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Cannabis and Mood Disorders

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Abstract

Purpose of review—The present review will provide an overview of the neurobiology, epidemiology, clinical impact, and treatment of cannabis use disorder (CUD) in mood disorders.

Recent findings—Patients with mood disorders including major depressive disorder (MDD) and bipolar disorder (BD) have higher rates of cannabis use, and CUD compared to the general population. Reasons for this association are not clear, nor are the putative therapeutic effects of cannabis use, or its components delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), in these illnesses. The evidence surrounding treatments for patients with this comorbidity is lacking, with more support for psychotherapeutic treatments compared with pharmacological treatments.

Summary—Cannabis use may be associated mood disorders, but more research is needed to increase our understanding of the mechanisms for this association, and to develop more effective treatments for this comorbidity.

Keywords

Mood Disorders; Cannabis; Major Depression; Bipolar Disorder; Antidepressants; Mood Stabilizers; Cannabis Use Disorder

Introduction

Cannabis is the most widely used illicit substance in the United States, with ~9.5% of adults endorsing use in the past year [1*]. California, the most populous state (~40 million

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Compliance with Ethics Guidelines

Conflict of Interest: Aliya M. Lucatch, Dr. Tony P. George, Alex S. Coles, and Dr. Kevin P. Hill declare that they have no conflicts of interest.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

residents), legalized recreational cannabis use on January 1, 2018. Growing acceptance of cannabis use, decreased perception of risk, and debates surrounding individual rights and freedoms in North America are the root of the decision to legalize. The ethical stance at the forefront of legalization is the “harm principle”, where adults want the freedom to engage in acts so long as they do not harm others. As of February 2018, nine states and the District of Columbia (DC) have legalized recreational cannabis, and twenty-nine states and DC have legalized cannabis for medicinal purposes. However, there are some negative effects that are critical to consider with widespread legalization, including the impact upon adolescents and people with psychiatric illnesses such as mood disorders. There is evidence demonstrating increased adolescent cannabis use [2] and increased cannabis use disorder (CUD) diagnoses [1*] in states that have legalized recreational cannabis. Furthermore, relatively little is known about the burden of problematic cannabis use on vulnerable populations such as the mentally ill and adolescents.

Cannabis is a plant that is made up of upwards of 113 different chemical components, or cannabinoids [3]. The two cannabinoids that have been most widely studied are delta-9-Tetrahydrocannabinol (THC) and cannabidiol (CBD), with THC being the main psychoactive component and CBD contributing to many of the therapeutic benefits. Different strains of the cannabis plant have variable concentrations of each of these components, and modern strains have notably high concentrations of THC due to genetic modifications which leads to greater potency [4]. Cannabinoids interact with the G protein-coupled CB1 receptors of the endocannabinoid system (eCB), which in turn influence emotional regulation [5, 6], reward processing [7], and various cognitive functions [8–10]. Additionally, administration of CB1 antagonist, rimonabant, has been found to produce changes in symptoms of mood and anxiety [11]. Together, these findings provide good evidence that substances targeting endocannabinoid receptors have the ability to modulate mood and also that symptoms of mood disorders are linked to endocannabinoid function.

Mood disorders are primarily comprised of Major Depressive Disorder (MDD) and Bipolar Disorder (BD). There is evidence to demonstrate increased problematic cannabis use in individuals with these disorders [12]. Thus, this review will focus on identifying the links between cannabis use and mood disorders, as well as identifying gaps in the literature, particularly in treatment approaches for this population. Further research on this topic towards developing better treatment and prevention strategies for this vulnerable population should be a priority.

Methods

Original articles were searched for using PubMed, MEDLINE, and PSYCHINFO. The keywords “(Major Depressive Disorder) or (Depression) or (Bipolar Disorder) or (Mood Disorder)” in combination with “(cannabis) or (marijuana)” were used. The information was extracted independently by two of the authors (AML and ASC).

Major Depressive Disorder (MDD)

MDD is a devastating illness with a current prevalence of ~ 5% (15% lifetime), and the leading cause of disability globally [13]. MDD is characterized by depressed mood, reduced

experience of pleasure, changes in sleep, changes in appetite, loss of energy, feelings of guilt, difficulty concentrating, and suicidality [14]. Due to widespread co-occurrence of both cannabis use and MDD diagnoses, as well as the effect that cannabinoids have been found to have on mood regulation [5, 6], it is critical to understand whether any reciprocal effect exists between these two phenomena. The main research questions we sought to address in this review are whether cannabis use increased the risk for onset of MDD and whether cannabis use exacerbates symptoms of depression.

Table 1 summarizes the studies that examine the association between cannabis use and MDD. Two separate studies independently identified a four-fold risk of developing depression in individuals that use cannabis [15, 16]. One of these studies [15] was based on epidemiological data from 1980 with a 16 year follow-up interview. Several additional cross-sectional studies have been conducted that examine the comorbidity, and have found an association between CUD and MDD [17, 18]. However the same limitations apply across all studies using a cross-sectional design of not being able to determine causation. Fortunately, there have also been research studies on this topic that have employed a longitudinal design. A recent meta-analysis assessed 14 longitudinal studies with population-based data that examined this risk for cannabis users to develop depression, and found a moderate association [19**]. The studies evaluated provided inconsistent results with regards to significance of the association [19**]. However, there was a lack of consistency within the definition and measure of cannabis use, as there have been no validated measures developed to assess this. This meta-analysis grouped heavy users as those fitting the criteria for CUD or weekly users in attempt to create more consistency across the studies, but it is important that future researchers work to create a validated measure of cannabis use across the research discipline [19**]. Finally, a recent twin study has helped to elucidate the temporal relationship of the association, and provided a model for understanding the development of this comorbidity [20]. They found that CUD risk factors lead to MDD symptoms using a model fitting approach [20].

In terms of our second research question of whether cannabis use worsens symptoms of depression in patients with MDD, the available literature is limited with the exception of one recent study. The study was a longitudinal design using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which examined substance use and psychiatric symptoms in the general population at two time points [21**]. Researchers examined whether varying levels of cannabis use at baseline affected clinical outcomes at the follow-up time point in individuals with a diagnosis of MDD [21**]. They found that cannabis use was associated with an increased number of depressive symptoms at follow-up, including anhedonia, changes in body weight, insomnia, hypersomnia, and psychomotor problems [21**]. This study is the first of its kind to examine the effects of cannabis on symptom progression in individuals with MDD. Further studies with this population using well-controlled designs are warranted to remove the confounding factors and more precisely capture this effect. Several longitudinal studies did examine cannabis use and depressive symptoms over time, but used community samples rather than a MDD patient sample [22, 23]. Interestingly, two studies examined the effects of reducing cannabis use on psychiatric symptomology [24*, 25]. The first study was a secondary analysis of a randomized control trial (RCT) for motivational interviewing in cannabis using young

female adults, and found that decreasing cannabis use improved depressive symptoms in those with a baseline level of depression [24*]. The second study used a sample of cannabis-dependent patients with schizophrenia who achieved extended cannabis abstinence for a 28-day period, and found a reduction in depressive symptoms with biochemically-confirmed abstinence [25]. Further research is warranted on cannabis use within the MDD diagnostic category to determine an answer to our second research question.

Bipolar Disorder (BD)

BD is characterized by alternating moods, from extreme emotional highs (mania) to extreme emotional lows (depression). It is estimated that 2.6% of adults in the US are afflicted with symptoms of bipolar disorder in a 12 month period, and that 82.9% of these cases are deemed severe [32]. According to data extracted from the NESARC study, individuals with bipolar disorder have a specific predisposition for increased rates of cannabis use and CUD diagnoses compared to other psychiatric diagnoses [12]. Specifically, individuals with lifetime prevalence of BD have 7.2% past year rate of CUD compared with 1.2% in the general population [33**]. Additionally, when compared with MDD, individuals with BD use cannabis more frequently and in higher quantities [34]. Due to this specific tendency towards problematic cannabis use in patients with BD, it is important to assess the impact this has on outcomes of the disorder. Using the same research questions as before, we reviewed the current literature to determine how cannabis use effects onset and symptom progression of BD.

Table 2 provides a summary of the literature on the association between cannabis use and BD organized by date of publication. A recent longitudinal study using the NESARC data found a significant association between lower age of onset in individuals with CUD [33**]. The average age of onset of a manic or hypomanic episode was 19.5 years in individuals with CUD compared with 25.1 years in individuals without CUD [33**]. The average age of onset of first depressive episode was 18.5 years in individuals with CUD compared to 24.4 years in individuals without CUD [33**]. Two studies specifically assessed whether cannabis use affects age of onset of symptoms [35*, 36*]. Both studies employed a cross-sectional design in adults with a diagnosis of BD, but one study only looked at manic symptom onset [36*], and the other looked at onset of manic episodes, depressive episodes, and hypomanic episodes [35*]. Both studies indicate a dose-response relationship between cannabis use and the onset of these symptoms. However, due to the cross-sectional design, causal inferences cannot be made and a longitudinal design of the development of BD in cannabis users would provide better precision and accuracy of measures.

The existing literature suggests moderate evidence that cannabis exacerbates symptoms of bipolar disorder. The study based on the NESARC data demonstrated an association between CUD and a higher frequency of bipolar-related symptoms as well as other substance use comorbidities (alcohol and nicotine) [33**]. The bipolar-related symptoms assessed in this study included manic, hypomanic, and depressive episodes, indicating an overall worse course of illness in individuals with comorbid BD and CUD [33**]. A recent meta-analysis which assessed longitudinal designs found a significant relationship between cannabis use and exacerbation of mania [37]. However, only two studies met criteria for

inclusion in the meta-analysis and they were based on community samples [37]. Additionally, the two studies included did not control for psychotic symptoms which may be an important confounding factor when assessing mania in individuals with BD [37]. Interestingly, a recent retrospective analysis found that adults with BD and comorbid CUD performed better on cognitive tasks related to attention, processing speed, and working memory compared to those without CUD, but were more likely to have a psychotic episode [38]. The researchers speculate that this may be due to the higher cognitive and social function required to acquire cannabis [38]. Finally, a secondary analysis of a longitudinal study in adults with BD found that symptom exacerbation of cannabis use on BD dissolved following cannabis cessation [39**]. The researchers separated patients into three groups based on their cannabis use: i) previous use, ii) current use, or iii) never use [39**]. They followed these patients over the course of 2 years and assessed measures of remission, recovery, recurrence, and relapse of symptoms [39**]. Further clinical studies are warranted of cannabis abstinence and its potential to improve outcomes of bipolar disorder.

Pharmacological Treatments

Pharmacological treatments for mood disorders has been well-established. In treating MDD, there is strong evidence supporting the use of antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), dopamine-norepinephrine reuptake inhibitors (DNRI), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [42]. Moreover, the first-line treatment for chronic patients with BD is the use of mood stabilizers (e.g. lithium, valproate) [43], but second generation antipsychotic medications have also been found effective for managing acute symptoms of mania [44].

In contrast, pharmacological treatments for cannabis use have demonstrated inconclusive results based on RCTs, and no medications have been FDA approved for this purpose. Cannabinoid agonists such as dronabinol and nabilone have been explored, but the evidence for these medications have been inconsistent. Three studies found nonsignificant results for improvement on cannabis use measures [45–47] and two studies that found a decrease in withdrawal symptoms following drug administration [48, 49]. N-acetylcysteine may have some potential in reducing craving [50] and improving abstinence rates [51], but subsequent studies demonstrated nonsignificant results [52]. Gabapentin, baclofen, and nabiximols are additional agents that hold potential for managing cannabis misuse by reducing quantity of use, craving, and withdrawal, respectively [53–55]. A recent study found that topiramate in combination with psychotherapy reduced rates of cannabis use in adolescents, but was poorly tolerated [56]. All of these drugs have yet to be investigated in individuals with psychiatric comorbidities.

Fortunately, a few recent studies have begun to investigate potential treatments for cannabis use in individuals with comorbid mood disorders. Only two studies utilized a sample with comorbid MDD and CUD to investigate whether antidepressants (Fluoxetine and Venlafaxine) improve outcomes for both conditions [57*, 58*]. Unfortunately, both studies found no support for the use of these drugs for improving comorbid outcomes including depressive and cannabis-related symptoms [57*, 58*]. One study investigated the effect of

lithium on cannabis use outcomes in an open-label trial and found improved abstinence outcomes and decreased symptoms of anxiety and depression [59]. Finally, another open label trial investigated the effects of the second generation antipsychotic quetiapine in cannabis-dependent individuals and found a significant decreased in urine THC levels [60]. Patients with co-occurring mood disorder diagnoses were not included in these open-label trials, so further research is warranted on the effects of these drugs on comorbid mood disorders with cannabis use.

Behavioral Treatments

Cognitive Behavioral Therapy (CBT) is the first-line evidence-based psychotherapeutic treatment for all mood disorders [42, 44]. This psychotherapy is tailored to the individual diagnosis and also has demonstrated some efficacy in the treatment of CUD [61–63]. The first two studies are based on a large RCT which involved tailored psychotherapy for CUD, including Motivational Enhancement Treatment (MET), CBT, and Psychosocial Problem-Solving training (PPS) [61, 62]. The researchers found that this combined treatment was effective for improving abstinence rates and decreasing cannabis use in both experimental and clinical settings [61, 62, 64]. The other study was an open trial of a group therapy, Integrated Group Therapy (IGT), that incorporated elements of CBT directed to mood and drug use outcomes in patients with BD [62]. IGT lead to better abstinence outcomes for patients with bipolar disorder and substance dependence [62]. Multidimensional Family Therapy (MDFT) has also been explored in an RCT for individuals with CUD [63]. Researchers found that MDFT is equally effective at reducing cannabis use compared to CBT, but that adolescents with comorbid psychiatric disorders such as MDD or BD may benefit more from MDFT [63].

Motivational Enhancement Therapy (MET) may be useful at invoking initial behavioral change in individuals with a CUD based on the results of two RCTs [24*, 65]. Finally, Contingency Management (CM) has also been investigated as a method to target cannabis use. Several longitudinal studies have demonstrated that CM is an effective way at promoting cannabis abstinence in patients with mental illness [66, 67].

Integrated Treatments

There is little existing literature on an integrated treatment approach which combines validated pharmacological with psychotherapeutic treatments on patients with this comorbidity. However, the psychotherapeutic strategies for reducing substance use mentioned previously in combination with the pharmacological agents that have produced favorable results (e.g. gabapentin and n-acetylcysteine), may lead to reductions in cannabis use [68]. Future researchers might consider a combination of psychotherapeutic and pharmacological strategies to reduce mood symptoms, withdrawal symptoms, craving, and improve rates of abstinence.

Conclusions

Given the shifting political and legal landscape surrounding cannabis legalization and the high prevalence of comorbid mood disorders and problematic cannabis use, it is critical that

further research be conducted to better understand this population. There are many gaps in the literature on the effects of cannabis on mental illness, and this might be in part due to the classification of cannabis as a Schedule 1 substance by the Drug Enforcement Administration (DEA), and this heavy regulation might have hindered the ability of researchers to obtain and study the substance. Another barrier may be the lack of funding priority that goes towards research focusing on addictions and mental illness, particularly with cannabis due to it being perceived as less harmful compared to other illicit drugs. Research on comorbidities with cannabis has focused to date mainly on schizophrenia due to interest in the cognitive and clinical effects of cannabis [12]. However, given that recreational legalization of cannabis is spreading across the United States and Canada, it is imperative that priority should be given to developing a pre-post legalization surveillance strategy to monitor health outcomes and rates of onset of in people with mood disorders, given their higher population prevalence compared to psychotic disorders [69]. Research on outcomes and potential treatments for vulnerable populations, such as individuals with mood disorders, should be expected and funded by the governmental organizations that are ultimately responsible for public policy changes. According to the currently available research, there is sufficient evidence to suggest an association between cannabis use and the development of depressive symptoms, and some evidence to support exacerbation of MDD symptoms from cannabis use. Much of the literature is based on population-based data, but clinical studies are warranted to more closely examine the progression of depressive symptoms in individuals using cannabis. There are clearly higher rates of cannabis use in individuals with BD, and there is moderate evidence to support an earlier onset of symptoms in problematic cannabis users. There is also moderate evidence that cannabis use exacerbates symptoms in individuals with BD, which is provided by both population-based and clinical research. There are no current pharmacological treatments that have sufficient evidence to warrant recommendation for use in this population, but psychotherapeutic techniques show promise. Particularly CBT, MET, and MDFT have been shown to be efficacious. There is a clear need for more controlled, longitudinal, clinical research on the effects of cannabis use and abstinence on outcomes of mood disorders to better prepare for these potential impacts and minimize potential burdens on health. Moreover, future research may also shed light on treatment approaches that would be beneficial to this population as policy changes continue to take place.

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Table 1**Cannabis and Major Depression¹**

Author	Sample Size and Population	Study Design	Primary Outcome	Results
Bovasso et al., 2001 [15]	N=1920 Adult community sample	Longitudinal	Depressive symptoms	Cannabis users are four times more likely to have depressive symptoms at follow-up (14–16 years later). Suicidal ideation and anhedonia were specific symptoms that were affected.
Wittchen et al., 2007 [26]	N=1395 Adolescent community sample	Longitudinal	Prevalence of comorbid CUD ² and psychiatric disorders	Depressive and bipolar disorders are associated with cannabis use and CUD when controlling for externalizing factors.
Cornelius et al., 2008 [27]	N=170 (92 males and 78 females) Comorbid MDD/CUD	RCT for fluoxetine	Cannabis withdrawal symptoms	Withdrawal is common in patients with comorbid depressive symptoms and cannabis dependence.
Dorard et al., 2008 [17]	N=32 (27 males, 5 females) Cannabis users	Cross-sectional	Depressive and anxiety symptoms	Cannabis dependence is commonly comorbid with mood and anxiety disorders.
Lee et al., 2008 [16]	N=106 (57 males, 49 females) Indigenous community sample	Cross-sectional	Depressive symptoms and cannabis use	Heavy cannabis users are 4× more likely to have a diagnosis of moderate to severe depression.
Ehlers et al., 2010 [28]	N=2524 (678 males and 1086 females) Community sample	Family study	Psychiatric symptoms and cannabis use	CUD and CUD-associated depressive symptoms are both heritable. 29.1% of individuals that abuse cannabis experienced depression.
Horwood et al., 2012 [22]	N= 6900 Child and adolescent community samples	Longitudinal	Depressive symptoms	Significant association between increasing cannabis use frequency and depressive symptoms.
Osuch et al., 2013 [18]	429 (271 males and 158 females) Adolescent and young adult patients from first episode mood and anxiety clinic	Cross-sectional	Depressive symptoms and cannabis use	High risk for CUD associated with disorders of mood and anxiety. Comorbid CUD is associated with greater functional impairment in these patients.
Lev-Ran et al., 2014 [19**]	N= 76,058 Longitudinal studies examining association between cannabis use and depression	Meta-analysis	Odds ratio for cannabis users developing depression	Cannabis use is associated with moderately increased risk for depressive disorders.
Danielsson et al., 2016 [29]	N=8598 (3616 males and 4982 females) Adult community sample	Longitudinal	Depressive and anxiety symptoms	Associations between cannabis use at baseline and risk for future depression was nonsignificant after

Author	Sample Size and Population	Study Design	Primary Outcome	Results
				adjusting for confounders.
Moitra et al., 2016 [24*]	N=332 (all females) Cannabis-using female young adults	RCT ³ for motivational interviewing	Depressive symptoms (BDI-II)	Decreasing cannabis use improves depressive symptoms in those with at least mild depression.
Stapinski et al., 2016 [30]	N= 2508 (1379 males and 1129 females) Chilean adolescents (9 th graders)	Longitudinal	Frequency of cannabis use	Trend towards significant findings that those with depression and anxiety showed greater cannabis use frequency at 18-month follow-up.
Womack et al., 2016 [23]	N=264 (all males) Adolescent and young adult low SES community sample	Longitudinal	Depressive symptoms and cannabis use frequency	Cannabis use increases occurrence future depressive symptoms in mildly depressed patients. However, initial depressive symptoms only predicts slight increases in future cannabis use.
Hill et al., 2017 [31]	N= 34,653 (14,564 male and 20,089 females)	Longitudinal	Strength of association between cannabis use and Incidence of psychiatric disorders	Cannabis use was not found to be associated with future mood or anxiety disorders, but did increase rates of other SUDs ⁴ .
Feingold et al., 2017 [21**]	N=2348 Adults with MDD	Longitudinal	Outcomes of MDD	Level of cannabis use associated with depressive symptoms at follow-up.
Rabin et al., 2017 [25*]	N=39 (all males) Schizophrenia patients (n=19) and controls (n=20) both with CUD	Longitudinal	Psychiatric symptoms	Schizophrenia patients demonstrated a significant reduction in depressive symptom scores after 28-day abstinence.
Smolkina et al., 2017 [20]	N= 2410 (565 MZ ⁶ twins and 640 DZ ⁷ twins)	Twin Study	Depressive symptoms and cannabis use (SSAGA-OZ)	Indicates directionality for association between CUD and MDD is from CUD → MDD

Abbreviation Key:

¹ MDD Major Depressive Disorder

² CUD Cannabis Use Disorder

³ RCT Randomized Control Trial

⁴ BDI Beck Depression Inventory

⁵ SUD Substance Use Disorder

⁶ MZ Monozygotic

⁷ DZ Dizygotic

⁸ SSAGA-OZ Semi-Structured Assessment for the Genetics of Alcoholism

Table 2**Cannabis and Bipolar Disorder¹**

Author	Sample Size and Population	Study Design	Primary Outcome	Results
Van Rossum et al., 2009 [40]	N=3459 (1543 males and 1916 females) Adult bipolar disorder patients	Longitudinal	Symptoms of bipolar disorder and psychosocial outcomes	Cannabis users exhibited poorer illness-related functional outcomes.
Braga et al., 2012 [38]	N=200 (50 with CUD ² and 150 without) Adults with bipolar disorder	Retrospective	Psychiatric symptoms (SCID-IV) and neurocognitive measures	Bipolar patients with CUD demonstrated better neurocognitive performance, but were more likely to have psychotic episodes.
Heffner et al., 2013 [41]	N=80 Adolescents with comorbid bipolar disorder and CUD that have used tobacco	Cross sectional	Smoking status and nicotine dependence	High co-use of tobacco and cannabis in bipolar patients.
Lev-Ran et al., 2013 [33**]	N= 43,093 (1905 bipolar disorder) Adults with comorbid bipolar disorder and CUD	Longitudinal	BD illness outcomes	Significant findings in the association between CUD and lower age of onset and higher frequency of bipolar-related symptoms. Additionally, co-occurring CUD is associated with significant co-morbidities (nicotine and alcohol).
Lagerberg et al., 2014 [35*]	N=324 Adults with bipolar disorder	Cross-sectional	Cannabis use and interaction with bipolar characteristics	Significant dose-response relationship between cannabis use and age of onset of bipolar disorder.
Gibbs et al., 2015 [37]	N = 2391 Individuals with experience of manic symptoms	Meta-Analysis	Manic symptoms	Significant relationship between cannabis use and exacerbation of mania symptoms.
Zorilla et al., 2015 [39**]	N= 1922 Adult patients with bipolar disorder	Longitudinal	Manic symptoms	Patients who stop using cannabis have similar outcomes to patients who never used. Thus, abstaining has potential beneficial effects on outcome.
Kvitland et al., 2016 [36*]	N= 101 Adults with bipolar I disorder	Cross-sectional bipolar-related symptoms	Cannabis use and age of onset of manic episode and more lifetime suicide attempts in bipolar disorder I.	Cannabis use associated with lower

Abbreviation Key:

¹BD Bipolar Disorder²CUD Cannabis Use Disorder