Cannabis and Depression

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Abstract

There is a growing body of evidence pointing to the co-occurrence of cannabis use and depression. There is also some evidence that the use of cannabis may lead to the onset of depression; however, strong evidence points to the inverse association; i.e. that depression may lead to the onset or increase in cannabis use frequency. Observational and epidemiological studies have not indicated a positive long-term effect of cannabis use on the course and outcome of depression. The association between cannabis use and depression may be stronger among men during adolescence and emerging adulthood and stronger in women during midlife. There is an indication for potential genetic correlation contributing to the comorbidity of cannabis dependence and major depression, namely that serotonin (5-HT) may mediate such association and there is also evidence for specific risk alleles for cannabis addiction. There is preclinical evidence that alteration in the endocannabinoid system could potentially benefit patients suffering from depression. However, the issue of using cannabis as an anti-depressant is at an early stage of examination and there is little evidence to support it. Finally, there has been little support to the notion that selective serotonin reuptake inhibitors (SSRIs) may be effective in decreasing depressive symptoms or rates of substance use in adolescents treated for depression and a co-occurring substance use disorder. In conclusion, despite methodological limitations, research in the past decades has broadened our knowledge on the association between cannabis use and depression from epidemiological, neurological, genetic, and pharmacological perspectives.

Keywords

Cannabis · Mental illness · Mood disorders · Major Depressive Disorder · Bipolar Disorder · Anxiety Disorders

5.1 Introduction

Major depressive disorder (MDD) is a psychiatric condition characterized by continuous low mood and loss of interest or pleasure in enjoyable activities. The past-year prevalence of MDD has been estimated to be 4.7% globally and it is considered as one of the most severe mood disorders (Ferrari et al. 2013), associated with high mortality due to suicide and a major functional impairment caused directly and indirectly. In 2010, MDD was the most disabling mental disorder worldwide, accounting for more than 40% of the disability-adjusted life years

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(a combination of premature mortality and disability) caused by mental illness (Whiteford et al. 2013). Therefore, extensive effort has been made throughout the years in order to identify risk factors associated with the onset of MDD and its clinical course, including the literature published concerning the effect of substance use and substance use disorders (Moore et al. 2007; Whiteford et al. 2013).

Following tobacco and alcohol, cannabis is the most commonly used addictive substance, with the estimated worldwide past-year prevalence rate of 3–4.5% (Degenhardt et al. 2011; United Nations Office on Drugs and Crime 2012). The number of cannabis users continues to increase globally by roughly 16% between 2006–2016, currently estimated at around 190 million worldwide (WHO 2016). In accordance with an incline in the number of cannabis users, the prevalence of the past-year diagnostic and statistical manual of mental disorders (DSM)-IV cannabis use disorder (i.e. cannabis abuse or cannabis dependence) was 1.4% and 8.5% in 2005 (Stinson et al. 2006), while in 2013, the prevalence of DSM-5 cannabis use disorder (CUD) was 2.54% (Hasin et al. 2016).

In this chapter, we will first review evidence on the co-occurrence of depression and cannabis use reported in cross-sectional studies. We will then present data on the longitudinal association between cannabis use and depression, exploring two inverse causal pathways. We will then review the possible contribution of age and gender to the association between cannabis use and depression, as well as newly emerging evidence on possible genetic and neurological factors that may underline this association. Finally, we will review the preclinical and clinical evidence for the use of cannabis as an antidepressant, and pharmacological treatment for comorbid cannabis use disorder and depression.

5.2 Co-Occurrence of Cannabis Use and Depression

5.2.1 Cannabis Use among Individuals with Depression

With a growing number of studies reporting on the co-occurrence of cannabis use and depression, Degenhardt et al. (2003) concluded in an early review that "there is increasing evidence that regular cannabis use and depression occur together more often than we might expect by chance" (p. 1497). Results from the United States National Comorbidity Survey have indicated that more than half of the individuals with MDD reported lifetime use of cannabis (Chen et al. 2002). Data from the national epidemiological survey on alcohol and related conditions (NESARC) focusing on adults with past-year MDD or dysthymia ($N = 6534$) have indicated that the past-year prevalence of cannabis use among these individuals was 10%, with nearly equally distributed between regular users (those using cannabis at least once a week; 4.5%) and occasional users (using less than weekly; 5.4%) (Aspis et al. 2015). According to data from the National Survey on Drug Use and Health, the past-year prevalence of cannabis use among adolescents with depression was substantially higher compared to adult population, estimated at 25%, compared to only 12% among those without depression (SAMHSA 2007).

Concerning the co-occurrence of MDD and CUDs, a recent study encompassing more than 28,000 cannabis users indicated that past year major depressive episode was associated with the increased number of DSM-IV cannabis dependence criteria, regardless of cannabis frequency of use (Dierker et al. 2018). In this study, participants with depression were significantly more likely to use cannabis than they intended to and spent much time on acquiring cannabis, using it or recovering from the effect of cannabis use compared to those without depression. They were also more likely to have continued to use cannabis despite negative consequences, repeatedly failed in efforts to stop

or reduce cannabis use, have important activities in life superseded by cannabis use and needed an increasing amount of cannabis in order to obtain its effect.

5.2.2 Depression among Cannabis Users

According to data from the Epidemiologic Catchment Area study, more than half of the individuals who qualify for a lifetime diagnosis of DSM-IV CUD had a concurrent diagnosis of mental illness (Regier et al. 1990). According to a Dutch survey, the three-year incidence of MDD among cannabis users was 11.7% compared to 5% among nonusers (Van Laar et al. 2007). Data from NEASRC indicated that lifetime and past-year CUD were associated with a nearly three-fold increase in the risk for the past-year diagnosis of MDD (Odds Ratio (OR) = 2.8, 95% Confidence Interval (CI) = 2.33–3.41 for past-year use, and OR = 2.6, 95% CI = 2.26–2.95 for lifetime use) (Hasin et al. 2016). Odds for concurrent MDD were even higher among adolescents, with a study among 14–17 years old Europeans indicating that the lifetime prevalence of MDD was higher among individuals with lifetime cannabis use (OR = 2.7, 95% Confidence Interval (CI) = 1.6–4.4) and those with lifetime CUD (OR = 4.7, 95% CI = 2.3–9.4) compared to those who did not use cannabis (Wittchen et al. 2007).

In conclusion: Cross-sectional studies have indicated that depression and cannabis use tend to co-occur.

5.3 Cannabis Use and Depression: Longitudinal Evidence

Longitudinal studies allow for further interpreting the cross-sectional association between cannabis use and depression by addressing two inverse temporal hypotheses. The first addresses the extent to which cannabis use is associated with a future onset of MDD or an incline in depressive symptoms. While earlier studies suggested that baseline cannabis use was associated with a higher risk for future MDD (Bovasso 2001; Fergusson and Horwood 1997), accumulating evidence from latter studies has indicated that cannabis users, including heavy cannabis users, were, in fact, not more likely to be diagnosed with MDD over the course of time compared to nonusers (Degenhardt et al. 2013; Georgiades and Boyle 2007). A meta-analysis focusing on longitudinal evidence in the effect of cannabis use on depression has suggested that cannabis use, and particularly heavy cannabis use, may be associated with a mild significant increased risk for developing depression (AOR = 1.17, 95% CI = 1.05–1.30 for any cannabis use and AOR = 1.62, 95% CI = 1.21–2.16 for heavy cannabis use) (Lev-Ran et al. 2013). However, the authors concluded that findings should be regarded with caution, given lack of consistency in terms of statistical adjustment for possible confounding variables implemented in these studies.

Two population-based longitudinal studies have supported the notion that when taking into account of such confounders, cannabis use may not elevate the risk for depression. In a Swedish population-based study, crude analyzes have indicated that cannabis use at the baseline was associated with greater odds for consequent depression (Rate Ratio (RR) = 1.22, 05% CI = 1.06–1.42), yet after controlling for baseline confounders significance was not maintained (RR = 0.99, 95% CI = 0.82–1.17) (Danielsson et al. 2015). In another study that implied a similar methodology, based on Waves 1 and 2 of NESARC, following the control for baseline confounders cannabis use even daily, was not associated with increased incidence MDD at a follow-up (Feingold et al. 2015). Two separate reports, published in Europe by the World Health Organization (WHO, 2016) and in the U.S. by the National Academies of Sciences, Engineering, and Medicine (2017), have concluded that evidence concerning the effect of cannabis use and CUD on depression incidence is limited and warrant further attention, with the latter stating that "cannabis use does not appear to increase the likelihood of developing depression" (p. 12–1).

An inverse notion has focused on the possible contribution of depression to the initiation or increase in cannabis use in the future. The notion that substance use may be triggered by low mood has been reported in several clinical observations (Khantzian and Albanese 2008), retrospective studies (Gruber et al. 1997), and exploratory studies (Ogborne et al. 2000). It has long been suggested that individuals suffering from psychological distress may 'self-medicate' their negative effect by using substances (Khantzian 1985), yet this notion has received only little support in longitudinal research (Degenhardt et al. 2003). In a population-based survey, approximately 9% of the individuals, who qualified for a diagnosis of MDD have reported using drugs or misusing prescription medication for the purpose of relieving depressive symptoms (Bolton et al. 2009); however, cannabis use was not specifically addressed.

A longitudinal study by Feingold et al. (2015) has indicated that among lifetime cannabis abstainers, baseline MDD predicted the initiation of cannabis use throughout a three-year period (Adjusted Odds Ratio (AOR) = 1.72, 95% CI = 1.10 2.69). However, this was not replicated in the study by Danielsson et al. (2015), in which following control for additional illicit drug use, baseline depression was not associated with higher odds for cannabis use initiation at the follow-up (RR = 1.24, 95% CI 0.99–1.54).

In conclusion: There is a weak evidence pointing that cannabis use may lead to the onset of depression; however, there is strong evidence pointing to the inverse association; i.e. that depression may lead to the initiation or increase in frequency of cannabis use.

5.4 Cannabis Use and Depression: Contributing Factors

5.4.1 Age and Gender as Possible Moderators of the Association between Cannabis Use and Depression

Cannabis use is highly prevalent among adolescents and may be prevalent as early as by age 13 (EMMDDA 2017). Initial estimations suggest that nearly 14 million adolescents aged 15–16 use cannabis each year, equivalent to the rate of nearly 6% (WHO 2016). The relatively high availability of cannabis, along with low-harm perception associated with cannabis, makes it one of the most common substances used during adolescence. Based on national monitoring data collected in 2012, the prevalence of cannabis peaks at about 20 years of age, with a general decrease in through age 25 and above (SAMHSA 2014), suggesting that cannabis use may decrease with age and its increasing responsibilities (work, family, and so on). In recent years, it has been suggested that the association between cannabis use and depression may peak at younger age. For example, cannabis use at adolescence was associated with more depressive symptoms compared to nonusers at ages 13–18 (Kaasbøll et al. 2018) and frequency of past-year cannabis use was associated with more current depressive symptoms at ages 16–19 (Leadbeater et al. 2018). However, the association between cannabis use and depression may decrease in its magnitude with time. For example, at age 18 and above, no differences across age were found between the frequency of cannabis use and number of depressive symptoms (Leadbeater et al. 2018). In addition, regular cannabis use at ages 14, 16, and 21 was not associated with increased risk for developing MDD by age 33 (Guttmannova et al. 2017). An integration of four Australian longitudinal cohorts has indicated that cannabis use prior to age 17, even at a daily level, was not associated with increased odds for depression by age 30 (AOR = 1.02, 95% CI = 0.52–2.01) (Silins et al. 2014). These

findings suggest a gradually decreasing time-varying effect of cannabis use on depression.

A recently published 40-years follow-up study of adolescents has evaluated the effects of cannabis use on the odds for developing MDD, taking into account the age of cannabis use initiation and frequency of cannabis use. Adjusted analyzes suggested that early cannabis use initiation (age < 18) was significantly associated with increased odds for consequent MDD compared to nonusers, both among frequent (AOR = 8.83, 95% CI = 1.29–70.79) and infrequent users (AOR = 2.41, 95% CI = 1.22–4.76). However, late cannabis use initiation (age > 27) was not significantly associated with higher odds for the onset of MDD at a follow-up, for both frequent (AOR = 0.68, 95% CI = 0.10–2.65) and infrequent users (AOR = 2.23, 95% CI = 0.26–14.94) compared to nonusers (Schoeler et al. 2018). Additional analyzes have indicated that the early initiation of cannabis use predicted a more rapid onset of MDD, regardless of cannabis use frequency, implying that age at the first cannabis use may play a significant role in the duration to onset of MDD (Fig. 5.1).

Exploring the inverse notion that MDD may lead to the onset of cannabis use, particularly at younger ages, yield conflicting results. On one hand, integrated finding from four Australian cohorts has indicated a moderate positive association between baseline frequent cannabis use and depression scores at a follow-up (Horwood et al. 2012). In this study, the association between cannabis use frequency and future depression has been found to decrease with age, peaking at age 15 and declining at age 30. In another study, a one standard deviation increase in cumulative depression symptoms counts between ages 12 and 15 (defined as the sum of depression symptoms during this time) was associated with a 150% risk for qualifying for a DSM-IV CUD (abuse or dependence) at age 18 (Rhew et al. 2017). On the other hand, in an 18-month follow-up of Chilean ninth-graders, baseline depression was associated with an increased use of cannabis at the follow-up (AOR = 1.21, 95% CI = 1.09–1.34), yet significance was not obtained after controlling for additional sociodemographic and clinical variables (AOR = 1.08, 95% CI = 0.94–1.23) (Stapinski et al. 2016).

There is some indication that the association between cannabis use and depression varies across gender. For example, between ages 18 and 25, the association between cannabis use and depressive symptoms was stronger among men compared to women (Leadbeater et al. 2018). This finding may be attributed to heavier use of cannabis, yet it also may be attributed to higher impulsivity, more sensation seeking, and tendency for avoidant coping strategies presented by men at this age. Notably, in the same study at age 25 and above, the association between cannabis use and depressive symptoms was stronger among women compared to men, suggesting that at these ages, women present a "telescoped" trajectory from cannabis use to pathological use.

In conclusion: Cannabis use is more likely to increase the risk for depression at younger age. The association between cannabis use and depression may be stronger among men at adolescence and emerging adulthood, yet stronger among women during midlife.

5.5 The Effect of Cannabis Use on the Course of Depression

5.5.1 The Effect on Natural Outcome of Depression: Population-Based Studies

Unfortunately, there is little data concerning the effect of cannabis use on the severity and course of depression is scarce. An early study indicated that cannabis use may be associated with an elevated feeling of dysphoria among individuals with depression (Ablon and Goodwin 1974). Participants with lifetime depression and current CUD were likely to experience depression and sadness while intoxicated and were reluctant to report experience of happiness or euphoria (Arendt et al. 2007). In a study focusing on individuals with MDD or dysthymia, women using cannabis regularly (at least weekly) reported of lower mental quality of life compared

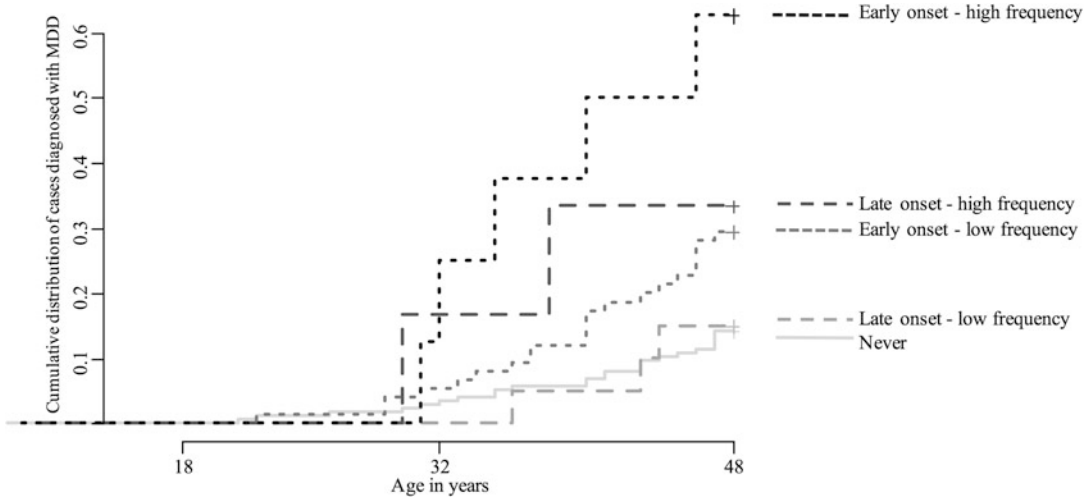

Fig. 5.1 Survival curves of cannabis use pattern and time until diagnosis of MDD. This plot illustrates the cumulative odds of developing the major depressive disorder (MDD) from age 18 to 48. Individuals with early onset of cannabis use exhibited a more rapid onset of MDD, regardless of cannabis use frequency (Schoeler et al. 2018)

to women who did not use cannabis (Aspis et al. 2015).

Several longitudinal studies have suggested that cannabis use may alter the course of illness among individuals with depression. Otten and Engels (2013) have reported that individuals who used cannabis presented more depressive symptoms through adolescence. In another study based on the NESARC sample, individuals who qualified for a baseline diagnosis of MDD ($N = 2300$) were followed throughout a three-year period. Results have indicated that cannabis use and CUD throughout the course of the study was associated with more symptoms of depression at the follow-up, specifically anhedonia, insomnia or hypersomnia, changes in body weight, and psychomotor problems (Feingold et al. 2017). However, the authors have concluded that for the most part, preliminary differences in sociodemographic and clinical factors rather than cannabis use per se were responsible for poorer clinical and functional outcomes of depression. Notably, the results from this study have not indicated a positive effect of cannabis use on the course and outcome of depression, suggesting that "self-medication" may not be effective.

There is evidence suggesting that cannabis use, and frequent cannabis use, in particular, may result in a reduced efficiency of pharmacological treatment for depression in clinical populations (Bricker et al. 2007). In another study, among 300 psychiatric outpatients receiving treatment for depression, baseline cannabis use predicted more suicide ideation, less treatment utilization, less improvement in depressive symptoms, and poorer quality of life compared to nonusers at a 12-month follow-up (Bahorik et al. 2018).

In recent years, technological and methodological advances allow for a more sensitive investigation of the effect of cannabis use on the depressed mood. For example, Cuttler et al. (2018) have analyzed data from the Strainprint™ app, designed to allow users of medical cannabis to track changes in their affective symptoms in relation to different cannabis dosing and chemotypes. Exploring more than 3000 contacts made by app users, participants reported a reduction in depressive symptoms from before to after using cannabis in 89.3% of tracked sessions. No gender differences were found in the magnitude of this change, yet a greater reduction in symptom rating was observed among individuals using low-THC/high-CBD strains of cannabis

compared to those who used high-THC/low-CBD strains.

Notably, analyzing sessions made by users over time in this study, authors have reported that participants' rates of baseline depression (right before using cannabis) significantly increased with time/sessions (Cuttler et al. 2018). This may indicate that the effects of cannabis use on depression may act in two inverse paths, decreasing depressive symptoms on the short run, but increasing baseline depression in the long run. This notion is supported by findings from a study in which during 28-days of monitored period, abstinent adolescent cannabis users reported a significant decline in the level of depression compared to nonusers (Jacobus et al. 2017).

In conclusion: Observational and epidemiological studies did not indicate a positive long-term effect of cannabis use on the outcome of depression.

5.5.2 Genetics and the Neurological Basis of the Association between Cannabis Use and Depression

5.5.2.1 Genetic Studies on CUD

There is evidence for genetic associations in CUD shown in epidemiological and in clinical studies (see Benyamina et al. 2016 for review). Epidemiological studies have investigated the roles of environmental and genetic factors in cannabis use disorders and in the progression from experimentation to CUD. Studies on CUD have shown correlations between parents and children that range from 0.3 to 0.47; among siblings, these figures are between 0.39 and 0.47 (Agrawal and Lynskey 2006; Meller et al. 1988; Verweij et al. 2010). Large-scale twin studies have also estimated the role of genetic, environmental, and shared environmental factors Verweij et al. (2010). Thus, genetic factors would seem to contribute significantly to progression to CUD.

Genetic studies have examined many genes that could be associated with CUD. One gene that was investigated was catechol-O-methyltransferase (COMT), which regulates dopamine (Batalla et al. (2014), AKT_1 polymorphism (rs 1,130,253) (Bhattacharyya et al. 2014), DRD_2, (Colizzi et al. 2015; Taurisano et al. 2014), and the cannabinoid receptor 1 gene (CNR1) (Agrawal et al. 2009).

Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that show an association between schizophrenia, depression, and CUD. Sherva et al. (2016) have studied 14,754 participants and they have found three SNPs rs143244591, rs146091982 (SLC35G1), and rs77378271 in the CUB and Sushi multiple domain 1 gene (CSMD1) that were associated with CUD. They also found genes that were affecting both MDD and CUD and risk for schizophrenia. This is the first study that has identified specific cannabis addiction risk alleles and potential genetic factors contributing to the comorbidity of cannabis dependence with major depression and schizophrenia.

5.5.2.2 Specific Genetic Studies on the Association between Cannabis Use and Depression

A major study inking cannabis use and depression by Lynskey et al. (2004) has measured correlations between early cannabis use and lifetime cannabis dependence and MDD, and suicidal ideation and attempts for suicide. They have investigated 311 same-sex twins who differ in their early start of cannabis use (before 17) and 277 same-sex twins discordant for cannabis dependence. They have found that cannabis-dependent individuals compared with their twins who were not cannabis dependent had higher odds ratio of suicidal ideation and suicide attempts (2.5 to 2.9 times, respectively). Cannabis was also associated with higher risks for MDD in nonidentical twins. Those who initiated cannabis use, prior to age 17 years, had elevated rates of subsequent suicide attempt (OR = 3.5, 95% CI = 1.4–8.6]) but not of MDD or suicidal ideation. The risk of cannabis dependence was associated with early MDD and suicidal ideation in nonidentical twins who differed in cannabis use (discordant) but not in identical twins who

differed in cannabis use discordant dizygotic twins. This evidence supports the suggestion that the comorbidity of cannabis dependence and MDD (but not suicidal behavior) has both genetic and environmental vulnerability factors. Early-onset cannabis use may be a predisposition factor for MDD or it may share genetic and environmental predisposition,

The relationship between cannabis use and depression and the short allele of the 5-hydroxytryptamine (serotonin) transporter gene-linked polymorphic region (5-HTTLPR) genotype in 310 adolescents over 4 years has been studied by Otten and Engels (2013). Cannabis use was associated with an increase in depressive symptoms over time but only in those who had the short allele of the 5-HTTLPR genotype. This is further evidence for the genetic contribution to the co-occurrence of cannabis use and depression. Finally, Hodgson et al. (2017) have studied 1284 Mexican-Americans from 75 large multi-generation families and an additional 57 genetically unrelated spouses. A linkage peak for major depression on Chromosome 22 and a peak for cannabis use on Chromosome 21 was found. Chromosome 11 had a linkage peak that affected both cannabis use and MDD as well as an SNP 20 kb upstream of NCAM1 (rs7932341) that was associated with both disorders.

In conclusion: there seems to be a common genetic association between cannabis use and MDD, which is found in twins and family studies located on Chromosome 11.

5.5.3 The Use of Medical Cannabis for Treating Depression

Medical conditions such as chronic pain multiple sclerosis, post-traumatic stress disorder, and Parkinson's disease have been recently treated with medical cannabis (Amato et al. 2017; Borgelt et al. 2013; Pertwee 2001). In order to understand the potential therapeutic effects of medical cannabis, it is mandatory to learn about the interactions of cannabinoids and other neurotransmitters (Pertwee 2014; Cohen et al. 2019).

5.5.3.1 Pre-Clinical Studies on Cannabis as an Anti-Depressant

Preclinical studies have shown that cannabis may be therapeutically effective for depression (Scherma et al. 2018). The agonistic effect of cannabinoids to the central CB_1 receptors (CB_1Rs) may mediate this effect. Shearman et al. (2003) have evaluated the CB_1R modulation of antidepressant-like effects. They have administered mice with the CB_1R inverse agonist AM251 and tested on the tail-suspension test (TST) and on the forced swim test (FST). On both tests, AM251 has significantly reduced immobility without an increase in motor activity in the open field indicating and antidepressant effect. Inverse cannabinoid agonism of CB_1R may be therefore useful for the regulation of mood. Furthermore, a low dose of a CB_1R agonist WIN55,212–2 has a potential antidepressant effect in the rat forced swim test (Bambico et al. 2007). This effect was blocked by the CB_1R antagonist rimonabant and also by pretreatment with the 5-HT-depleting agent parachlorophenylalanine. CB_1R agonists may therefore have antidepressant effects and they modulate 5-HT neuronal activity via the medial prefrontal cortex in rats.

CB_1R density and function, as well as CB_1 messenger RNA (mRNA) levels, were high in the dorsolateral prefrontal cortex of depressed humans after suicide found in postmortem studies, (Hungund et al. 2004; Choi et al. 2012). However, patients suffering from major depression have not shown any alterations in CB_1R mRNA and protein levels in the dorsal prefrontal cortex (Eggan et al. 2010). Depressed patients treated with serotonin selective reuptake inhibitors (SSRIs) showed a reduced expression of CB_1R in the anterior cingulate cortex (Koethe et al. 2007), suggesting that an elevated CB_1 has antidepressant properties..

An association between polymorphisms in the CNR_1 gene and increased vulnerability to develop a depressive episode following exposure to life stress was shown by Juhasz et al. (2009), and increased risk of resistance to the effects of antidepressants (Domschke et al. 2008).

Susceptibility to bipolar disorder and MDD may be associated with CNR_1 and FAAH gene polymorphisms (Monteleone et al. 2010). Finally, the CNR_1 gene may be involved in the development of MDD and in the effects of Citalopram, an SSRI (Mitjans et al. 2013). *In conclusion*, deficient endocannabinoid signaling may be associated with depression; and therefore, activating the endocannabinoid system could be an effective treatment for MDD but the mechanism of elevated CB_1 as an anti-depressant needs further examination.

5.5.3.2 Clinical Studies on Cannabis as an Anti-Depressant

Cannabis users often use cannabis as self-medication for depression and manic symptoms (Grinspoon and Bakalar 1998; Ashton et al. 2005). This is supported by five cases described by Gruber et al. (1996). Individuals who have used cannabis occasionally or even daily have lower levels of depressive symptoms than those who have never tried cannabis (Denson and Earleywine 2006). Depressed patients also have used cannabis to improve their sleep they developed (Babson et al. 2013). There are seven cross-sectional studies that showed clear evidence of an improvement in depressed mood by cannabis (Walsh et al. 2017). In conclusion, the evidence so far is anecdotal and it relies heavily on single case studies and cross-sectional studies and there are no placebo-controlled clinical trials that show that cannabis is useful for the treatment of depression.

5.5.4 Discussion

This issue of using cannabis as an antidepressant is at an early stage of examination and there is little evidence to support it. Psychiatric outpatients who used medical cannabis showed worse mental and physical health function compared with nonusers. Nonmedical cannabis correlated with increased suicidal ideation and mental health problems and fewer psychiatry visits (Bahorik et al. 2018). Nonmedical cannabis over time correlated with lowered improvement in depression symptoms and suicidal ideation. Cannabis use in depressed patients can prevent improvement in depressive symptoms and impair patients' treatment.

The evidence in favor of cannabis treatment for anxiety and mood disorders relies on few single-dose studies with a small sample size and flawed design (Turna et al. 2017). Furthermore, there are other factors such as interactions with other medications, frequency of use, dose of cannabis, time of use, way of delivery, and characterization of patients who may have influenced the results (D'souza and Ranganathan 2015). It remains to be investigated whether cannabis should be used alone or together with other medications, what patients should be treated, should it be prescribed only to those who do not respond to other medications (such as in the case of pain for example), and whether cannabis is efficient in the long term in comparison with SSRIs, considering its long-term side effects (D'souza and Ranganathan 2015).

5.6 Pharmacological Treatment for Individuals with Comorbid Depression and CUD

5.6.1 Pharmacological Treatment for CUD

There is an increase in the number of patients who are treated for CUD and most patients find it difficult to achieve and maintain abstinence from cannabis use. Hence, there is an urgent need to find medications for the treatment of CUD (see Weinstein and Gorelick 2011; Gorelick 2016 for review). Currently, no medication has been approved for the treatment of CUD. Medications have been tested for their ability to alleviate withdrawal symptoms, influence endogenous cannabinoids, or those that have been used for drug abuse treatment and other psychiatric conditions (Weinstein and Gorelick 2011). Four trials have been documented for the treatment of specific intoxication symptoms, seven trials for withdrawal, and 12 phase II trials for CUD (Gorelick 2016). The only effective medications

were gabapentin and N-acetylcysteine (in adolescents). Three trials of antidepressants for CUD with comorbid depression revealed inconsistent results.

In conclusion: There is a need for double-blind placebo-controlled clinical trials in order to test the clinical efficacy of medications for the treatment for CUD.

5.6.2 Treatment of Patients with Comorbidity of Cannabis Dependence and Depression

There are few studies evaluating the use of antidepressant medication for the treatment of comorbid CUD and depression. Preliminary findings in 13 patients treated with fluoxetine an SSRI antidepressant (20–40 mg daily), showed a reduction in cannabis and alcohol dependence and depressive symptoms (Cornelius et al. (2005). However, after a five-year follow-up of 10 patients, although symptoms of cannabis and alcohol dependence have been reduced and academic ability has improved, clinical depression remained. A double-blind, placebo-controlled study using fluoxetine (20 mg daily) for 12 weeks to treat 70 adolescents and young adults with comorbid MDD and CUD showed no greater efficacy than placebo for treating either the depressive symptoms or the cannabis-related symptoms (Cornelius et al. 2010). The negative findings may be due to a small sample size, limited medication efficacy, or high efficacy of the psychosocial treatment.

Finally, a randomized eight-week double-blind and placebo-controlled study of fluoxetine in 29 male and five female adolescents with depressive illness and a comorbid substance use disorder showed no difference in depression ratings between patients treated with fluoxetine and placebo, nor was there any differences in positive urine samples for cannabis (Findling et al. 2009). This study has also suffered from the limitations of a small sample size and a high placebo response rate, limited dose of fluoxetine, and inclusion of participants with depressive disorders other than the major depressive disorder.

In conclusion: SSRIs, such as fluoxetine, do not show improved efficacy in treating depressive symptoms or treatment of CUD (indicated by clean urine samples) in adolescents with comorbid depression and CUD.

5.7 Summary

When exploring the association between cannabis use and depression, one should take into account several methodological limitations. The study of cannabinoids often does not allow for a precise measure of dose, frequency, or chemical composition of the substance used by participants (Mariani et al. 2011), while epidemiological studies also indiscriminately use different definitions of cannabis use, thus standardization is seldom achieved. Likewise, the definition of depression may vary according to the classification method used, i.e. the diagnostic and statistical manual of mental disorders (DSM) (American Psychiatric Association 2013) or the international classification of diseases (ICD) (World Health Organization 1992), and according to the method of assessment used (i.e. clinical assessment, semi-structured interviews, questionnaires, and so on). Furthermore, depression is often defined as the presence of depressive symptoms rather than a full diagnosis.

Despite these limitations, research in the past decades has shed light on the association between cannabis use and depression from epidemiological, neurological, genetic, and pharmacological perspectives. Given the growing prevalence of both cannabis use and depression globally, integrative research is needed in order to comprehend the possible pathways through which these factors interact. In addition, in light of the debate on the legalization of cannabis, further research should assess the direct and indirect effects of cannabis use on co-occurring physical and mental disorders, including depression.

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