a component of the 'runner's high' which is associated with increased anandamide concentrations (67, 68) and that the cannabinoid receptor antagonist, rimonabant, causes anxiety in psychiatrically normal subjects (75).

The amnesic effect of cannabis, even in small doses, has been demonstrated in a large variety of tests including immediate digit recall, prose material and word-picture combinations (93). The deficit appears to be because of impairment of memory acquisition and may result from defects in attention, inability to filter out irrelevant information and the intrusion of extraneous thoughts (45). The poor word recall of recreational cannabis users is well illustrated from many observations that their speech is frequently incoherent because they have forgotten what they said at the start of the sentence before they reach the end of it.

There appear to have been no investigations into endocannabinoid activity in anxiety, but preclinical and clinical data strongly suggest that anxiety is associated with decreased endocannabinoid tone. Increased endocannabinoid activity may be a mechanism to protect an individual from anxiety (excess cortical excitation) in stressful situations and, because of the amnesic effects, to prevent their after effects such as post-traumatic stress disorder (PTSD).

Suicide. Suicide is an unfortunate outcome of some psychiatric disorders. Depression, chronic pain, alcohol dependence and schizophrenia are reported in many of those who complete suicide, and about 15–20% of bipolar patients end their life in this way, of whom about 50% have marked depression (94). There is evidence from *post mortem* studies that elevated levels of endocannabinoids (anandamides and 2-AG) are present in the dorsal prefrontal cortex of depressed suicide victims and also in alcoholic suicides compared with controls and in the prefrontal cortex and anterior cingulate gyrus in schizophrenia (8, 95). All these conditions were associated with polymorphisms of the CNR1 gene that codes for CB_1 receptors (96, 97). There are numerous alleles of the CNR1 gene, including single nucleotide polymorphisms and triplet repeats (8). Some alleles are associated with schizophrenia, obesity-related phenotypes, binging/purging types of anorexia nervosa, substance abuse, depression and other disorders (8). It is not clear whether the changes found in suicide victims are causative or an indication of compensatory adaptations to initial low levels of endocannabinoids. Tzavara and Witkin (8) suggest that

sensitization of CB_1 receptors in the prefrontal cortex is a factor in the pathophysiology of suicide.

Schizophrenia. Köfalvi and Fritszche (95) review evidence concerning the endocannabinoid system and schizophrenia. Three studies cited in the review have demonstrated increased CB_1 receptor binding in the *post mortem* brains of patients with schizophrenia, involving the dorsolateral prefrontal cortex and the posterior cingulate cortex, areas that are implicated in the symptoms of schizophrenia. However, the evidence is conflicting as, in contrast, Eggan et al. (98) reported a significant reduction in the levels of CB_1 receptors in the dorsolateral prefrontal cortex in the post mortem brains of patients with schizophrenia compared with normal subjects and patients with major depressive disorder.

Leweke et al. (99) showed that concentrations of endogenous cannabinoids, including anandamide, were considerably higher in the cerebrospinal fluid of patients with schizophrenia than in healthy controls. In addition, schizophrenia is associated with polymorphism of the CNR1 gene, and it is suggested that variations in this gene may predispose to different phenotypes of schizophrenia (100).

Bipolar disorder. There appears to be no evidence concerning brain endocannabinoid levels, CB_1 receptor density or expression of the CNR1 gene in bipolar disorder. However, it is possible that such changes in the endocannabinoid system are also present in this condition. The classical Kraepelinian distinction between schizophrenia (dementia praecox) and manic depression (unipolar and bipolar disorders) is under question by present-day psychiatrists, with mixed states, as typified by schizoaffective disorder, being increasingly recognized.

However, clinical observations suggest that the endocannabinoid system is dysfunctional in schizophrenia and in bipolar affective disorder and fails to control the level of cortical excitation and inhibition in the brain. Thus, excessively high endocannabinoid tone (positive schizophrenic symptoms, mania) or excessively low endocannabinoid tone (negative schizophrenic symptoms, depression) may be manifest in both these disorders.

This suggestion is also supported by the effects of some doses of cannabis and THC. High intake of cannabis can cause acute psychosis, sometimes with marked hypomanic features (43). Adverse reactions are more common with potent cannabis preparations such as 'skunk' which delivers high doses of THC but contains little CBD. Intravenous infusion of THC in normal subjects can also induce psychotic symptoms and perceptual distortion (42). Such effects are probably due to widespread overstimulation of CB_1 receptors by THC as mentioned earlier (under Cannabis). Psychiatric effects are more common in individuals with mental illness. Cannabis aggravates positive symptoms in schizophrenia and prolonged or heavy use in childhood or adolescence increases the risks of later schizophrenia, suicide, depression and other psychiatric disorders (101, 102).

Yet subjects with bipolar disorder report that cannabis can allay the racing thoughts, flight of ideas and hyperactivity associated with hypomanic/manic phases. This may be partly because of anxiolytic and sedative effects of low/moderate doses of THC, but the major contribution is probably provided by the antipsychotic, sedative and anxiolytic effects of CBD and its antagonism of the psychomimetic effects of THC (reviewed by Zuardi) (24). CBD has been proposed as a possible treatment for both bipolar disorder (11) and schizophrenia (95). Clinical trials of CBD are few but small studies suggest a positive effect in schizophrenia (54, 103) although CBD was ineffective for a manic episode of bipolar disorder in two patients reported by Zuardi et al. (104).

Electroencephalographic (EEG) studies. Anticonvulsant drugs such as sodium valproate, carbamazepine and lamotrigine are being increasingly used as 'mood stabilizers' in bipolar disorder, and EEG studies suggest a background for their utility. Some early studies of bipolar patients showed temporal lobe dysrhythmias consisting of paroxysmal runs of theta activity, sometimes becoming generalized and interspersed with slow waves and occasional sharp waves and spikes, often with a background of fast beta-activity (105, 106). Such abnormalities were most marked in bipolar patients with poor outcome and poor response to treatment (107, 108). Similar temporal lobe EEG changes are found in some patients with epilepsy and suggest a link between bipolar disorder and epilepsy (109, 110) and also relate to the fact that both conditions respond to anticonvulsant drugs (111).

A study of young euthymic patients with bipolar disorder using quantitative spectral brain mapping (QEEG) found highly significant ($P < 0.01$–00001) increases in power in all wave bands (delta, alpha, theta, beta) in patients compared with controls (106). This finding suggested heightened cortical excitability (hyperarousal) in these patients, consistent with the proposed kindling model of bipolar disorder (109, 110). The increased temporal theta and beta power demonstrated in the QEEG study is consistent with the earlier findings

of temporal lobe arrhythmias in patients with bipolar disorder. The EEG findings and the link with epilepsy suggest diminished control of the general level of cortical excitation mediated by GABA and glutamate (7), the activity of which is modulated by the endocannabinoid system.

Electroencephalographic studies in unmedicated patients with schizophrenia (reviewed by Nuechterlein and Dawson 112) have shown a number of abnormalities including excessive fast and slow activity in different brain regions (113, 114), frequency variability, dysrhythmias and desynchronization. Shagass (114) suggests that dysregulation of brain activity may be a more basic problem in schizophrenia than hyperactivation *per se*.

With regard to cannabinoids, CBD possesses anticonvulsant activity in rodents, as mentioned earlier (under *Actions of CBD*). There have been few clinical studies but a small trial in patients with epilepsy (64), as well as single case studies and anecdotal reports, is suggestive. Further research is clearly needed on the therapeutic potential of CBD, both for its antipsychotic and for its anticonvulsant effects.

Discussion

Our hypothesis that the endocannabinoid system is dysfunctional in mood and related disorders, and the evidence we have reported strongly indicates the need for further research, both clinical and preclinical.

Laboratory and *post mortem* investigations are required to determine the blood concentrations of anandamide and other endocannabinoids, to examine CNRI gene polymorphism and to reveal CB_1 receptor density and distribution in key brain areas in various psychiatric disorders including anxiety states, depression, bipolar disorder and to extend studies in psychoses, schizophrenia and suicide victims.

The time is ripe for early clinical trials with cannabinoids such as THC and CBD and possibly synthetic cannabinoids in mood and related disorders. These agents could be given as add-on or perhaps first-line treatment, or as prophylaxis against recurrence. At present, polypharmacy is rife in clinical practice, especially in anxiety states, bipolar disorder, depression and chronic pain conditions, and many agents have only modest efficacy. Cannabinoids, as described earlier, can combine many of these actions: antidepressant, antipsychotic, anxiolytic, anticonvulsant, analgesic and sedative/hypnotic, and used singly or in combination could augment or provide alternatives to existing treatments.

In conclusion, the study of the endocannabinoid system in mood disorders may open up a whole new field of clinical psychopharmacology that is waiting to be explored.

Declaration of interest

CHA and PBM are non-executive directors of The North East Council on Addictions, a UK registered Charity delivering clinical services to those suffering addictions. Otherwise, CHA and PBM have no conflicts of interest. Both authors contributed equally to this article.

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The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research

Lester Grinspoon, M.D.* & James B. Bakalar**

Abstract—The authors present case histories indicating that a number of patients find cannabis (marihuana) useful in the treatment of their bipolar disorder. Some used it to treat mania, depression, or both. They stated that it was more effective than conventional drugs, or helped relieve the side effects of those drugs. One woman found that cannabis curbed her manic rages; she and her husband have worked to make it legally available as a medicine. Others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. Another case illustrates the fact that medical cannabis users are in danger of arrest, especially when children are encouraged to inform on parents by some drug prevention programs. An analogy is drawn between the status of cannabis today and that of lithium in the early 1950s, when its effect on mania had been discovered but there were no controlled studies. In the case of cannabis, the law has made such studies almost impossible, and the only available evidence is anecdotal. The potential for cannabis as a treatment for bipolar disorder unfortunately can not be fully explored in the present social circumstances.

Keywords—bipolar, cannabis, depression, lithium, mania, marijuana

[EDITOR'S NOTE: The following article is based in part on materials that appear in the revised and expanded edition of the authors' book, *Marijuana, The Forbidden Medicine*, republished in 1997 by Yale University Press, New Haven and London. While the interviews have previously appeared in print, they provide a reference point for the authors' discussion of cannabis' potential role in the treatment of bipolar disorder as it appears in this theme issue. In their revised and expanded book, Grinspoon and Bakalar discuss a wide range of what they refer to as "Common Medical Uses" and "Less Common Medical Uses" for cannabis. The former include treatment for the nausea and vomiting of cancer chemotherapy, glaucoma, epilepsy, the muscle spasms of multiple sclerosis, paraplegia and quadriplegia, the weight loss syndrome of AIDS, chronic pain, migraine, rheumatic diseases, pruritus, PMS, menstrual cramps and labor pains, depression and other mood disorders. The latter include treatment for asthma, insomnia, antimicrobial effects, topical anesthetic effects, antitumoral effects, dystonias, adult ADD, schizophrenia, systemic clerosis, Chron's disease, diabetic gastroparesis, pseudotumor cerebri, tinnitus, violence, PTSD, phantom limb pain, alcoholism and other addictions, terminal illness and aging.]

In bipolar or manic-depressive disorder, major depression alternates with uncontrollable elation, or mania. Symptoms of depression include loss of interest and pleasure in life, sadness, irrational guilt, inability to concentrate,

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appetite loss, lethargy, and chronic fatigue. Manic symptoms include sleeplessness, tirelessness (until exhaustion leads to a breakdown), and recklessly gregarious and expansive behavior, which sometimes turns to irritability, rage and paranoid delusions. Bipolar disorder is treated mainly with lithium salts and anticonvulsant drugs, which can have serious side effects. Thirty percent to 40% of patients with bipolar disorder are not consistently helped by or cannot tolerate standard medications. In the course of the authors' studies of the medical uses of cannabis (Grinspoon & Bakalar 1997), a number of sufferers were discovered who believed marihuana to be more effective than conventional anti-manic drugs, or who used it to relieve the side effects of lithium.

Our first account was written by a 47-year-old woman:

> I was born on Friday, October 13, 1950, a few months before my father had his first serious bout with manic depression. My mother said he was taking valuable art objects they owned and throwing them down the trash chute in their New York apartment building.
>
> I enjoyed my youth with a great deal of abandon. How much of this would be mood disorder I could not tell you. As a single person I didn't notice; I just rode the waves of emotional highs and lows and didn't think much about it. I was an old pro at this by the time I was 19 and met my husband. It was only through my association with him that I came to terms with my mood problems, although right before I met him I had checked myself in at a mental health clinic complaining that I sometimes felt unable to concentrate on one thing at a time.
>
> I think I was 22 years old when my troubles cropped up again. At one point my husband and I went to see a psychologist. We talked about my mood swings and spells of nervousness, anger, and depression. The tiniest negative thing happening would cause long-lasting rage, very hard to quell. We told the psychologist of my father's history, even longer and grislier by then. He must have been in every state mental institution along the east coast. My grandmother, his mother, was wasting away by this time, losing her lifelong battle with chronic depression. I don't know much about her case except that she was chronically sad and starved herself to death after her husband passed away.
>
> This man said my husband and I needed to lose weight; that was the extent of his advice. We did not see him much longer. By this time I was experiencing most of the symptoms I have today, although they have strengthened year by year. Sometimes I feel elated, exhilarated, with a great deal of energy. It sounds great, but you can get to be feeling so good that you scare the people around you, believe me! This is accompanied by light sleeping and nocturnal habits. I tend to become angry or aggressive when it is not appropriate, or just talk too loud. I often have a low self-image or feel sad. I sometimes have a hard time getting up to work, a heaviness that keeps me from moving. I get racing thoughts that make concentration hard. I have strong emotions that change rapidly. I tend to be physically clumsy. I develop unexplained skin rashes, and sometimes feel like I'm generating electricity and shooting it out my fingers and toes. My judgment is often poor.
>
> It was in my early twenties that I first used cannabis for my condition. I had been exposed to it several times, the first when I was quite young. My mother had taken me to a mental health center after my initial signs of trouble as a child. After a group therapy session there, some of the other kids took me riding and gave me a joint. Nothing at all happened, and I concluded it must be a mild drug.
>
> When I was exposed to it later, I would actually choose it over alcohol because it didn't have such strong and negative effects on me. This is how I discovered that it was effective against most of my symptoms. Suppose I am in a fit of manic rage—the most destructive behavior of all. A few puffs of this herb and I can be calm. My husband and I have both noticed this; it is quite dramatic. One minute out of control in a mad rage over a meaningless detail, seemingly in need of a strait jacket, and somewhere, deep in my mind, asking myself why this is happening and why I can't get a handle on my own emotions. Then, within a few minutes, the time it takes to smoke a few pinches—why, I could even, after a round of apologies, laugh at myself!
>
> But this herb is illegal and I have a strong desire to abide by the law. My father was having great success with a new drug, lithium carbonate. I saw my father's physician and he recommended that I try it. I took lithium for six months and experienced several adverse side effects: shaking, skin rashes, and loss of control over my speech. But I would still be taking it if it had worked for me as it did for my father. It literally restored his life. I had gotten worse, if anything.
>
> The combination of lithium side effects and increased manic depressive symptoms drove me back to the use of cannabis. Some years later I tried to go without it again, this time because of increased social pressure against illegal drug use. It was a very difficult time for my family. Whenever I started to become manic, my husband and son would get scared and cower, triggering rage and making matters worse. When depression struck it was a black funk on our household. And I can tell you from the experience with my father that this can really destroy a family. After a while the knowledge that a little bit of marihuana would help me so much became irresistible. At first I tried eating cannabis, but soon returned to smoking because I could control the dose better.
>
> I don't at all consider myself a drug abuser. I am doing what any rational person in my position would do. Cannabis does not cure my condition and over the years it has probably continued to worsen. But with judicious use of this medicine my life is fine. I can control things with this drug that seems so harmless compared to the others I've tried, including tranquilizers as well as lithium. I am constantly concerned that I will be cut off from my supply of marihuana or caught with it in my possession. I feel my sanity may depend on it. Cannabis lessens what is troubling me and returns me to a more normal state. Often I do not experience a "high" at all, just a return to normal.

This patient's husband bears witness to the usefulness of cannabis:

> I've been mates with my full-blown manic-depressive (M-D) wife for 26 years. Her father was the classic, well-studied and well-written-about manic-depressive, and she's the one who inherited it. She's lovely, and as I've always truthfully told her, she has the perfect personality, blemished only by M-D.
>
> I've always been smooth-sailing. Smoking marihuana only makes me sleepy. I never use it. She requires it, or, I

swear she'd be institutionalized just like her father. There wouldn't be any other way.

We've tried Marinol [dronabinol]. It works for her too, but to get the same effect as marihuana she must take 10 mg about six times a day, which costs about $65 a day. What's worse is that it takes forty-five minutes to engage and tapers off within two hours maximum. Timing of capsule ingestion must be exact or the symptoms can print through. Marihuana [smoked] lasts a little longer and is smoother, and, most importantly takes effect quickly.

What does marihuana do for my wife? It "recenters" her personality and her interaction with the immediate family moves back into a normal range—no highs, no lows, at least not the highs and lows that are abnormally extreme and that you can tell are from a crazy person with active M-D. Narcoleptic drugs really "zone" her out, like a temporary lobotomy in a medicine bottle. Marihuana never does that! It normalizes, that's all. If there's an overdose, which is rare, it's not dangerous and is very short.

Yesterday we went downtown (one and a half hour's drive one way). However, going several hours without the medicine can be quite calamitous. The worst kind of getting along badly ensued. That's the exact nature of M-D. You tear at your mate with unfounded suspicions, accusations, insane bitterness—enough to make you hate each other. It makes no sense. That's why it's crazy behavior. If you're lucky, like my wife, your mate understands and gets you home right away to have a smoke. It used to be that you could take trips, but the police have cracked down so hard that you don't dare smoke a joint in the car.

I can bear witness to the probability of a near normal life situation for a manic-depressive if they've got good marihuana, a lifestyle that allows one to be home nearly always, and an understanding partner.

Here is the account of another woman with bipolar disorder who finds cannabis more useful than conventional medications:

I am a 35-year-old woman with severe manic depression. When I was growing up I was hypersensitive, cried all the time, and fought with my brothers and sister. My parents always said they had to handle me with kid gloves. I had more energy than most and used it to the hilt. I was an agile gymnast and one of the fastest swimmers in my school. I was also at the top of my class in algebra and good at art and creative writing. I used to stay awake at night and dream up stories.

Around age 14 my mood swings began to get more intense. I was agitated, restless, and constantly fighting at home. I lay awake at night and lost a lot of weight. Eventually I snapped and was sent to a mental hospital, where I was diagnosed as having manic-depressive disorder. They put me on lithium and told me I would have to take it the rest of my life. But lithium made me lethargic. I had trouble communicating and lost all my animation and creativity. Eventually I quit taking it. Recently I have also tried Tegretol [carbamazepine] and Depakote [valproic acid], neither of which helped. Tegretol started a manic episode, and Depakote had some very bad side effects. I'd like to find something else, but I don't have health insurance or the money to spend trying out new medications.

Since the age of 14 I have had manic episodes regularly about once every six months. It would always start with not being able to sleep or eat. After two weeks I would just break down and seem to trip out into another world. Usually I ended up in a mental hospital.

I smoked marihuana for the first time in high school and couldn't believe how good it made me feel. My normally chaotic emotions subsided and I had a sudden sense of calm, peace, and well-being. My perceptions of others and life changed dramatically. The world no longer seemed hostile but more within my control. I could sleep easily and actually had cravings for food. There were practically no side effects. When I had enough marihuana I would just naturally stop, because once you've gotten a certain effect you really don't want any more.

Only another manic-depressive using marihuana could possibly know how much this has changed the quality of my life. Although they don't know it, my family actually likes me better when I'm stoned than when I'm taking lithium or not taking anything. When I'm stoned they can predict my moods and actually get close to me. But I can't tell my family or the doctors because it's illegal. I have to live a double life to get along.

I've often tried to quit marihuana, but I have a manic episode every time. Last year I decided I could control my emotional ups and downs without marihuana, but it led to one of the worst episodes I've ever experienced. I had been having trouble sleeping as usual, I began to get super clear vision that a disastrous earthquake was going to hit Los Angeles. I was feeling so good I was sure I was right. Soon I had my roommate convinced that we didn't have much time and would have to buy as many supplies as possible and then leave. We thought that after the quake the New World Order would be implemented and everyone would have to take the number that Revelations talks about in the Bible. We planned to go to El Salvador, where her family lives, and hide out for the next three and a half years. Crazy! But I really believed it. I maxed out all my credit cards, quit my job, and packed up all my things, including disguises I thought we were going to need. Eventually I had to return home with no job and major bills.

I knew then and there that I would have to go back on marihuana. It's been seven months now since I resumed smoking marihuana, and I don't know what else to do. I have to choose between obeying the law and staying sick or breaking the law and being well.

J.P. is a 45-year-old health professional and the mother of a 20-year-old son:

In late 1994 and early 1995 my son Michael, age 18, began to go out of control. He was unable to sleep, attend school, or function in a normal fashion. He was running around nonstop, acting on impulse without any sense of normal judgment. He was in serious danger of accidentally harming himself or others. There was no way to reason with him, because he was unable to think or listen long enough to understand what you were trying to say. He had become a human time-bomb.

Then, on February 14, 1995, he had a full-blown psychotic manic episode and refused treatment. I had to petition a court to commit him to a psychiatric hospital in Portland, Maine, where he was given a diagnosis of manic-depressive disorder. Both Michael's father and my grandmother suffered from the same disorder, which is now called bipolar disorder.

During his nine days in the hospital (the time allotted by my insurance company) Michael was given lithium and Trilafon [perphenazine]. We were told that he would need lithium for the rest of his life. They explained that it worked very well in 60% of people with this disorder.

We returned home, and for the first month or two, the mania seemed to have ended. At the end of the second month the Trilafon was discontinued, but Michael was still taking a high dose of lithium. At that point he developed a rash on his neck and chest; he also had dark circles under his eyes, and he was incoherent most of the time. The lithium level in his blood was exactly where the doctor wanted it, but now he was acting like an Alzheimer's patient. He couldn't read or comprehend a paragraph, let alone finish school. He was detached from his surroundings and himself. There was no emotional content left in him. He was becoming unrecognizable. He had always been very much like [comedian] Robin Williams in personality and extremely athletic—a skier, football player, and weight lifter. It was heartbreaking to watch him lose himself in a medicated stupor. I became convinced that lithium did not eliminate the disease but instead was drowning his brain so the symptoms could not be activated. I could still see tiny mood swings and moments of complete restlessness, but in a body that was unable to become hypomanic.

Michael decided to cut his lithium in half. I knew this would be dangerous but I agreed that something had to be done. Soon he was more himself, laughing and talking and almost back among the living. Then he started to become more hypomanic, and I knew we were headed for trouble. He was back to the energy level of someone on high doses of speed, and this lasted for months. He was running through life like a high-bred stallion, while I was gathering everything ever written on manic-depressive disorder.

Then one day he came home and was perfectly normal in every respect. I thought that maybe he was in remission because the disease is known to do that, and I was thrilled at the possibility. Later that night he was back to full speed ahead, and all hope sank within me. This continued as the weeks passed. There would be times when he was perfectly normal, but only for short intervals. I could not figure it out. I started to chart his sleep pattern, his food intake, the kinds of foods, what chemicals he was subjecting himself to, and so on. Finally one day I discovered that he was smoking pot. Of course I freaked out. We talked about it at length and he told me point blank, "I only feel normal when I smoke a joint." By this time I was ready to blame the disease on his pot smoking. I was totally irrational about this. Michael and I fought constantly for a month about it. Finally he asked me to research cannabis and let him know what I found. I figured I would be able to find enough damaging information to put the subject to rest. The next week was my week of discovery. Not only could I not find what I was looking for, but I became convinced that there was no permanent damage, and that cannabis was actually helpful for people with mood disorders.

I went on-line on the computer to talk to other people suffering from bipolar disorder, and I was overwhelmed by first-person stories of the benefits that others had found.

The hardest part of this entire thing was rearranging my value system. I was raised to be a law-abiding citizen. Although I grew up in the sixties and had tried pot and inhaled, I was never a regular user because it was illegal. I raised Mike right. He was taught to respect elders, do what you are supposed to do, and above all follow the law.

It is hard enough to live with an 18 year old during a naturally rebellious time, but to be forced to participate in an illegal activity is the absolute worst scenario. But that is exactly what I'm doing. Mike has been smoking pot for two months now. He does not smoke daily, but when the mania begins he smokes and within five minutes he is fine. He never appears to be "high," just happy and relaxed. We don't have to deal with mood swings anymore. He can work on his home-schooling program, and I don't doubt that he will finish by the end of summer. He has been repairing lobster traps with a friend and will be lobstering six days a week by the end of April.

At this point I expect to be arrested some day, because if Mike gets arrested, they will have to take me right along with him. I plan to grow a plant this summer for his use. I know I could end up in jail, but I also know that without some kind of medication that works, my son could end up in jail, institutionalized, or dead. What choice do I have?

Another account of cannabis use by a person with bipolar disorder emphasizes the reduction of lithium side effects:

I am 29 years old, born and raised in North Carolina. My academic background is in English literature, computer science, and law; I now work as a technology consultant and writer, although I am contemplating returning to graduate school. I am divorced. I am reasonably active in my community, though work takes much of my time these days.

I was first diagnosed with bipolar disorder about five years ago, when I was in law school (a psychiatrist also tentatively ventured this diagnosis during my undergraduate years), but I suspect that I have had a mood disorder for most of my life. I was certainly clinically depressed as early as age nine, and my first hypomanic episode occurred at 17. There is also a family history of mood disorders, especially on my mother's side. All three of her brothers had "mercurial" personalities, and they all experienced tremendous successes and notable failures in business. Their extravagance and outgoing personalities resemble my behavior while manic or hypomanic. Although none of them was formally diagnosed with a mood disorder, both my parents have been treated for clinical depression.

Before I was diagnosed and found the right treatment, I had the typical symptoms of bipolar disorder. During depressive phases I became withdrawn, uncommunicative, and preoccupied with suicide. I found it nearly impossible to function in school or at work. During hypomanic or manic phases I spent freely, traveled all over the country (and world), made poor personal and business decisions, engaged in risky sexual behavior, and so forth. The illness has caused me a great deal of personal pain as well as financial woes. I separated from my wife (who eventually divorced me) the summer before I was diagnosed. I've lost jobs, ruined friendships, and alienated members of my family. Fortunately, much of this damage has been repaired with time and understanding. I thank God that my ruined credit rating is the only apparent lasting harm.

Thanks to lithium and sensible therapy, including the judicious use of cannabis, I have been relatively stable and sane for the past three years, although my sleep is often disturbed and I still have (very much milder) hypomania and depression in much the same cyclic pattern as before.

I first used cannabis in my freshman year of college (1984). I preferred it to alcohol as an intoxicant, and used it a few times a week, almost always by smoking (I still prefer to take it that way). In retrospect, it seems clear to me that I was medicating myself for bipolar disorder even then. When depressed and anxious, I found that cannabis was soothing and enhanced my ability to enjoy life. When I was in a manic phase, it relaxed me and helped me get to sleep. I often felt as though I had so much energy inside me that I would jump out of my skin; the cannabis helped tremendously with that. But there was a downside. Manics have a big problem with impulse control, and cannabis seemed to exacerbate it. ("Drive to Canada? Great idea. Let's go!") It also ratcheted up my already overactive libido a notch or two, which wasn't the healthiest thing in the world.

When I was diagnosed and began treatment with lithium, I got almost immediate relief, but I also suffered from nausea, pounding headaches, hand tremors, and excess production of saliva. A friend suggested that I try getting high, reasoning that if cannabis helped chemotherapy patients deal with their nausea and discomfort, it might help me too. My doctor thought the idea was absurd but admitted that it would be safe to take cannabis together with lithium. So I tried it, and the results were remarkable. The hand tremors subsided, the headaches vanished, and the saliva factory resumed normal production levels. All I needed was one or two puffs on a marihuana cigarette. When lithium side effects get bad, the availability of cannabis has been an absolute godsend. It is also nice to be able to use cannabis as an intoxicant, knowing that, unlike the combination of lithium and alcohol, it cannot damage my kidneys.

Every one of the many thousands of Americans who use marihuana as a medicine runs a risk of being arrested. They have to worry about financial ruin, the loss of their careers, and forfeiture of their automobiles and homes. Some have an additional burden because mandatory school drug programs and Parents for a Drug-Free America advertisements have given their children an exaggerated idea of the dangers of using marihuana. Many of these children become concerned about the health and well-being of their marihuana-using parents. A few of those parents have been arrested because their worried children informed on them to the police officers who serve as instructors in the popular school drug program known as Drug Abuse Resistance Education (DARE).

The following accounts are by a 40-year-old software engineer and his 37-year-old wife, who suffers from bipolar disorder. He speaks first:

My wife and I and our two boys live in Tyngsboro, Massachusetts. My wife was given a diagnosis of bipolar disorder in 1982 and has been taking lithium since 1992. She also uses marihuana for her symptoms. She has had six psychiatrists in the past 14 years and has been interviewed by many more. I have always told them that she uses marihuana regularly, and not one of them has told her to stop. They do not even seem to care or pay attention.

I posted a question about this to the alt.support.depression.manic newsgroup on the Internet. I asked whether doctors knew something about marihuana but could not recommend it because of its illegality. The responses were varied, but most people who were manic-depressive said marihuana helped them, and one said that some doctors considered it effective in controlling mood disorders.

My wife functions much better when she uses marihuana. When she is hypomanic, it relaxes her, helps her sleep, and slows her speech down. When she is depressed and would otherwise lie in bed all day, the marihuana makes her more active. When she runs out of marihuana and can't get more, she becomes more irritable and hard to live with. Lithium is also effective, but it doesn't always keep her in control.

Our dilemma is that our 13 year old has been through the DARE program and has learned about the evils of drugs and alcohol. He opposes all substance use, legal or illegal—and I want it that way. But he knows that my wife uses marihuana and it "eats" at him, although he also knows about her illness and how marihuana helps. Understandably, all this confuses him.

I believe that marihuana could help some people if it were made available as a prescription medicine. Certainly there are other health and social issues involved, and I can't decide what would be right for the country as a whole. All I know is that in this family it has relieved us all of much suffering.

Now his wife:

I am 37, and I have been using marihuana for 20 years. I was diagnosed bipolar in 1982. I take lithium and Wellbutrin [bupropion], although I dislike these drugs. I've gained about 40 pounds since I started taking lithium, but otherwise there are no side effects.

My 13-year-old son knows about my illness. He has also known about my marihuana smoking for about five years. He realized what I was doing after he participated in the DARE program in school. It bothers me when he comes home and says they talked about drugs and he was thinking that his mother is "one of them." He doesn't want anyone to know his mother is a "druggie," and until now we've kept it as our secret. I don't think he would tell anyone, but I'm still afraid something might get out. Sometimes these programs use tricks to get kids to inform on their friends and relatives. They say, "If you really care about this person, the only way you can help them is to report them." My husband has talked to him about it. He has explained that lithium and the other medications I'm taking are drugs. He also explained that many legal drugs are far more dangerous than marihuana and that no one has ever died from using marihuana. But my son insists that if it is illegal, then it is wrong. This bothers me so much that I have considered stopping.

The trouble is that at times when I feel tired and rundown, just a couple puffs of marihuana bring me back to life. Sometimes I think it brings me to a level of normalcy that everyone else achieves naturally. At other times, when everything seems to be going like a whirlwind around me and I can't keep track of what I'm thinking about or saying or feeling, the marihuana just seems to slow the world down a bit. When I have trouble sleeping, it helps zonk me out, but if I have trouble waking up it brings me to life. I don't like being thought of as a "drug-abusing mother," but I actually think I'm a better mom when I'm feeling in control because of marihuana.

In some ways cannabis today is in a position analogous to that of lithium in 1949, when J. F. J. Cade, after observing its sedative effect on guinea pigs, administered it to patients suffering from "chronic and recurrent mania." His seminal paper, "Lithium Salts in the Treatment of Psychotic Excitement," presented ten one-paragraph case histories, and this compelling anecdotal evidence attracted the attention of psychiatrists around the world because there was no adequate treatment for bipolar disorder. In his paper Cade (1949) mentioned the need for "controlled observation[s] of a sufficient number of treated and untreated patients." In 1951, Noack and Trautner followed up by reporting on the treatment of another 30 patients with "mania alone." But they pointed out that not all patients improved, that many discontinued the treatment, and that "it does not appear to be justified to accept the lithium treatment of mania as invariably safe." (Noack & Trautner 1951).

In 1954, Schou and colleagues published a controlled study in which they alternated lithium and a placebo at two-week intervals. Lithium was clearly beneficial for 12 patients; 15 showed improvement that was "not as clear-cut," and three did not improve at all. Schou and his colleagues found it "rather astonishing that [lithium's success] has failed to arouse greater general interest among psychiatrists." One explanation they offered was its low therapeutic ratio. Another explanation was "the difficulties encountered in attempts to convey to others in a quantitative manner . . . the effect of a new psychiatric therapy," i.e. to move beyond anecdotal data to controlled studies (Schou et al. 1954). But there was an even more compelling reason for the delay in lithium's acceptance in the United States. In this country, drugs are introduced by pharmaceutical companies which invest in the studies necessary for official acceptance. They do this because they receive a patent (in the 1950s, for 17 years) on the new drug which allows them to recoup their investment. Lithium salts, of course, could not be patented.

Similar obstacles face the medical use of cannabis today. Lithium had a reputation for toxicity that grew out of its use as a salt substitute for cardiac patients in the 1940s. There were a number of deaths before its dangers were fully appreciated, and today blood levels are carefully monitored. Because of its nonmedical use, cannabis also has a reputation for toxicity, in this case undeserved. Lithium was unpatentable, and so is cannabis. Finally, like the evidence for lithium in 1949, the evidence for the therapeutic value of cannabis in bipolar disorder today is anecdotal. Although it has been repeatedly considered as a treatment for affective disorders in the Western medical literature since 1845, when Jacques-Joseph Moreau de Tours (1857) recommended it for melancholia, there is little in the medical literature on the use of cannabis as a mood stabilizer (see Parker & Wrigley 1950; Pond 1948; Stockings 1947).

Today drugs must undergo rigorous, expensive, and time-consuming tests to win approval by the Food and Drug Administration (FDA) for marketing as medicines. The purpose of the testing is to protect the consumer by establishing both safety and efficacy. First the drug's safety (or rather limited toxicity) is established through animal and then human experiments. Next, double-blind controlled studies are conducted to determine whether the drug has more than a placebo effect and is at least as useful as an available drug. As the difference between drug and placebo may be small, large numbers of patients are often needed in these studies for a statistically significant effect. Because no drug is completely safe (nontoxic) or always efficacious, a drug approved by the FDA has presumably satisfied a risk-benefit analysis. When physicians prescribe for individual patients they conduct an informal analysis of a similar kind, taking into account not just the drug's overall safety and efficacy but its risks and benefits for a given patient and a given condition. The formal drug approval procedures help to provide physicians with the information they need to make this analysis.

But devotion to formal procedures may have caused us to undervalue anecdotal evidence. Regulators today are willing to accept the experience of physicians and patients as evidence of adverse effects but not as evidence of therapeutic effects (Lasagna 1985). Yet case histories and clinical experience are the source of much of our knowledge of synthetic medicines as well as plant derivatives. Controlled experiments were not needed to recognize the therapeutic potential of chloral hydrate, barbiturates, aspirin, curare, insulin, or penicillin. More recently, the uses of propranolol for angina and hypertension, diazepam for status epilepticus, and imipramine for childhood enuresis were discovered in the same way, although these drugs were originally approved by regulators for other purposes.

A related source of evidence is the experimental method known as the "N of 1" clinical trial or single-patient randomized trial. This is the kind of experiment used by Schou and his colleagues (1954), in which active and placebo treatments are administered in alternation or succession to a patient. The method is often used when large-scale controlled studies are impossible or inappropriate because the disorder is rare, the patient is atypical, or the response to treatment is idiosyncratic. Several patients the authors have encountered carried out somewhat similar experiments on themselves. They alternated periods of cannabis use with periods of no use and discovered that cannabis was effective.

The familiar deficiency of anecdotal evidence is the risk of counting successes and ignoring failures. If many people suffering from clinical depression take, say, St. John's Wort after unsuccessful treatment with conventional antidepressants and a few recover, those few stand out and come to attention. Bipolar disorder is a cyclical condition, so it is essential to avoid confusing natural remission with drug-induced improvement. At present we do not know how many patients with bipolar disorder would benefit

from cannabis. The promising anecdotal evidence points to the need for more systematic clinical investigation, just as it did 50 years ago in the case of lithium.

Thousands of years of widespread use as well as recent research designed to discover toxic effects have made it clear that cannabis is an unusually safe drug. In fact, its long-term safety is better established than that of St. John's Wort. Yet unlike St. John's Wort, cannabis would be subject to government regulations that demand further time-consuming and unnecessary safety tests. The classification of cannabis as a Schedule I drug creates further obstacles to clinical research. But given the disinterest of pharmaceutical companies, there is no immediate prospect of such studies being funded even if the political obstacles are removed. We are left with the tantalizing possibility that cannabis (or one or more of its constituent cannabinoids) is useful in the treatment of bipolar disorder and the sad knowledge that in the present circumstances little can be done to explore that potential.

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DEPRESSION 4:77–80 (1996)

DO PATIENTS USE MARIJUANA AS AN ANTIDEPRESSANT?

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Several lines of evidence suggest that cannabis may have antidepressant effects. However, methodologic limitations in available studies make the results difficult to interpret. We review this literature and present five cases in which the evidence seems particularly clear that marijuana produced a direct antidepressant effect. If true, these observations argue that many patients may use marijuana to "self-treat" depressive symptoms. Depression 4:77–80 (1996).
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Key words: cannabis; depression; antidepressant agents; self medication

The effect of cannabis on mood has been debated for many years. Although it is generally acknowledged that cannabis has a temporary euphoriant effect during the period of acute intoxication, there is disagreement as to whether it may possess an antidepressant effect that extends beyond acute intoxication. Some investigators suggest that the drug may have antidepressant effects, whereas others suggest that it may have no consistent effect on mood, or may even exacerbate depression. We review below several types of studies which bear on these questions, and then present a series of cases from our center.

CASE SERIES

Several authors have described individual cases or case series (Keeler, 1967; Tunving, 1985; Weil, 1970) in which marijuana appeared to precipitate depression, whereas others have described individuals who appeared to experience a mood-elevating effect from marijuana (Keeler, 1968; Zelwer, 1994; Musty, 1988; Mirin et al., 1971, Grinspoon and Bakalar, 1993). These reports are difficult to interpret, however, because it is difficult to be certain that marijuana played a causative role in the mood changes observed.

In a recent pilot study, we recruited and interviewed 37 individuals who had smoked marijuana on at least 5,000 separate occasions (Gruber et al., in press). Fourteen (38%) of these long-term heavy users reported that marijuana "frequently" relieved depression, whereas only one (3%) reported that the drug "frequently" produced depression. Again, however, these findings are based on retrospective self-reports.

EFFECTS OF MARIJUANA IN PSYCHIATRIC DISORDERS

Two lines of evidence, both suggesting that marijuana may have antidepressant effects, arise from studies of marijuana use in other psychiatric disorders. First, several case studies present patients who appeared to become manic following marijuana use (Stoll et al., 1991; Knight, 1976; Rohr et al., 1989; Harding and Knight, 1973; El-Guebaly, 1975) and two studies found that patients with "cannabis-induced psychosis" displayed hypomanic symptoms (Rottanburg et al., 1982; Thacore and Shukla, 1976). Admittedly, if a drug induces mania one cannot be certain that it has antidepressant properties, but such a possibility must be entertained. Second, several investigators have reported that marijuana use may ameliorate the negative symptoms of schizophrenia (Dixon et al., 1990; Peralta and Cuesta, 1992; Warner et al., 1994; Mueser et al., 1990; Dixon et al., 1991). There is also a group of studies comparing the prevalence of depression in populations with different degrees of marijuana use (Kupfer et al., 1973; Beauburn and Knight, 1973; Halikas et al., 1972; Weller and Halikas, 1985), but these studies are not reviewed here, because such studies cannot address causality.

CANNABIS ADMINISTRATION STUDIES

Two investigators have administered marijuana to groups of eight and 13 depressed patients, respectively, hoping to find an antidepressant effect (Ablon and Goodwin, 1974; Kotin et al., 1973). Although neither produced positive findings, both were subject to methodological limitations: drug administration was not double-blind; patient samples were small and most subjects did not complete the trial because of adverse events; marijuana was administered for only 1 (Kotin

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et al., 1973) or 2 weeks (Ablon and Goodwin, 1974), a time interval briefer than that required by standard antidepressants; and the patients studied were so depressed that they were hospitalized and thus perhaps more refractory to treatment than more mildly depressed patients.

In several studies THC was administered to patients with cancer, but only one study, of 54 patients, systematically evaluated for an antidepressant effect (Regelson et al., 1976). Of 34 patients who completed the 2-week double-blind placebo-crossover study, depression as rated by the Zung scale was significantly lower during the THC week compared with the placebo week ($P = 0.05$). However, this study is subject to many of the same methodologic limitations as the administration studies above, as well as the confounding effects of serious medical illness.

In studies where marijuana was administered to healthy volunteers, clear effects on mood have not been described. However, these studies were not specifically designed to evaluate the effect of marijuana on mood (Ross et al., 1974; Jones and Benowitz, 1976; Meyer et al., 1971; Renault et al., 1974; Chait and Perry, 1994.).

In summary, case reports, case series, studies in psychiatric patients, and administration studies, offer only tentative evidence that marijuana may have an antidepressant effect that extends beyond its temporary euphoric effect during acute intoxication. In our clinical experience, however, we and our colleagues have regularly observed patients who seem to use marijuana as an antidepressant. We present below five example cases where the observations provide particularly clear evidence that marijuana was directly responsible for antidepressant effects in individuals with mood disorder.

CASE 1

Mr. A was a 20-year-old, single, white, male college student who displayed major depression with psychotic features. He also reported a clear history of attention-deficit hyperactivity disorder (ADHD). His family history was positive for recurrent major depression, requiring hospitalizations, in his mother, and for ADHD in his brother. He described hopelessness, feelings of worthlessness and guilt, and hypersomnia beginning in tenth grade. It was at this time that he also began using marijuana, at first weekly, then escalating to two to three times every day by his freshman year of college. He reported that marijuana consistently made him "feel better," and decreased his social anxiety. He also used the drug as a sedative when he had insomnia, which he attributed to anxiety about school and social situations. However, after a year of daily use, he developed paranoid ideation and auditory hallucinations, and therefore stopped marijuana use completely for a time. The psychotic symptoms remitted within a day, but he promptly developed an episode of major depression, with depressed mood, anhedonia, insomnia, impaired concentration, feelings of guilt, worthlessness, and hopelessness, as well as inability to function in social situations because of severe anxiety. Despite aggressive pharmacotherapy with antidepressants and anxiolytics, and intensive biweekly psychotherapy, his symptoms remained only partially controlled; he was forced to take a leave of absence from school and curtail his social life significantly. During the last 2 years, Mr. A has attempted to resume regular marijuana use several times. On each occasion, he has reported a full remission of his depressive symptoms, enabling him to "have fun" and "go out" with his friends. However, within a week, he experiences the recurrence of severe paranoia, is forced to discontinue marijuana use, and returns to his previous state of only partial remission of his symptoms.

CASE 2

Mr. B, a 16-year-old single, white, male high school student, with a history of dysthymia and ADHD, was hospitalized for his first episode of major depression. His family history was significant for depression in his mother and maternal aunt, both of whom had major depressive episodes and were being treated successfully with fluoxetine 20 mg per day. He described extreme irritability, anhedonia, lack of interest in his friends and activities, loss of appetite with weight loss, decreased concentration, and feelings of worthlessness and guilt, symptoms severe enough to result in expulsion from school and deterioration in his previously good relationship with his mother. Mr. B reported the onset of his depressive symptoms in eighth grade, and the onset of his marijuana use several months later. Initially, he used marijuana one to two times per week with his friends, but he soon began to use marijuana daily "to improve his mood." He reported that his depressive symptoms increased when he was unable to use marijuana, and he took risks, including stealing, to obtain it. A period of close supervision and inability to use marijuana led to a steady increase in depressive symptoms, which precipitated his hospitalization. In the hospital, his desire for marijuana remained so strong that he managed to grow marijuana plants successfully in the field behind his hospital building while he was an inpatient. Following his discharge, he reported only partial relief of his depressive symptoms with fluoxetine, but marijuana produced full relief during intervals when he was able to surreptitiously resume using it.

CASE 3

Ms. C, a 27-year-old, single, white female was hospitalized for treatment of her bipolar disorder and poly-substance abuse. Her family history was positive for bipolar disorder in her sister and father, and major depressive episodes in her mother, all of whom were receiving medication. Since childhood, she had experienced depressed mood, fatigue, anhedonia, social withdrawal, and a desire to "escape" from her problems. She began using marijuana in fifth grade, in-

creasing her use until it was stable at three or more joints per day through junior high and high school. She reported that marijuana definitely improved her mood and social life, and that she made great efforts and took risks, such as selling marijuana, to ensure a constant supply. She reported that the marijuana "high" was very similar to the feeling she had when hypomanic. Starting at the age of 16, she added cocaine to her drug use regimen, thus making the role of marijuana more difficult to assess during the interval from age 16 to 27. Since her hospitalization, the combination of a mood stabilizer and an antidepressant has effectively prevented major affective episodes, but has left her with residual depressive symptoms similar to those she had as a child. She reports that she had discontinued all cocaine and other drug use except for marijuana. Closely monitored for substance abuse, she has rarely been able to use marijuana undetected. Whenever she has had the opportunity, such as a family vacation, she has used marijuana, and reports that her mood reliably improves during these periods, and depression recurs after her access to marijuana is again lost.

CASE 4

Ms. D, a 23-year-old, single, white, college student, reported a history of bipolar disorder dating back to a first depressive episode at the age of 16. Her most severe depressive episode, at the age of 21, was characterized by insomnia, a 35-pound weight loss, psychomotor retardation, anhedonia, and a suicide attempt in which she tried to jump from a building. Six months later, she developed a manic episode during which she believed that she was a world leader, slept 3 hours a night, and spent money far beyond her ability to pay. Following the resolution of this episode, she again entered a depressive episode, which persisted for nearly a year. When asked about her history of substance use, she described an initial period of polysubstance abuse at age 16–17, following which she used marijuana almost exclusively, one to four times every day, during her depressive periods. In contrast, when manic, she used marijuana very little. When asked about her reasons for using marijuana, she reported that psychiatrists had treated her depressive symptoms with tricyclic antidepressants and fluoxetine, but that none of these medications was nearly as effective as marijuana. Accordingly, she used marijuana regularly in conjunction with lithium carbonate and sodium valproate as a component of her "medications" for her bipolar disorder.

CASE 5

Mr. E, a 28-year-old, single, white man, developed his first episode of depression after his sophomore year in college. At that time, his marijuana use escalated from one to two times per week to one to two times per day. He reported that his marijuana use at that time was prompted by its antidepressant effect. However, in the fall of that year, he developed a manic episode, was hospitalized, and was placed on lithium and fluphenazine. After discharge, he quickly became non-compliant with treatment, resumed using marijuana, and devoted the next several months to hitchhiking around the country and attending rock concerts. Over the course of the next 5 to 6 years, this pattern repeated itself frequently: he would be hospitalized for an acute psychotic episode, treated with antipsychotic medications, develop depressive symptoms after discharge, and promptly revert to marijuana use, leading to another relapse and hospitalization. After six such hospitalizations, Mr. E. began to disclose the severity of his post-psychotic depressive symptoms, and revealed that none of the various antidepressants prescribed gave him reliable relief for depression. Only marijuana, he stated, produced a full antidepressant effect. It was for this reason, he explained, that he promptly resumed using marijuana during each depression, even though he recognized that it might provoke a new psychotic episode. When this history was fully recognized, an attempt was made to treat his depression much more aggressively. He was thus started on venlafaxine 375 mg per day together with lithium carbonate. This combination seemed to give him a better antidepressant effect than he had previously experienced, and for the first time in many years, he was able to abstain from surreptitious marijuana use. He has now been out of the hospital for more than a year and has resumed college.

DISCUSSION

In conclusion, several lines of evidence suggest that marijuana may possess antidepressant effects, although it is difficult in many reports to be certain that marijuana played a causal role in alleviating depression. In this paper, we present five case examples in which the evidence seems particularly clear that marijuana exerted an antidepressant effect. All five patients reported that marijuana relieved their depressive symptoms, and that they deliberately used it for this purpose. All reported that marijuana was more effective in treating their depressive symptoms than traditional antidepressants, except for Mr. E, who found this to be true until he responded to venlafaxine. Additionally, the patients in the first three cases all reported that their mood deteriorated when they were not able to use marijuana, and that their mood reliably improved upon resuming marijuana.

These case reports must be interpreted with the usual cautions which apply to such retrospective observations. The cases presented are not good subjects for studying depressive symptoms. All five cases fulfilled DSM-IV criteria for either cannabis or polysubstance dependence at some time, and only observations following a period of several weeks of abstinence in such individuals would permit a firm judgment regarding the effects of cannabis on mood. We cannot, for example, rule out the influence of compulsive drug seeking as a confounding variable in the reports of these patients regarding their mood changes.

This evidence favors the hypothesis that cannabis may indeed exert a direct antidepressant effect which extends beyond the immediate period of euphoria during acute intoxication. If true, this effect is of clinical importance, in that it may prompt large numbers of depressed patients to "self-treat" with cannabis. The underlying depression may go unrecognized in many of these patients who present for treatment of cannabis-related disorders, or psychiatric disorders comorbid with cannabis use (Brady et al., 1991). Recognition of the role of cannabis as "self-treatment" might facilitate the diagnosis and treatment of this group of patients, many of whom might be effectively treated with conventional antidepressants. Thus, more systematic studies of cannabis use are clearly needed to delineate the prevalence of this phenomenon.

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Original article

Treating depression with cannabinoids

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Abstract

Although a variety of drugs are available for the treatment of depression, therapy is not effective in all cases and finding alternative options is desirable. Results from animal studies, anecdotal experience reported by patients using cannabis and observations from clinical studies where cannabinoids were used in serious diseases suggest an anti-depressive potential of cannabinoid receptor agonists. From 2003 to 2006, 75 patients suffering from depression, stress and burnout syndrome were successfully treated in a practice for general medicine with the cannabis ingredient dronabinol, alone or in combination with other antidepressants. Two case studies will be presented. The presented observations suggest that dronabinol has an antidepressive potential that can readily be used in medical practice.
Key words: Depression, burnout, cannabinoid, cannabis, dronabinol

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Introduction

In several prospective studies, consumption of cannabis was associated with an increased risk of developing depression and anxiety, particularly when cannabis had been used during adolescence [1,2]. There appears to be less evidence for a correlation between depression and cannabis use during adulthood [3,4]. On the other hand, patients have, in numerous surveys and interviews, reported anti-depressant and anxiolytic effects of cannabis [5-11]. Patients suffering from a range of chronic illnesses have reported that they use cannabis not only to mitigate physical symptoms, such as pain, nausea and lack of appetite, but also to improve general well-being and to mitigate anxiety and depression [8-10,12].

In several clinical studies, during which subjective parameters were monitored, cannabinoids not only improved physical symptoms but also improved well-being and produced measurable antidepressant effects [13-15]. A study by Musty (2002) with healthy volunteers, smoking cannabis showed a positive correlation with the ratings on a scale of depression (MMPI), indicating an antidepressant effect [16]. These indications of a therapeutic potential of symptoms of depression encouraged the author to start administering dronabinol to select patients suffering from depression.

Experiences in Medical Practice

The author operates a practice for general medicine in downtown Vienna, where a large population of younger people lives and works. In the late 1990s I began administering dronabinol to individual younger patients, who were dissatisfied with available antidepressants because of side effects or lack of effectiveness. In Austria, the active ingredient of cannabis has been available for medical therapy since 1998. The majority of these early patients, who suffered from a reactive depression or burnout syndrome, was well aware of the therapeutic potential of cannabis and considered a trial with dronabinol reasonable.

Between 2003 and 2006 some 250 patients who suffered from a wide range of illnesses were treated in my practice with dronabinol. Some 75, or 30%, of them suffered from depression, a sense of being overwhelmed or from burnout syndrome. The initial dose of 2.5 mg dronabinol in capsules was raised, over a period of several days, to generally 5 or 7.5 mg per day. For almost 80% of the patients, use of the medication cor-

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related with swift improvement of the depressed mood or the sense of being overwhelmed. Only 20% of patients did not experience any significant mood brightening. To that group a combination therapy of dronabinol and a selective serotonin reabsorption inhibitor (SSRI), such as fluoxetine hydrocholoride at a dose of 20 mg per day or a serotonin noradrenalin reabsorption inhibitor (SNRI), such as milnacipran at 50 mg per day, was administered. That therapy generally resulted in rapid and satisfactory improvement of depression and the lack of drive.
Side effects were generally low. Effective daily doses of dronabinol ranged generally from 7.5 to 12.5 mg per day. Only few patients required a higher dosage, generally those also suffering from a sleeping disorder.

Case Reports

In the following two exemplary cases from a large number of successful treatments are presented.

Case 1

Ms. H. came to my practice six years ago, at the age of 48. She had a long psychiatric record with episodes of depression and the abuse of alcohol and drugs, particularly of benzodiazepines. A former teacher, she is now retired but continues to work as an actress.
At the onset of the therapy the patient was in a difficult situation. Her father had recently passed away; she was highly depressed, sometimes even suicidal. Heavy abuse of drugs, such as oxazepam, and of alcohol further complicated her situation. Following an extensive discussion a treatment with oral dronabinol of 5 – 7.5 mg per day was started.
After 6 years of using dronabinol Ms. H. is now very experienced with the use of the drug. Depending on her symptoms, she takes between 2 and 4 capsules of 2.5 mg per day. She is no longer addicted to benzodiazepines and does currently not drink alcohol. As supplementary therapy she takes 2.5 mg per day of olanzapin (an atypical neuroleptic), 25 mg of venlafaxin (an SNRI) and, if needed, trazodon, SSRI. She reports that the dronabinol therapy has improved her quality of life significantly. She feels more stable than before and the chronically reoccurring episodes of depression are less severe. Her speed of reaction when operating a vehicle is impaired. Before extended car trips she has thus periodically suspended dronabinol for typically one week, which has resulted in psychological withdrawal symptoms.

Case 2

Ms. F. first visited our practice at the age of 22 where she received treatment over a 12-month period. At that time, the patient suffered from stress related headaches, migraine, asthma, neurodermatitis and an instable emotional personal disorder. Most prominent was an acute depressive syndrome, for which Ms. F. had already received treatment in the psychiatric clinic at Vienna General Hospital.
After repeatedly dropping out of school and frequent job changes the patient tried, despite a lack of family contacts, to improve her dismal social and physical conditions. She was also rather unhappy with her having to consume up to ten prescription medications. In addition to anti-depressants, such as fluoxetine and mianserin, neuroleptics, such as prothipendyl, sedatives and anti-allergic agents, such as hydroxyzine, NSAR, such as diclofenac, proton pump inhibitors, such as rabeprazole, analgesics, such as propyphenazone and tramadol, she daily consumed anti-asthmatics, such as terbutaline sulfate as prescribed by several other physicians.
Because the patient did not want to continue this multidrug treatment she came to our practice in search for a more simple and natural treatment, involving no more than two drugs. Primary objective of the treatment was to improve her acutely depressive condition, which had not improved despite the use of multiple drugs. Following an extensive consultation the patient opted for a monotherapy with dronabinol. After several days the initial dose of 2.5 mg was raised to 7.5 mg daily. After several days of treatment we observed a significant improvement of her depressive condition and of the concurrently occurring illnesses.
During the first month of therapy the daily dronabinol dose was raised to 10 mg and 12 month after starting her therapy the physical and psycho-social condition of the patient had stabilized at that dose. Subsequently, the patient resumed relationships with her family, relocated to a different state and left our practice.

Conclusions

In summary, the experience presented here suggests that general practitioners are able to treat a large number of patients suffering from depression and burnout syndrome without significant complications. Most patients were not reimbursed for dronabinol by their health insurance, unlike for patients with physical illnesses, such as cancer or multiple sclerosis, where the local health insurance in Vienna pays for nearly 60% of the cost of dronabinol.
These findings agree with the results from patient interviews, observations from clinical studies on the impact of cannabinoid use on mood and the results from animal experiments. In the latter, exogenous cannabinoid receptor agonists [17,18] as well as the inhibition of the deactivation of the endocannabinoid anandamide [18,19] resulted in antidepressant effects. To date no clinical studies have studied primarily the effectiveness of cannabinoids for the treatment of depression. In my opinion, such studies are desirable and promising.

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

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Abstract

A high dose of Δ^9-tetrahydrocannabinol, the main *Cannabis sativa* (cannabis) component, induces anxiety and psychotic-like symptoms in healthy volunteers. These effects of Δ^9-tetrahydrocannabinol are significantly reduced by cannabidiol (CBD), a cannabis constituent which is devoid of the typical effects of the plant. This observation led us to suspect that CBD could have anxiolytic and/or antipsychotic actions. Studies in animal models and in healthy volunteers clearly suggest an anxiolytic-like effect of CBD. The antipsychotic-like properties of CBD have been investigated in animal models using behavioral and neurochemical techniques which suggested that CBD has a pharmacological profile similar to that of atypical antipsychotic drugs. The results of two studies on healthy volunteers using perception of binocular depth inversion and ketamine-induced psychotic symptoms supported the proposal of the antipsychotic-like properties of CBD. In addition, open case reports of schizophrenic patients treated with CBD and a preliminary report of a controlled clinical trial comparing CBD with an atypical antipsychotic drug have confirmed that this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia. Future studies of CBD in other psychotic conditions such as bipolar disorder and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly indicated.

Key words
- Cannabidiol
- Δ^9-Tetrahydrocannabinol
- Cannabinoid
- Anxiety
- Antipsychotic
- Schizophrenia

Introduction

The use *Cannabis sativa* (cannabis) extracts as medicine was described in China and India (1) before the birth of Christ. The therapeutic use of cannabis was introduced in Western medicine in the first half of the 19th century and reached its climax in the last two decades of the same century. At the turn of the century, several pharmaceutical companies were marketing cannabis extracts and tinctures which were prescribed by doctors for many different complaints including pain, whooping cough and asthma, and as a sedative/hypnotic agent (2). However, the use of cannabis as a medicine almost completely disappeared at about the middle of the 20th century. The main reasons for this disappearance were the variable potency of cannabis extracts, the erratic and unpredict-

able individual responses, the introduction of synthetic and more stable pharmaceutical substitutes such as aspirin, chloral hydrate and barbiturates, the recognition of important adverse effects such as anxiety and cognitive impairment, and the legal restrictions to the use of cannabis-derived medicines (2).

Today this situation has changed considerably. The main active psychotropic constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), was isolated, identified and synthesized in the 1960's. Almost three decades later, cannabinoid receptors in the brain were described and cloned and the endogenous cannabinoids were isolated and identified (3). As a result of these discoveries the interest in cannabis research has remarkably increased. For instance, the number of publications using the key word "brain", compiled by the ISI Web of Knowledge, increased 26 times from 1960-1964 to 2000-2004, while the number of publications about 'cannabis' increased 78.5 times during the same period. As a consequence, the research on the use of cannabis as medicine has been renewed.

Although Δ^9-THC is commonly accepted as the main factor responsible for the effects of cannabis, several reports have demonstrated that other components of the plant influence its pharmacological activity (4). One of these components is cannabidiol (CBD), which may constitute up to 40% of cannabis extracts (5) and is devoid of the typical psychological effects of cannabis in humans (6). Studies on the interaction between Δ^9-THC and CBD have produced apparently contradictory results (7). Although potentiation of the effects of Δ^9-THC has been observed (8,9), this phenomenon probably involves pharmacokinetic interactions since CBD is a potent inhibitor of hepatic drug metabolism (10) and increases Δ^9-THC concentrations in the brain (11). Several studies, however, have reported antagonism of the effects of Δ^9-THC when both compounds are administered simultaneously to animals (12,13) or humans (6,14).

CBD (1 mg/kg) co-administered with Δ^9-THC (0.5 mg/kg) significantly reduced the anxiety and the psychotomimetic symptoms induced by the latter drug in healthy volunteers (6). Since the dose of CBD used in that study did not change Δ^9-THC levels in blood (15), it was suggested that CBD blocked the effects of Δ^9-THC by some intrinsic pharmacological properties. Actually, when administered alone CBD produced its own effects, including hypnotic (16), anticonvulsive (17), neuroprotective (18), and hormonal (increased corticosterone and cortisol levels) effects (19,20). These effects led to the hypothesis that CBD could have anxiolytic and/or antipsychotic effects.

Anxiolytic effect of cannabidiol

The anxiolytic properties of CBD has been demonstrated by several pre-clinical studies that employed different paradigms such as the conditioned emotional response (21), the Vogel conflict test (22) and the elevated plus-maze (23,24). In the later study (24), the effective doses of CBD ranged from 2.5 to 10 mg/kg, and the drug produced an inverted U-shaped dose-response curve, the higher doses being no longer effective in rats. This could explain the negative results obtained with high doses of CBD (above 100 mg/kg) in a previous study employing the Geller-Seifter conflict test (25).

To evaluate a possible anxiolytic effect of CBD in humans, a double-blind study was conducted on healthy volunteers submitted to a simulation of the public speaking test. CBD (300 mg, *po*) was compared to ipsapirone (5 mg), diazepam (10 mg) or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated the anxiety induced by the test (26). The anxiolytic-like effect of CBD in healthy volunteers was also observed in a more recent double-blind study that investigated its effects on regional cerebral blood flow by

single-photon emission computed tomography. Because the procedure, by itself, can be interpreted as an anxiogenic situation, it permits the evaluation of anxiolytic drugs. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity (27). Therefore, similar to the data obtained in animal models, results from studies on healthy volunteers have strongly suggested an anxiolytic-like effect of CBD.

Antipsychotic effect

Studies employing animal models

Animal models used for screening antipsychotic drugs are based on the neurochemical hypothesis of schizophrenia, involving mainly the neurotransmitters dopamine and glutamate (28).

Antagonism of dopamine D_2 receptors may be a common feature of most clinically effective antipsychotic drugs, especially those active against hallucinations and delusions (29). The dopamine-based models usually employ apomorphine, a direct agonist, or amphetamine, a drug that increases the release of this neurotransmitter and blocks its re-uptake. Another common effect of antipsychotic drugs is hyperprolactinemia that results from the antagonism of D_2 receptors on anterior-pituitary mammotrophic cells. These cells are tonically inhibited by dopamine produced in the hypothalamic arcuate nucleus (30). Conventional or typical antipsychotic drugs, especially those with high affinity for D_2 receptors (haloperidol being the standard compound), induce motor side effects characterized by a Parkinson-like syndrome. On the contrary, atypical antipsychotic drugs, of which clozapine is the prototype, are therapeutically effective at doses that induce fewer or no Parkinson-like effects (29). The probability of an antipsychotic agent to induce Parkinson-like symptoms may be evaluated in the catalepsy test (31). Atypical antipsychotics inhibit the stereotypies and hyperlocomotion induced by dopamine agonists at lower doses than those that produce catalepsy.

As a first step in the investigation of possible antipsychotic-like properties of CBD, the drug was compared to haloperidol in rats submitted to dopamine-based models (32). However, blocking D_2 receptors is not necessarily the only mechanism for the antipsychotic activity. Several lines of evidence suggest that the glutamatergic N-methyl-D-aspartate (NMDA) receptor is involved in the mechanism of action of clozapine (33). The glutamate-based models of schizophrenia employ sub-anesthetic doses of ketamine, a glutamate NMDA receptor antagonist, or its related compound phencyclidine, to induce psychotic symptoms. A more recent study investigated the effects of CBD in both dopamine and glutamate-based models predictive of antipsychotic activity. The study compared the ability of CBD, haloperidol and clozapine to prevent the hyperlocomotion induced by amphetamine or ketamine in mice (34). The results of these two studies are summarized in Table 1.

CBD (15-60 mg/kg), like haloperidol (0.25-0.5 mg/kg), reduced the apomorphine-induced stereotyped behavior in rats in a dose-related manner. These drugs also increased the plasma levels of prolactin. However, higher doses of CBD were needed (120 and 240 mg/kg) to obtain such effects. Moreover, in contrast to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg/kg. In agreement with the results obtained in rats, CBD (15-60 mg/kg) inhibited the hyperlocomotion induced by amphetamine in mice in a dose-related manner. In addition, the drug also attenuated the hyperlocomotion induced by ketamine, expanding its antipsychotic-like effects to a glutamate-based model. As expected, while both haloperidol (0.15-0.6 mg/kg) and clozapine (1.25-5.0 mg/kg) inhibited hyperlocomotion, only haloperidol induced cata-

Table 1. Summary of two studies employing animal models for the screening of antipsychotic drugs, which compared cannabidiol, haloperidol and clozapine in rats (32) and mice (34).

Rats

Cannabidiol (mg/kg)	0	15	30	60	120	240	480
Apomorphine stereotypy (biting) [% of animals]	83.3	83.3	50.0	16.71*	-	-	-
Prolactin levels (ng/mL) [mean (SEM)]	4.1 (0.7)	11.1 (1.0)	12.2 (1.6)	13.5 (2.6)	29.8* (3.1)	38.1* (13.5)	-
Catalepsy time (s) [median]	150	-	-	365	214	626	646

Haloperidol (mg/kg)	0	0.06	0.125	0.15	0.25	0.3	0.5	0.6	1.0
Apomorphine stereotypy (biting) [% of animals]	83.3	-	83.3	-	50.0	-	0.0*	-	-
Prolactin levels (ng/mL) [mean (SEM)]	3.0 (1.0)	14.3 (4.2)	28.3* (3.1)	-	33.3* (3.0)	-	39.5* (1.7)	-	-
Catalepsy time (s) [median]	150	-	713	-	1684*	-	1408*	-	4737*

Mice

Cannabidiol (mg/kg)	0	15	30	60	120	240	480
Amphetamine hyperlocomotion distance (cm) [mean (SEM)]	5326 (1160)	4838 (683)	2689* (383)	1730* (378)	-	-	-
Ketamine hyperlocomotion distance (cm) [mean (SEM)]	5154 (235)	4191 (985)	3264+ (506)	4127 (962)	-	-	-
Catalepsy time (s) [mean (SEM)]	8.3 (2.2)	2.4 (0.4)	4.1 (1.0)	3.7 (1.3)	-	-	-

Haloperidol (mg/kg)	0	0.06	0.125	0.15	0.25	0.3	0.5	0.6	1.0
Amphetamine hyperlocomotion distance (cm) [mean (SEM)]	4111 (571)	-	-	1039* (90)	-	804* (166)	-	473* (134)	-
Ketamine hyperlocomotion distance (cm) [mean (SEM)]	5218 (561)	-	-	3277 (513)	-	1392* (376)	-	728* (197)	-
Catalepsy time (s) [mean (SEM)]	7.7 (4.1)	-	-	109.4* (40.5)	-	108.3* (29.6)	-	241.4 (30.0)	-

Clozapine (mg/kg)	0	1.25	2.5	5
Amphetamine hyperlocomotion distance (cm) [mean (SEM)]	6437 (1858)	4964 (1079)	3906 (699)	2803* (938)
Ketamine hyperlocomotion distance (cm) [mean (SEM)]	4852 (588)	620* (200)	93* (42)	148* (77)
Catalepsy time (s) [mean (SEM)]	5.3 (1.3)	30.1 (9.3)	21.7 (6.1)	12.6 (6.0)

N = 6 to 10 animals per group.
*P < 0.05 and +P < 0.10 compared to the baseline level (Kruskal-Wallis test or ANOVA followed by Duncan test).

lepsy in this dose range. Therefore, similar to clozapine, CBD did not induce catalepsy at doses that inhibited hyperlocomotion in mice. These results support the view that CBD exhibits a profile similar to that of atypical antipsychotic drugs.

In addition to being tested on behavioral models, typical and atypical antipsychotics may also be distinguished according to their pattern of neural activation. This may be detected by the expression of the proto-oncogene *c-Fos*. For example, haloperidol induces Fos immunoreactivity in the dorsal striatum, probably reflecting its motor side effects, while clozapine induces Fos immunoreactivity in the prefrontal cortex but not in the dorsal striatum (35). The Fos immunoreactivity pattern induced by CBD (120 mg/kg) was compared to that of haloperidol (1 mg/kg) and clozapine (20 mg/kg) in rats. Only haloperidol increased Fos immunoreactivity in the dorsal striatum, while both CBD and clozapine, but not haloperidol, induced Fos immunoreactivity in the prefrontal cortex (36,37). These results are consistent with the behavioral data obtained when comparing CBD with these prototype antipsychotics.

In conclusion, animal models employing behavioral as well as neurochemical techniques suggest that CBD has a pharmacological profile similar to that of an atypical antipsychotic drug.

Safety studies

Safety studies of CBD were required before human tests. CBD was extensively investigated in laboratory animals to detect possible side or toxic effects (17). Acute CBD administration by the oral, inhalatory or intravenous route did not induce any significant toxic effect in humans (38). In addition, chronic administration of CBD for 30 days to healthy volunteers, at daily doses ranging from 10 to 400 mg, failed to induce any significant alteration in neurological, psychiatric or clinical exams (17). Finally, in patients suffering from Huntington's disease, daily doses of CBD (700 mg) for 6 weeks did not induce any toxicity (39). Therefore, confirming results from animal studies, the available clinical data suggest that CBD can be safely administered over a wide dose range.

Clinical use

In 1848 the French psychiatrist Jacques-Joseph Moreau de Tour began to investigate the effects of cannabis. He proposed for the first time the use of the plant as an experimental psychotomimetic (40). Results from a recent study, obtained with more appropriate measurements and scales, agreed with Moreau's observation that Δ^9-THC administration induces subjective, cognitive and behavioral changes that resemble endogenous psychosis, suggesting that Δ^9-THC can, indeed, be used as an experimental psychotomimetic drug (41).

In 1982, a study investigating a possible interaction between Δ^9-THC and CBD in healthy volunteers demonstrated that the latter drug could inhibit Δ^9-THC-induced subjective changes that resembled symptoms of psychotic diseases (6) (Figure 1). 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 much higher frequency of acute psychotic episodes than in other countries (42). These lines of evidence led to several investigations of a possible antipsychotic effect of CBD.

In order to evaluate the antipsychotic effects of new drugs in healthy volunteers, a useful model is the perception of binocular depth inversion. When a picture is presented separately to each eye, with a slight difference in the angle, it induces a three-dimensional perception. The inversion of this picture from one eye to the other normally

induces a change in convexity. This change may not be perceived if familiar objects (faces, for example) are presented, with the expected image predominating, which is illusory. Schizophrenic patients have difficulty in perceiving this illusory image, reporting a more veridical judgment. During antipsychotic treatment, the inverted faces were seen as more illusionary (43). This veridical judgment may also be obtained by the administration of psychotomimetic drugs such as nabilone, a Δ^9-THC analogue. In this model, impairment of the perception of the illusory image induced by nabilone was attenuated by CBD, suggesting an antipsychotic-like effect of this compound (44).

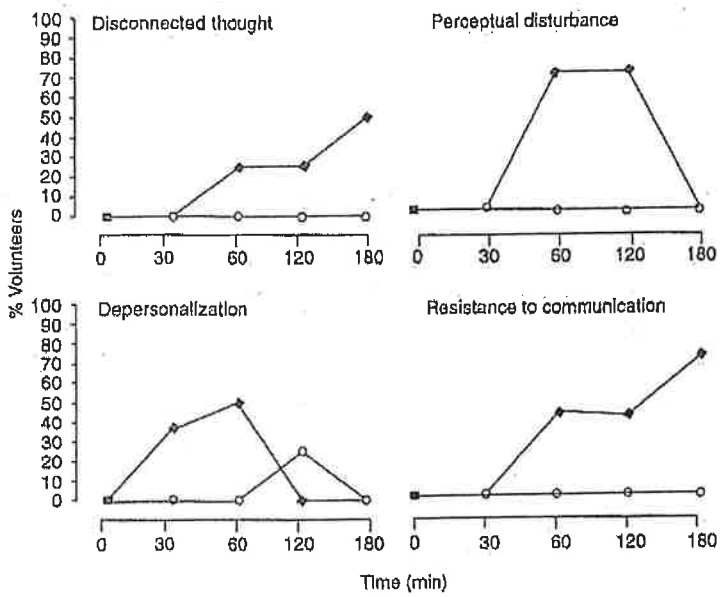

Figure 1. Percentage of healthy volunteers who exhibited psychotic-like effects after the ingestion of 0.5 mg/kg Δ^9-tetrahydrocannabinol (Δ^9-THC; lozenges) and a combination of 0.5 mg/kg Δ^9-THC + 1 mg/kg cannabidiol (circles).

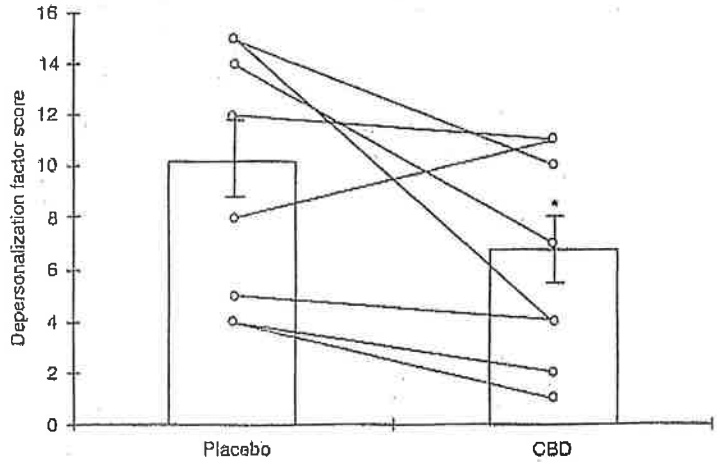

Figure 2. Depersonalization factor scores of the Clinician-Administered Dissociative States Scale for each healthy volunteer (lines) during intravenous ketamine infusion, after oral placebo or cannabidiol (CBD) (600 mg) administration. Bars indicate the mean ± SEM. *P < 0.05 compared to placebo (paired *t*-test) for 9 volunteers.

Another important model used to evaluate antipsychotic-like activity in healthy volunteers is the administration of sub-anesthetic doses of ketamine. This glutamate-based model induces a psychotic reaction that mimics both positive and negative symptoms of schizophrenia (45). A double-blind crossover procedure was performed to study the effect of CBD in this model (46). Nine healthy volunteers were assigned randomly to the placebo or CBD (600 mg) groups in two experimental sessions separated by a 1-week interval. After being submitted to psychiatric assessment scales, the volunteers received placebo orally or the drug and rested for 65 min. An infusion pump was then installed and an intravenous bolus of S-ketamine (0.26 mg/kg) was administered during 1 min followed by a maintenance dose of 0.25 mg/kg for 30 min. A Clinician-Administered Dissociative States Scale (CADSS) was applied at the beginning of the sessions and 90 min after the bolus injection. The volunteers were asked to respond the scale according to the period during which they felt most symptomatic. CBD attenuated the effects of ketamine on the total score of the CADSS and also on each of its factors separately. This effect was significant for the depersonalization factor, further reinforcing the antipsychotic-like properties of CBD (Figure 2).

In view of the safe profile of CBD administration in humans and in laboratory animals, we decided to perform open-label clini-

cal trials in a reduced number of patients. In 1995, CBD was tested in a case study with a 19-year-old schizophrenic female patient who presented serious side effects after treatment with conventional antipsychotics (47). Following a wash-out period of 4 days this patient received increasing oral doses of CBD dissolved in oil, reaching 1500 mg/day, for 4 weeks. After this period, CBD administration was interrupted and placebo was administered for 4 days. Finally, the treatment was shifted to increasing doses of haloperidol that reached 12.5 mg/day. The psychiatric interviews were video-recorded and the symptoms were assessed by a blinded-psychiatrist using the Brief Psychiatric Rating Scale (BPRS). A significant improvement was observed during CBD treatment, while a worsening was observed when the administration was interrupted. The improvement obtained with CBD was not increased by haloperidol (Figure 3, patient A). Further supporting the safe profile of CBD, no side effects were observed, as assessed by the Ugvalg for Kliniske Undersgelser (UKU) scale (47).

More recently, CBD was administered to three 22- or 23-year-old male patients with a diagnosis of schizophrenia who had not responded to typical antipsychotic drugs (48). They received placebo for 5 days in the hospital followed by CBD from the 6th to the 35th day. After this period, they received placebo for an additional 5 days, followed by olanzapine for at least 15 days. The dose of CBD was increased from 40 up to 1280 mg/day. The patients were assessed by two psychiatrists, who were blind to the doses administered, using the BPRS and UKU scales. No side effects were observed during CBD treatment, even at the higher dose of 1280 mg/day. A partial improvement was observed in one patient (Figure 3, patient B) while slight or no improvement was observed in the other two (Figure 3, patients C and D). However, the patients (C and D) were considered to be refractory, since they did not even respond to clozapine, a fact that may explain the lack of CBD effectiveness (48). Figure 3 shows the results obtained with the 4 schizophrenic patients treated so far with CBD. These studies suggest, therefore, that CBD has an antipsychotic-like profile in healthy volunteers and may possess antipsychotic properties in schizophrenic patients, but not in the resistant ones.

Confirming this suggestion, a preliminary report from a 4-week, double-blind controlled clinical trial, using an adequate number of patients and comparing the effects of CBD with amisulpride in acute schizophrenic and schizophreniform psychosis, showed that CBD significantly reduced acute psychotic symptoms after 2 and 4 weeks of treatment when compared to baseline. In this trial CBD did not differ from amisulpride except for a lower incidence of side effects (49).

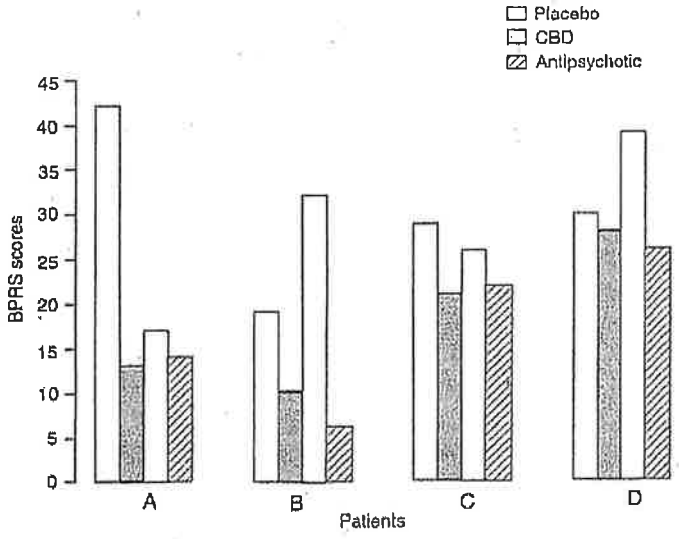

Figure 3. Brief Psychiatric Rating Scale (BPRS) scores for 4 schizophrenic patients treated with cannabidiol (CBD). Patient A received up to 1500 mg/day CBD and patients B, C, and D received up to 1280 mg/day. Bars indicate BPRS scores for each schizophrenic patient at the end point after the oral administration of placebo, CBD and a control antipsychotic drug (haloperidol for patient A and olanzapine for patients B, C and D). Placebo was administered before and after CBD treatment. Patient A is a woman who presented serious side effects with typical antipsychotics. Patients B, C, and D are men previously treated with typical antipsychotics with no response.

In conclusion, results from pre-clinical and clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients. Future trials of this cannabinoid in other psychotic conditions such as bipolar disorder (50) and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly needed.

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S14.02

Cannabidiol as an antipsychotic agent

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Background: The human endocannabinoid system interacts with various neurotransmitter systems and the endocannabinoid anandamide was found significantly elevated in CSF and inversely correlated to psychopathology (Giuffrida et al. 2004) providing a link to the neurobiology of schizophrenia. While delta-9-tetrahydrocannabinol, the psychoactive compound of Cannabis sativa, shows psychedelic properties, the major herbal cannabinoid compound cannabidiol was suggested recently a re-uptake inhibitor of anandamide. In addition potential antipsychotic properties have been hypothezised.

Methods: We performed an explorative, 4-week, double-blind, controlled clinical trial on the effects of purified cannabidiol in acute schizophrenia compared to the antipsychotic amisulpride. The antipsychotic properties of both drugs were the primary target of the study. Furthermore, side-effects and anxiolytic capabilities of both treatments were investigated.

Results: 42 patients fulfilling DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis participated in the study. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4 weeks as assessed by BPRS and PANSS. However, there was no statistical difference between both treatment groups. In contrast, cannabidiol induced significantly less side effects (EPS, increase in prolactin, weight gain) when compared to amisulpride.

Conclusions: Cannabidiol proved substantial antipsychotic properties in acute schizophrenia. This is in line with our suggestion of an adaptive role of the endocannabinoid system in paranoid schizophrenia, and raises further evidence that this adaptive mechanism may represent a valuable target for antipsychotic treatment strategies.

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S14.03

Anxiolytic effects of cannabidiol

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Background and Aims: Cannabidiol (CBD) constitutes up to 40% of cannabis sativa plant and has quite different psychological effects to the plant's best-known constituent, delta-9-tetrahydrocannabinol (delta-9-THC). This study examines the current knowledge of the effects of CBD on anxiety.

Method: Articles were identified through a search of MEDLINE using the key word cannabidiol and anxiety. No search limits were included. Additional references were located through review of the bibliographies of the articles identified.

Results: In animal studies CBD has shown similar effects to anxiolytic drugs in conditioned emotional paradigms, the Vogel conflict test, and the elevated plus maze test. In humans, oral administration of CBD in healthy volunteers decreases and antagonizes the anxiogenic effect of high doses of delta-9-THC. CBD may thus posses inherent anxiolytic properties unrelated to THC-type activity. This is consistent with its anxiolytic effect on anxiety elicited by simulated public speaking test. In addition, SPECT and fMRI neuroimaging studies have confirmed that CBD has anti-anxiety properties and that these effects are mediated by an action on limbic and paralimbic brain areas.

Conclusions: These results support the hypothesis that CBD may be a future therapeutic option for anxiety. However, future studies of CBD in clinical anxiety such as panic and social anxiety disorder and comparative studies of its anxiolytic effects with those produced by benzodiazepines and other anti-anxiety compounds are clearly indicated.

S14.04

CBD and the neural correlates of anxiety

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Aims: The study sought to examine the neurophysiological effects of cannabidiol (CBD) on the emotional processing using functional Magnetic Resonance Imaging (fMRI).

Method: Fifteen healthy male participants (age range 18-35) with a lifetime exposure to cannabis of 15 times or less were recruited in a double blind event-related fMRI design. Prior to each scanning session, participants were given an oral dose of either 600mg CBD or a placebo. The blood levels of drugs were monitored via an intravenous line, while systolic and diastolic blood pressure and heart rate (beats per minute) were recorded manually. During the scan, subjects were presented with 10 different facial identities, each identity expressing 50% or 100% intensities of fear or a neutral expression. Neuropsychological performance and symptoms ratings were recorded at baseline, immediately before scanning (1 hr), immediately after scanning (2 hr), and one hour post scanning (3 hr).

Results: CBD had no significant effect on the gender discrimination task. Reaction times were significantly faster when processing 100% fearful faces than compared to 50% fearful and neutral faces. CBD had a significant effect on brain activation in response to faces with emotional expressions, decreasing activation in the right posterior cingulate gyrus and in the right cerebellum, when compared to placebo. Furthermore, a significant interaction effect was observed. In the right cingulate gyrus CBD attenuated activation during the processing of intense fearful faces but had no effect of neural response to neutral or mild fearful faces.

Conclusion: CBD significantly modulates the neurophysiological response associated with anxiety.

S14.05

Cannabis and psychosis

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Cannabis use is approximately twice as high among people with schizophrenia as among the general population. Evidence for cannabis use predisposing to psychoses later in life came many years ago from a study of Swedish conscripts. A dose-response relationship was observed

between cannabis use at conscription and diagnosis of schizophrenia 15 years later. In 2002, similar findings were reported from The Netherlands where cannabis use was found to increase the risk of psychosis in psychosis-free individuals. A birth cohort study from Christchurch examined the relationship between cannabis use and the development of schizophrenia. Individuals who were cannabis dependent at age 18 years had a 3.7-fold increased risk of psychotic symptoms than those who were not cannabis dependent. Furthermore, the development of psychotic symptoms tended to decrease the consumption of cannabis. The Dunedin study showed that individuals using cannabis at ages 15 and 18 years had increased rates of developing psychotic symptoms, and carriers of the COMT val allele were most likely to develop schizophreniform psychosis after adolescent cannabis use street drug users know that cannabis can induce delusions (though not hallucinations). There is also some preliminary evidence that one of the reasons for the increase in the incidence of schizophrenia is south London is the increased consumption of cannabis. Our most recent studies concern the mechanism of action of cannabis.

W05. Workshop: NEUROPSYCHIATRIC SYMPTOMS MANAGEMENT IN HIV POSITIVE PATIENTS: A CASE DISCUSSION

W05

Neuropsychiatric symptoms management in HIV positive patients: a case discussion

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Abstract not available at the time of printing

S15. Symposium: TRANSITION FROM PSYCHIATRIC IN PATIENT TO COMMUNITY CARE: A EUROPEAN PERSPECTIVE (Organised By The AEP Section On Epidemiology And Social Psychiatry)

S15.01

Effect on outcomes of advance statements of patient preferences

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An 'advance statement' allows a patient to state treatment preferences in anticipation of a time in the future when, as a result of a mental disorder or disability, he or she may no longer be able to make treatment decisions. A number of types of advance statements in psychiatry can be described: 'advance directives' (and 'facilitated advance directives'), 'crisis cards' and 'joint crisis plans'. They differ according to a number of characteristics – the degree to which they have legal force, whether the clinical team is involved in their formulation, and whether a third party acts as a facilitator. There is accumulating evidence that some forms of advance statement empower patients and reduce the need for coercive treatments. The results of a randomized controlled trial of 'joint crisis plans' carried out by our research team in SE England will be discussed. A significant reduction in compulsory admissions to hospital was an important finding.

S15.02

Deinstitutionalization in the Netherlands and the effectiveness of act to maintain contact with the severe mentally ill

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Background and Aims: Deinstitutionalisation may put part of the severe mentally ill patients at risk to deteriorate in the community, mainly because they are difficult to engage with services. Assertive community treatment (ACT) is widely seen as an adequate answer for these difficult to engage patients. ACT is now rapidly implemented in many European mental health services, but recently the evidence base is questioned. Positive results of randomised trials in the US could not be replicated in the UK.

Method: In Groningen (The Netherlands) a psychiatric case register (PCR) is in operation since 1986, and now covers a catchment area of 1.6 million inhabitants. It is a perfect tool to study the transition from inpatient to community care.

We did a randomized controlled trial (RCT) to study the effectiveness of the first ACT team in our region, using the PCR to measure primary outcomes. It is the only RCT of ACT in the Netherlands. In total 118 patients were randomized to two conditions. The primary research questions were:

- Is ACT better than standard care in maintaining contact with patients?
- Is ACT better than standard care in reducing the use of inpatient care?

Results: ACT was superior in engaging patients to services, but no effect on the use of inpatient beds were found. Moreover, we did not find benefits in functioning, quality of life and unmet needs.

Conclusions: Too many patients are lost in standard care and therefore we highly value the sustained contact ability of ACT.

S15.03

An overview of the Nordic comparative study on sectorized psychiatry 1987 - 2000

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The aims of the study were to investigate how the characteristics of the psychiatric services, the environmental factors and the patient characteristics are related to contact rates and use of psychiatric services.

The study included all new patients contacting the psychiatric services during one year in 7 Nordic catchment areas. For each patient a 1-year follow-up of service use in terms of inpatient care, day

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Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential

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Abstract

Bipolar affective disorder is often poorly controlled by prescribed drugs. Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to alleviate symptoms of both mania and depression. We undertook a literature review of cannabis use by patients with bipolar disorder and of the neuropharmacological properties of cannabinoids suggesting possible therapeutic effects in this condition. No systematic studies of cannabinoids in bipolar disorder were found to exist, although some patients claim that cannabis relieves symptoms of mania and/or depression. The cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert sedative, hypnotic, anxiolytic, antidepressant, antipsychotic and anticonvulsant effects. Pure synthetic cannabinoids, such as dronabinol and nabilone and specific plant extracts containing THC, CBD, or a mixture of the two in known concentrations, are available and can be delivered sublingually. Controlled trials of these cannabinoids as adjunctive medication in bipolar disorder are now indicated.

Keywords

bipolar disorder, cannabidiol, cannabinoids, cannabis, CBD, depression, dronabinol, mania, nabilone, tetrahydrocannabinol, THC

Introduction

The treatment of bipolar affective disorder (BAD) remains problematic despite several guidelines or consensus statements (Sachs *et al.*, 2000; Geddes and Goodwin, 2001; Goodwin, 2003; Lloyd *et al.*, 2003). The mean time to relapse after the first episode is 5 years (Geddes *et al.*, 2003) and periods of remission shorten as the illness progresses, regardless of treatment. Most patients with BAD are prescribed a combination of drugs, all of which have their disadvantages. Lithium, although efficacious, has limited effectiveness because of low acceptance and occurrences of mania on withdrawal. Many anticonvulsants can produce unacceptable side-effects (Porter *et al.*, 1999; Ashton and Young, 2003). Sodium valproate, the most commonly prescribed mood stabilizer, carries risks in women of childbearing age (Committee on Safety of Medicines, 2003; Goodwin and Sachs, 2004). Lamotrogine, although effective in biplar depression, requires careful dosage control to prevent skin complications, which may prove to be serious. Conventional antidepressants and electroconvulsive therapy can induce mood elevation, which may progress to rapid mood cycling. Antipsychotic drugs have many undesirable effects and the atypical antipsychotics quetiapine, olanzapine and risperidone have all been reported to induce mania in some cases (Mishra *et al.*, 2004). Psychosocial measures have been shown to complement medication, but they remain at an early stage of development and their widespread use is limited by available resources.

Thus, there is a clear need to explore new ways of managing bipolar disorder. Patient reports and observations, backed by known pharmacology, suggest that the cannabis derivatives Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may have mood stabilizing properties. The present study aimed to review the evidence for this. The use of controlled substances in medicine is

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widespread, especially in children with psychological difficulties and in pain management. Nevertheless, the consequences of extending the use of controlled substances need careful consideration.

It is well known that there is a high prevalence of comorbid drug abuse in people with BAD (Brown *et al.*, 2001). A 61% lifetime prevalence of substance abuse in Bipolar I patients and 48% in Bipolar II patients has been reported compared to 6% in the general population (Regier *et al.*, 1990). Some studies have provided data on individual drugs that are abused by these patients (Estroff *et al.*, 1985; Miller *et al.*, 1989; Regier *et al.*, 1990; Marken *et al.*, 1992; Mueser *et al.*, 1992; Sonne *et al.*, 1994; Winokur *et al.*, 1998). The results indicate high rates of lifetime use of cannabis (30–64%) and stimulants (amphetamines 31–39%, cocaine 15–39%) and lower rates for opiates (6–25%). The extent to which bipolar patients use cannabis as self-medication is not clear, although anecdotal reports suggest that some patients find it alleviates both depression (Gruber *et al.*, 1996) and mania (Grinspoon and Bakalar, 1998). Although cannabis can cause adverse effects, including psychosis and mania, some cannabinoids have properties that could be of value in psychiatric disorders, and a literature review was therefore undertaken to investigate their therapeutic potential in bipolar affective disorder.

Methods

Electronic searches for relevant papers were performed, employing Medline (1966 to present), Embase (1980 to present), ISI Web of Science (1990 to present) and Psychoinfo (earliest available to present). Search terms were 'bipolar', 'manic depression', 'mania', 'antidepressant', 'antimanic', 'mood stabilizer', 'cannabinoid', tetrahydrocannabinol', 'THC', 'cannabidiol', 'CBD', 'cannabis, "marijuana", 'nabilone' and 'dronabinol'.

In addition, Medline reviews and investigations of pharmacological, psychiatric and therapeutic effects of cannabis/cannabinoids (1970–2003) were consulted and a manual searching of all relevant articles was performed.

Results

The literature search revealed no systematic studies of the therapeutic use of cannabis or cannabinoids in BAD, although there are several anecdotal reports. Grinspoon and Bakalar (1998) described five cases in which cannabis appeared to alleviate mania. For example, one woman with BAD quoted in their report chose cannabis over alcohol to control her manic behaviour: 'A few puffs of this herb and I can be calm ... this drug seems harmless compared to other drugs I have tried, including tranquillisers and lithium'. A husband, describing his wife with BAD said: 'My wife functions much better when she uses marijuana. When she is hypomanic, it relaxes her, helps her sleep, and slows her speech down. When she is depressed and would otherwise lie in bed all day, the marijuana makes her more active ... Lithium is also effective, but it doesn't always keep her in control'.

Personal observation of a patient attending the local outpatients also indicated an apparent antimanic effect of cannabis. The patient was a 39-year-old male who had been diagnosed 10 years previously as having BAD. His illness mainly took the form of manic episodes for which he had a history of five hospital admissions. These episodes were difficult to control because the patient was intolerant of antipsychotic drugs, including quetiapine and risperidone, and non-compliant with lithium and sodium valproate. Diazepam controlled his symptoms but he often used up his 2-week prescription for 30 mg daily in 1 week.

A recent manic episode was associated with a severe behaviour disturbance involving a further possible detention order. The psychiatrist was called for a home visit, which he made some hours later. To his surprise, he found the patient calm, almost serene, sitting tranquilly in an armchair smoking a cannabis 'spliff'. (He offered the psychiatrist one of the same, which was declined). It was clear that the cannabis was responsible for the rapid change in the patient's behaviour. He maintained that, over the years, he had taken mainly cannabis, sometimes moderate amounts of alcohol, occasionally 'street' benzodiazepines, and infrequently heroin to regulate his mood.

Gruber *et al.* (1996) described five cases in which marijuana appeared to produce a direct antidepressant effect. Three of these patients had BAD and all but one found that marijuana relieved their depression better than standard antidepressant drugs. Two surveys of medicinal cannabis use in California, where this use is legalized, showed that 15–27% of patients were prescribed it for mood disorders, including depression, post-traumatic stress disorder, BAD and attention deficit disorder resistant to conventional pharmacotherapy (Gieringer, 2003).

It is noteworthy that, in the anecdotal reports, cannabis was not taken for the 'high' sought by recreational users and it is possible that its effects are different when taken in subeuphoric doses for medical reasons, such as in multiple sclerosis or pain conditions (Randall, 1991; Hodges, 1993). The effects are most probably due to cannabinoids present in cannabis smoke, including Δ^9-THC, CBD and possibly others, which have been less studied. Patients' accounts and the advances in the understanding of cannabinoid physiology suggest that they may have a therapeutic potential in BAD (Pertwee, 1999a,b).

Pharmacological basis of cannabinoid effects: the endocannabinoid system

THC and cannabinoid CB_1 receptors THC is the major psychoactive agent present in cannabis, and its primary metabolite, 11-OH-THC, is even more potent (Maykut, 1985; McPartland and Russo, 2001). These cannabinoids are agonists of endogenous cannabinoid CB_1 receptors that are present in the brain, spinal cord and peripheral nerves. CB_1 receptors are widely distributed throughout the brain (Table 1) and are present in the cerebral cortex, including the cingulate cortex, hippocampus, basal amygdala, corpus striatum and other areas possibly involved in the pathophysiology of BAD and its emotional and cognitive components (Drevets *et al.*, 1997; Strukowski *et al.*, 1999; Altshuler *et al.*, 2000; Phillips *et al.*,

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Table 1 Localization of cannabinoid CB_1 receptors

Density	Localization	
Very dense	Basal ganglia	- globus pallidus, substantia nigra pars reticulata, entopeduncular nucleus
	Cerebellum	- molecular layers
	Hippocampus	- dentate gyrus
Dense	Cerebral cortex[a]	- layers I and VI
	Hippocampus	- CA pyramidal cells
	Corpus striatum	- caudate putamen
Moderate	Hypothalamus[a]	
	Basal amygdala[a]	
	Central grey substance	
	Nucleus of solitary tract	
	Spinal cord	
	Peripheral nerve terminals	
Sparse	Thalamus	
	Pons and Medulla	
	Some non-neural tissues, including spleen and testes	

[a]Receptor density in the cingulate cortex, hypothalamus and amygdala is relatively greater in the human brain than in the same areas of rat and monkey brain (Herkenham, 1995; Pertwee, 1997).

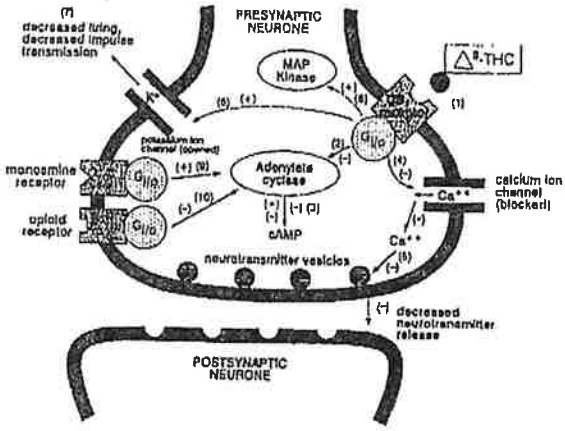

Figure 1 Schematic diagram of signal transduction mechanisms stimulated by CB_1 receptors. The CB_1 receptor (1) is coupled to a second messenger $G_{i/o}$ protein. Via this protein, activation of the receptor inhibits the enzyme adenylate cyclase (2) and decreases the production of cAMP (3). Via the G-protein, the inward flow of calcium ions is blocked (4), decreasing release of neurotransmitters (5). Also via the G-protein, the outward flow of potassium ions is enhanced (6), resulting in decreased neuronal firing and decreased impulse transmission (7). Stimulation of the G-protein also activates MAP kinase (8), affecting intracellular gene expression. Other receptors on the same neurone (for monoamines and/or opioids) may activate their own G-proteins but share a common adenylate cyclase, which they may stimulate (9) or inhibit (10). Anandamide is released in the post-synaptic membrane and acts retrogradely as an agonist on presynaptic CB_1 receptors (Howlett, 1995; Pertwee, 1997; Ameri, 1999; Joy *et al.*, 1999; Van der Stelt and di Marzo, 2003; Alger, 2004)

2003; Surguladze *et al.*, 2003). CB_1 receptors belong to a family of G-protein coupled receptors that includes receptors for aminergic neurotransmitters (noradrenaline, dopamine, serotonin and acetylcholine) and act through second messenger systems. CB_2 receptors are similar to CB_1 receptors but are present mainly in immune cells in the periphery and are not considered further here.

Activation of the CB_1 receptor (Fig. 1) inhibits adenylate cyclase and decreases the production of cAMP (3,5-adenosine monophosphate) (Pertwee, 1997), an action which affects many intracellular processes and ultimately affects intracellular neurotransmission (Shiloh *et al.*, 1999). CB_1 receptors also modulate transneuronal ion channels. They are negatively coupled to calcium channels (N and P/Q type) and inhibit the inward flow of calcium ions, decreasing the release of neurotransmitters, either excitatory or inhibitory, at presynaptic nerve terminals (Pertwee, 1997). At the same time, CB_1 activation enhances the outward flow of potassium ions (through A-type potassium channels), a G-protein coupled event that may also depend on inhibition of cAMP production (Deadwyler *et al.*, 1995). The result is inhibition of neuronal depolarization, decreased action potential generation and hence reduced impulse propagation.

CBD and anandamides The endogenous ligands for cannabinoid receptors, both CB_1 receptors in the nervous system and CB_2 receptors in peripheral tissues, are a family of arachidonic acid derivatives, sometimes termed endocannabinoids (Pertwee, 1999a,b). The two that appear to be of most physiological importance are arachidonylethanolamide (anandamide) and 2-arachidonyl glycerol (2-AG). Anandamide is present in the brain in the same areas as CB_1 receptors. It is enzymatically synthesized in cell membranes, binds to CB_1 receptors (Van der Stelt and Di Marzo, 2003) and, in animal models, shows many of the actions of THC (Stein *et al.*, 1996; Martin and Cone, 1999). However, unlike THC, the effects of anandamide are short-lived, lasting less than 15 min after intravenous injection in the rat (Stein *et al.*, 1996) because it is rapidly inactivated by enzymatic hydrolysis and removed from its site of action by neuronal uptake mechanisms (Joy *et al.*, 1999; Pertwee, 1997, 1999b; Piomelli *et al.*, 2000; Alger, 2004). In addition, anandamide is synthesized and released at discrete loci on demand by neural activity or depolarization of postsynaptic membranes and then acts retrogradely as an agonist on presynaptic CB_1 receptors (Piomelli *et al.*, 2000; Christie and Vaughan, 2001; Wilson and Nicoll, 2001; Van der Stelt and Di Marzo, 2003; Alger, 2004). By contrast, the exogenous cannabinoid THC is widely distributed, reaching all areas of CB_1 receptors, is very slowly eliminated (Agurell *et al.*, 1986) and produces effects lasting several hours (Maykutt, 1985).

CBD binds only minimally to CB_1 receptors and is usually described as non-psychoactive. However, the clinical observations described below suggest that it has antipsychotic, anxiolytic, anticonvulsant and other psychological effects (Zuardi *et al.*, 1995; Mechoulam *et al.*, 2002). Its mode of action is not fully understood but CBD has recently been shown to block the reuptake of

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anandamide (Bisogno *et al.*, 2001) and to inhibit its enzymatic hydrolysis (Mechoulam *et al.*, 2002). CBD also reduces the hydroxylation of THC to its more psychoactive metabolite, 11-OH-THC (McPartland and Russo, 2001). It has been shown to inhibit serotonin reuptake and to increase catecholamine activity in rat brain synaptosomes (McPartland and Russo, 2001), an action also shown by anandamide (Steffens and Feuerstein, 2004). In addition, CBD is a potent antioxidative agent and is protective against glutamate toxicity, an action which is not affected by cannabinoid receptor antagonists (Mechoulam *et al.*, 2002). The possible contribution of each of these actions to the psychological effects of CBD is not clear.

The discovery of endocannabinoids and the realization that these are the biological ligands of cannabinoid receptors has opened a whole new vista in cannabinoid pharmacology. A system of cannabinoid receptors and endocannabinoids appears to modulate many important physiological processes (Di Marzo *et al.*, 1998). These processes have yet to be clearly defined but evidence is already accumulating that endocannabinoids are involved in the modulation of brain reward systems (Gardner, 1999), mood, anxiety and sleep (Musty *et al.*, 1995), pain (Pertwee, 2001), cognition and memory (Terranova *et al.*, 1995, 1996), appetite (Williams and Kukham, 1999; Di Marzo *et al.*, 2001), endocrine activity (Mendelson and Mello, 1999), cardiovascular regulation (Randall and Kendall, 1998) and other vital functions (Musty *et al.*, 1995; Ameri, 1999). The basic function of the endogenous system appears to be the regulation of interneuronal signalling, involving complex interactions with many neurotransmitters and neuromodulators, including monoamines, acetylcholine, opioids, GABA and glutamate (Ameri, 1999).

Psychological effects of THC

The psychological effects of cannabis and THC have been described by many authors (Paton and Pertwee, 1973; Ashton, 1999a; Johns, 2001). It is important to note that many of these are biphasic and bidirectional, depending on dose, mode of administration, environment, expectation, personality, degree of tolerance and other individual factors, as well as time-frame (Paton and Pertwee, 1973; Ashton *et al.*, 1981; Ashton, 1999b). Thus, acute effects in normal subjects can include euphoria or dysphoria, relaxation or anxiety, excitation followed by sedation, heightened perception followed by perceptual distortion, and increased motor activity followed by incoordination. Synthetic THC (dronabinol) and nabilone, a synthetic cannabinoid related to THC, exert similar actions depending on dosage and the other factors mentioned above. In healthy subjects under placebo-controlled laboratory conditions, THC (5 mg and 10 mg smoked in herbal cigarettes) was shown to produce relaxation with decreased subjective ratings of anxiety, tension and depression (Ashton *et al.*, 1981). However, D'Souza *et al.*, 2004) recently found that intravenous infusions of THC (2.5 mg and 5 mg) produced mild and transient schizophrenia-like symptoms, anxiety, detachment, perceptual distortion and cognitive impairment.

Patients using cannabis or synthetic THC compounds in moderate doses for chronic pain conditions or multiple sclerosis have reported improvement of mood and increased general well-being and mental health, as well as alleviation of their other symptoms (Martyn *et al.*, 1995; Notcutt *et al.*, 1997; Ashton, 1999b; Williams and Evans, 2000; Wade *et al.*, 2003; Svendson *et al.*, 2004). A few controlled studies have shown anxiolytic effects of nabilone in some patients (Glass *et al.*, 1980; Fabre and McLendon, 1981; Ilaria *et al.*, 1981) and an antidepressant effect of THC in cancer patients (Regelson *et al.*, 1976; Russo *et al.*, 2003).

Many of the adverse effects of cannabis (usually attributed to its THC content) result from relatively high dose or chronic use. Cannabis can cause an acute psychosis in previously normal individuals, but those with mental illness are more vulnerable (Johns, 2001). Such reactions are dose-related and appear to be becoming more common with the present-day recreational use of potent cannabis varieties such as 'skunk' and netherweed (Wylie *et al.*, 1995). Heavy cannabis use can also lead to an acute functional psychosis with marked hypomanic features (Rottenburg *et al.*, 1982; Johns, 2001). In patients with BAD, the duration of cannabis use is associated positively with the duration of manic, but not depressive, episodes (Strakowski *et al.*, 2000) and substance abuse in general appears to increase the severity of the illness (Cassidy *et al.*, 2001) and to increase suicide rate (Dalton *et al.*, 2003).

Cannabis is a well-known risk factor for schizophrenia and may precipitate the illness in genetically predisposed individuals (Johns, 2001). It aggravates positive symptoms in schizophrenia and may antagonize the effects of antipsychotic drugs (Negrete and Gill, 1999). A large number of studies, as reviewed by Arsenault *et al.* (2004) and Macleod *et al.* (2004), have implicated a dose-related association between the use of cannabis in childhood and adolescence with later development in young adulthood of schizophrenia, depression, violence and antisocial behaviour, use of other illicit drugs, lower educational attainment, and psychological distress. Whether or not these associations are causal are debated by the above authors.

Psychological effects of CBD

There is some evidence that CBD, which constitutes up to 40% of cannabis extracts, has anxiolytic, hypnotic, antipsychotic and anticonvulsant actions (Zuardi and Guimaraes, 1997; Mechoulam *et al.*, 2002). CBD antagonizes the anxiety, intoxication liability and psychotic-like symptoms produced by high doses of THC in normal subjects (Zuardi *et al.*, 1982; Russo, 2003) and has similar anxiolytic effects to diazepam in a simulated public speaking test (Zuardi and Guimaraes, 1997). Anxiolytic effects have also been demonstrated in animal models, including the behaviour of rodents on the elevated plus maze (Guimaraes *et al.*, 1990). In this test, the action of CBD, administered alone, was dose-dependent and biphasic, similar to many other cannabinoid effects (Sulcova *et al.*, 1998). Biphasic hypnotic effects in rats have also been demonstrated (Monti, 1997) and CBD significantly increased sleeping time compared to placebo in insomniacs (Carlini and Cunha, 1981).

Antipsychotic effects of CBD were suggested by the observation that it acted in a similar way to haloperidol in animal tests predictive of antipsychotic activity (Zuardi *et al.*, 1991, 1995). A placebo-controlled case study of a patient with schizophrenia who was

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intolerant of haloperidol showed antipsychotic effects of high-dose oral CBD with 60–69% improvement in scores on the Brief Psychiatric Rating Scale and Interactive Observation Scale for Psychiatric Inpatients after 4 weeks of CBD therapy (Zuardi *et al.*, 1995). Preliminary results with CBD in additional schizophrenic patients are reported as promising (Gerth *et al.*, 2002).

Anticonvulsant actions of CBD, comparable to those of diphenylhydantoin and other drugs that are clinically effective in major seizures, have been shown in a variety of animal models (Consroe and Snyder, 1986; Consroe and Sandyk, 1992). The effects are not reversed by CB_1 antagonists, indicating that they are not CB_1 receptor mediated. A small placebo-controlled clinical study of oral CBD as an add-on therapy in 15 patients with uncontrolled secondary generalized epilepsy with temporal focus was conducted by Cunha *et al.* (1980). Of the eight patients who received CBD over 4 months, four remained almost seizure-free and three others showed partial improvement, whereas the patients taking placebo showed no change.

Pharmacokinetic factors

When administered orally, the absorption of both THC and CBD is slow and erratic. Peak plasma concentrations are not reached for 2–6 h and the biological availability is 4–12% for THC (Grotenhermen, 2003) and 13–19% for CBD (Mechoulam *et al.*, 2002). Both cannabinoids undergo extensive first pass metabolism in the liver and THC is also degraded by stomach acids. By contrast, inhaled cannabinoids reach peak plasma concentrations within minutes and have a bioavailability of approximately 35% for both THC and CBD. For medicinal purposes, other modes of administration have been investigated and sublingual liquid solutions appear to be well absorbed, producing rapid effects comparable to inhalation (Whittle *et al.*, 2001; Grotenhermen, 2003; Wade *et al.*, 2003). Using a sublingual spray of THC and CBD, Wade *et al.* (2003) found that it was possible for subjects with pain conditions or multiple sclerosis to self-titrate small doses that relieved pain and muscle spasms without inducing intoxication.

After absorption, both THC and CBD are sequestrated in fatty tissues from which they are only slowly released (the tissue half-life is 5–7 days). Both cannabinoids form a large number of metabolites, which are gradually eliminated over days or weeks in the urine and faeces (Gold, 1992). There may be complex interactions between the two cannabinoids. CBD inhibits some cytochrome P450 enzymes and may inhibit the conversion of THC to its active 11-hydroxy metabolite (McPartland and Russo, 2001), but Zuardi *et al.* (1982) found no effect on THC levels in humans when the two cannabinoids were administered together. By contrast, THC and its metabolites, and even CBD on repeated administration, increase cytochrome P450 activity through enzyme induction (Grotenhermen, 2003).

Discussion

Despite the sparse anecdotal data in humans and the absence of controlled clinical trials, the evidence discussed above shows that both THC and CBD have pharmacological properties that could be therapeutic in patients with BAD. Furthermore, the available pharmacokinetic evidence indicates optimal methods of administration and dosage control. The underlying pathophysiology of BAD is unknown, but these cannabinoids, especially when used in combination, have several characteristics (Table 2) in common with drugs known to benefit this disorder, including antidepressants, antipsychotics, anticonvulsants (mood-stabilizers) and anxiolytics.

Table 2 Comparison of some effects of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Actions	THC	CBD
Agonist action on CB_1 receptors	+	–
Inhibition of anandamide reuptake and hydrolysis	–	+
Anxiolytic	+[a]	+
Psychotropic	+	–
Antipsychotic	–	+[b]
Anticonvulsant	–	+
Antidepressant	(+)[c]	–
Sedative/hypnotic	+	+
Antinociceptive	+	+
Neuroprotective (inhibition of glutamate release)	+	+
Antiemetic	+	–
Appetite stimulant	+	No data
Cardiovascular effects[d]	+	+

[a]THC is anxiolytic in some doses, but can be anxiogenic in higher doses or in drug-naïve individuals. [b]CBD also antagonizes some psychotropic effects of THC. [c]Shown in one study in cancer patients (Regelson *et al.*, 1976). [d]THC causes tachycardia and hypotension; CBD can cause bradycardia and hypotension.

THC, in some conditions and doses, has anxiolytic, hypnotic and antidepressant effects with improvement in mood and general well-being in normal subjects, and in patients with pain conditions, multiple sclerosis or cancer (Regelson *et al.*, 1976; Glass *et al.*, 1980; Ashton *et al.*, 1981; Fabre and McLendon, 1981; Ilaria *et al.*, 1981; Paton and Pertwee, 1981; Martyn *et al.*, 1995; Notcutt *et al.*, 1997; Ashton, 1999b; Wade *et al.*, 2003). These actions could be helpful in BAD, especially in depressive phases, which are often accompanied by anxiety (Goodwin and Sachs, 2004). CBD antagonizes the psychotic-like effects and intoxication liability produced by high doses of THC and has anxiolytic, hypnotic and anticonvulsant actions of its own in addition to a protective effect against glutamate toxicity (Cunha *et al.*, 1980; Carlini and Cunha, 1981; Consroe and Snider, 1986; Guimaraes *et al.*, 1990; Consroe and Sandyk, 1992; Zuardi *et al.*, 1995; Zuardi and Guimaraes, 1997; Gerth *et al.*, 2002; Mechoulam *et al.*, 2002; Russo, 2003). These actions do not appear to be mediated by CB_1 receptors but may result from enhancement of the endogenous anandamide system and effects on THC metabolism (Mechoulam *et al.*, 2002; McPartland and Russo, 2001). As well as adding to the anxiolytic effects of THC, the antipsychotic effects of CBD could be therapeutic in bipolar patients with psychotic symptoms, and the anticonvulsant and protective effects against glutamate toxicity may have a mood-stabilizing action similar to some other anticonvulsants of proven value in BAD (Porter *et al.*, 1999; Ashton and

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Young, 2003). In addition, both THC and CBD have extremely low toxicity (British Medical Association, 1997; Mechoulam *et al.*, 2002).

Cannabinoids have already been tested for therapeutic effects in acute and chronic pain conditions and multiple sclerosis (Wade *et al.*, 2003; Svendsen *et al.*, 2004). The evidence suggests that a placebo-controlled trial of cannabinoids as adjunctive therapy in BAD should now be undertaken. Such a trial might start with a pilot investigation in treatment-resistant bipolar patients who remain symptomatic despite standard medications, choosing patients over the age of 18 years who have used cannabis previously (but who undertake to abstain from cannabis during the trial). Standardized plant extracts containing THC and CBD in combination and matching placebo have been available for clinical research since 1988 (GW Pharmaceuticals plc, Salisbury, UK). These could be self-administered as a 1 : 1 THC : CBD mixture or placebo and delivered by metered dose pump action aerosol spray as described by Wade *et al.* (2003). These authors found that the product was well tolerated and that side-effects were minimal in patients with various neurological disorders. Bipolar patients could self-titrate their preferred dosage to control symptoms and dosage would be minimized by limiting the amount contained in each spray to 2.5 mg of cannabinoid and the total dosage in each daily container to 120 mg cannabinoids. Thus, the maximum amount of THC obtainable daily would be 60 mg; a single modern cannabis 'spliff' contains 60–150 mg THC or more (Ashton, 1999b). Treatment periods would possibly be for 4 weeks, perhaps in a crossover active treatment/placebo design. Assessments would include clinical ratings of mania and depression scores, subjective rating scales, neuropsychological performance and a record of adverse effects. The results would provide information on optimal dosage regimes, duration of treatment, adverse effects and other factors.

Possible adverse effects that would require close monitoring in such a trial include the precipitation of hypomania, mania and psychosis, although these effects are unlikely to be significant with small dose preparations and a 50% CBD content in the medication. Neurocognitive function, which is already impaired in BAD (El-Badri *et al.*, 2001; Ferrier and Thompson, 2002) may be further compromised by THC (Solowij, 1998). On the other hand, better symptom control with the THC/CBD preparation may improve cognition. Additive effects may occur with hypnotics, sedatives and alcohol. Induction of cytochrome P450 enzymes may result in interactions with drugs metabolized by the same enzymes, including many antidepressants and antipsychotics. However, these enzymes are already induced in BAD patients who smoke tobacco or take cannabis. Two patients who stopped or reduced tobacco and/or cannabis consumption when on clozapine or olanzapine experienced adverse effects due to increased plasma levels of the drugs, necessitating dosage adjustment (Zullino *et al.*, 2002). A possible interaction between lithium and marijuana was reported in one case resulting in elevated serum lithium levels, which dropped when the patient stopped using marijuana (Ratey *et al.*, 1981). The interaction was attributed to slowed gut motility caused by marijuana which increased lithium absorption.

Tolerance and dependence can result from chronic use of cannabis and withdrawal effects occur on ceasing use (Ashton, 1999a). However, little tolerance appears to develop to the putative therapeutic effects that have been studied. Some patients have found nabilone still to be effective for pain relief after 2–3 years of regular use (Notcutt *et al.*, 1997) and patients taking plant-based cannabinoid extracts long-term for pain have not so far reported tolerance (Whittle *et al.*, 2001). Any withdrawal problems could be minimized by tapering dosage if use was no longer required. Similar to cannabis, THC has abuse potential and precautions may be needed to limit patients' overuse of the cannabinoid aerosols.

In conclusion, BAD is often poorly controlled by existing drugs and often involves a polypharmacological medley, including lithium, anticonvulsants, antidepressants, antipsychotics and benzodiazepines. Many patients take street drugs in addition, including cannabis, amphetamines, cocaine and illicitly obtained benzodiazepines in an attempt to control their symptoms. Some claim that such self-medication is superior to the drugs prescribed by psychiatrists. There are good pharmacological reasons for believing that the prescription of synthetic cannabinoids or standardized plant extracts may have a therapeutic potential in BAD. We suggest that the time is ripe for carefully managed trials of prescribed cannabinoids to determine whether they are of value as adjunctive drugs in bipolar patients whose symptoms are not adequately controlled by standard medications.

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Section F

Letters of support for the use of medical *Cannabis* from physicians and or other licensed health care providers knowledgeable about Bipolar Affective Disorder

Presto Quality Care
THCF Patient Center
Cannabis Therapeutic Specialists for the Inland Empire
647 Main Street, Suite 1-B, Riverside CA 92501
Voice: 951-782-9898 FAX: 951-782-9889

February 14, 2012

To Whom It May Concern:

The enclosed research report, *Cannabinoids in biopolar affective disorder,* states:

Patient reports and observations, backed by known pharmacology, suggest that the cannabis derivatives delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may have mood stabilizing properties.

Many of our patients who have received recommendations from our clinic report cannabis to be highly effective in providing therapeutic relief from their bipolar disorder. They report no negative side effects as a result of their use of cannabis and state that they have significantly decreased or totally eliminated their use of pharmaceutical drugs to treat this problem.

Cannabis has been shown to provide safe, effective relief for bipolar disorder and many other ailments whose symptoms include pain, insomnia, depression and nausea. Our clinic provides recommendations for all of these ailments. We monitor our patients on an annual basis and almost all patients report substantial improvement in both their physical and mental health as a direct result of their use of cannabis.

Sincerely,

Paul Ironside, M.D.

Arkansas Department of Health

Proposed Rules Pertaining to the Medical Marijuana Act of 2016

Rules and Regulations Governing Medical Marijuana Registration, Testing, and Labeling in Arkansas

Public Comments Received

A public hearing was conducted on April 16, 2018 at 9:00 a.m. in the Arkansas Department of Health's auditorium, located at 4815 W. Markham, Little Rock, Arkansas. Oral comments were received during this meeting. During the public comment period, comments were also received via email. All comments and responses are documented below:

	Name	Meeting Comments	Response
1	Robert Brech, General Counsel ADH	This hearing is to consider a petition to add Bi-polar Effective Disorder (ICD code F31) submitted 1/30/18. The ADH will take public comments and the Director of ADH will make the final determination if this will be move forward to the rule making phase. The Director has 120 days to decide to go forward. At that time, we will start the rule changing process. This will take 6-7 months.	
2	Storm Nolan – Arkansas Cannabis Industry Association	3% of public suffer from this condition *Amendment 98 set low bar for Section 4, C, 2 - *In considering a petition, the department shall add medical conditions or treatments to the list of qualifying medical conditions set forth in § 2 of this amendment if patients suffering from the medical conditions or undergoing the treatments in question would derive therapeutic benefit from the use of marijuana, taking into account the positive and negative health effects of such use.* *The study shows that MMJ shows efficacy and lack of side effects. Main study indicates mood stabilization. Typical medication is lithium. Patients often develop renal failure from this medication. *Not considered carcinogenic effect due to many ways of consumption. *Arkansas patients are very agitated, there is no clear time frame for access to MMJ. A denial would feed into the opinion that the state is trying to delay MMJ.	
3	Laree Trece – Mother/Parent	Feels like cannabis would help her son who has bipolar disorder.	

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	Name	E-mail Comments	Response
1	Jeremy Brown	**Received April 15, 2018** To whom it may concern and with all due respect, in my personal experience with bipolar disorder, specifically bipolar 1 disorder, a disorder which is often quite debilitating and potentially life threatening at its extremes of mania and depression, I have found cannabis to be a superior and gentler alternative to the many medications and combinations of medication used to marginally treat the condition. These medications have immediate detrimental effects on the metabolism of the patients using them and have a high risk of toxicity for which patients must be closely monitored. In addition, these meds quite often lose their potency and effectiveness, even if patients comply strictly with their use. Often, due to extremely unpleasant and unbearable side effects, patients quit taking their meds, leading to relapse of symptoms and decline in quality of life and ability to function. I believe medical cannabis is an effective treatment for both extremes of the disorder and a superior maintenance therapy than the pharmaceutical options currently available. Insomnia is the most devastating aspect of the disorder and often occurs at both extremes (mania and depression). Cannabis effectively aids in maintenance of regular sleep cycles, promoting balance and wellbeing, and apart from any initial effects from thc, which wear off rather quickly, there are literally no apparent negative side effects like those found in pharmaceutical drugs. There are many useful and beneficial non psychoactive compounds, such as cbd present in cannabis which many independent studies and trials have confirmed to have medicinal qualities for the treatment of many conditions, including bipolar 1 disorder. Also, there are a vast many different strains of cannabis with varying ratios of cbd to thc, specific to treatment of many conditions, including bipolar disorder. High cbd to low thc ratios are said to greatly diminish any unpleasant or intense effects from thc. As you know, I'm sure, cannabis can be administered and utilized by many methods other than that of smoking it. I hope you will give this matter the due consideration it deserves and make a compassionate and informed	Responded by email – their comments would be added to the public comments

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		decision. Thank you very much! Sincerely, Jeremy S. Brown	
2	Steven Stubblefield	**Received April 15, 2018** To whom it may concern, I am writing because I understand that Bi Polar Disorder is under consideration to be added to the list of conditions that can be treated with medical cannabis in Arkansas. As a person that has lived with this debilitating condition all my life, I would fully support having cannabis as an option for treatment. I believe there are many other psychological disorders that could effectively be treated with cannabis. But, I'll stay on point. please add Bi Polar Disorder to the list. Sincerely, Steven Stubblefield	Responded by email – their comments would be added to the public comments
3	Jeremy Brown	**Received April 16, 2018** Hello, again! In addition to what I have already said, in my experience and personal contacts with bipolar patients I have seen the reality that many of the current an available medication while posing grave threats to the body, such as kidney and liver and thyroid dysfunction, along with sexual dysfunction and Chronic states of fatigue and increased risk of diabetes and heart disease make them a very unappealing but often horrifying alternative. 1/3 patients who take lithium over a ten-year period will develop renal failure as a result of their treatment. Also, many of these prescription drugs create a physical dependent which causes painful withdrawal upon discontinuation. In addition, these medications quite often create a flat effect or emotional deadening which greatly decreases the benefits of cognitive behavioral therapy and the ability to learn coping mechanisms and to discuss painful life experiences, which may in themselves ultimately be root causes of the psychological/ emotional imbalance. As a psychiatrist once told me- " psychiatry is akin to voodoo medicine," because psychiatrists really don't know much about how the brain functions in relation to the medications they are prescribing and because the human psyche is so fast and deep and unique as each individual and mostly incomprehensible. A patient may often spin their wheels in therapy without ever gaining the trust and confidence in their therapist to truly open up their	Responded by email – their comments would be added to the public comments

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		inner worlds to them. I'm not saying that I believe medical marijuana will help everyone universally and completely, but I believe it would make a positive impact in the lives of many while greatly lessening negative side effects. Keep in mind that lobotomy was once the leading edge treatment for nearly all mental disorders- effective, yes, with dramatic results while simultaneously robbing patients of a meaningful life quality. - history has already proven the practice barbaric and may yet prove current treatments to be barbaric. Again, thank you for your time! Sincerely, JSB	

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