

Journal of Dual Diagnosis

research and practice in substance abuse comorbidity

ISSN: 1550-4263 (Print) 1550-4271 (Online) Journal homepage: <https://www.tandfonline.com/loi/wjdd20>

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To cite this article: Lucia Sideli, Harriet Quigley, Caterina La Cascia & Robin M. Murray (2019): Cannabis Use and the Risk of Psychosis and Affective Disorders, Journal of Dual Diagnosis, DOI: [10.1080/15504263.2019.1674991](https://doi.org/10.1080/15504263.2019.1674991)

To link to this article: <https://doi.org/10.1080/15504263.2019.1674991>



Published online: 24 Oct 2019.



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Cannabis Use and the Risk of Psychosis and Affective Disorders

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ABSTRACT

Objective: This review discusses the relationship between cannabis use and psychotic, bipolar, depressive, and anxiety disorders, as well as suicide. It summarizes epidemiological evidence from cross-sectional and long-term prospective studies and considers possible etiological mechanisms. **Methods:** Systematic reviews and methodologically robust studies in the field (from inception to February 2019) were identified using a comprehensive search of Medline, PsychINFO, and Embase and summarized using a narrative synthesis. **Results:** Consistent evidence, both from observational and experimental studies, has confirmed the important role of cannabis use in the initiation and persistence of psychotic disorders. The size of the effect is related to the extent of cannabis use, with greater risk for early cannabis use and use of high-potency varieties and synthetic cannabinoids. Accumulating evidence suggests that frequent cannabis use also increases the risk for mania as well as for suicide. However, the effect on depression is less clear and findings on anxiety are contradictory with only a few methodologically robust studies. Furthermore, the relationship with common mental disorders may involve reverse causality, as depression and anxiety are reported to lead to greater cannabis consumption in some studies. Pathogenetic mechanisms focus on the effect of tetrahydrocannabinol (THC, the main psychoactive ingredient of cannabis) interacting with genetic predisposition and perhaps other environmental risk factors. Cannabidiol (CBD), the other important ingredient of traditional cannabis, ameliorates the psychotogenic effects of THC but is absent from the high-potency varieties that are increasingly available. **Conclusions:** The evidence that heavy use of high-THC/low-CBD types of cannabis increases the risk of psychosis is sufficiently strong to merit public health education. Evidence of similar but smaller effects in mania and suicide is growing, but is not convincing for depression and anxiety. There is much current interest in the possibility that CBD may be therapeutically useful.

KEYWORDS

Cannabis; marijuana; psychosis; mania; depression; anxiety; brain structure; genetic predisposition; early adolescence; interaction

Introduction

In all European countries, across all age groups, cannabis is the most popular illicit substance; the overall prevalence of use is approximately five times that of other substances (European Monitoring Centre for Drugs & Drug Addiction, 2016). In Portugal, possession of small quantities of cannabis has been officially decriminalized, while in the Netherlands cannabis can be legally obtained in so-called “coffee shops.” In many other countries such as the United Kingdom, the police generally turn a blind eye to personal use. Currently, several European countries are reviewing their legislation, prompted by the liberalization in North America. However, as in North America,

scientific research into the long-term effects of cannabis on psychiatric disorders plays little part in determining public policy.

In this narrative review, we will briefly review the cannabis plant, the endocannabinoid system, and the changing nature of recreational cannabinoids before focusing on cannabis use and psychotic, depressive, bipolar, and anxiety disorders.

Methods

The summarized evidence here comes from systematic reviews and meta-analyses published in English from inception to February 2019, which investigated the

effect of cannabis use or its active compounds on psychotic, depressive, bipolar, and anxiety disorders. The following keywords were used to screen Medline, PsychINFO, and Embase: (cannabis OR hash OR marijuana) AND (psychosis OR FEP OR depression OR bipolar OR mania OR suicide OR anxiety).

We sought to describe the detrimental effects of cannabis, with particular attention to the adolescence period, but also potential therapeutic applications. When systematic reviews were not available, large prospective controlled studies, both observational and experimental, were included. However, since the paper was conceived as a narrative review, the coverage of the literature did not pretend to be exhaustive.

More attention has been devoted to the relationship between cannabis and psychosis than with other psychiatric disorders. Consequently, in relation to psychotic disorders, we summarize the evidence, which is well-reviewed elsewhere, that heavy use of cannabis can induce psychosis, and discuss possible mechanisms as well as objections to this hypothesis. As there are far fewer studies investigating the relationship between cannabis and mood disorders and anxiety, here we shall also consider individual studies.

Results

Cannabinoids and the endocannabinoid system

The cannabis plant contains numerous cannabinoid compounds (Hanus, 2009) which are produced in crystal formations around the flowering tops of the plant, the most important of which are tetrahydrocannabinol (THC) and cannabidiol (CBD). There are approximately 400 other compounds such as terpenoids and flavonoids (Atakan, 2012).

Cannabinoids interact with the endocannabinoid system to exert their effects. This biological system is composed of endocannabinoids (endogenous lipid-based ligands), their receptors, and the enzymes that synthesize and degrade them (Mechoulam & Parker, 2013). The most important endocannabinoids are N-arachidonylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), which are synthesized postsynaptically “on demand” and cleared by a reuptake mechanism and enzymatic hydrolysis. There are two types of endocannabinoid receptors: cannabinoid receptor type-1 (CB1) and cannabinoid receptor type-2 (CB2). The CB1 receptors are located presynaptically and can be found throughout the brain, with highest concentrations in the neocortex, basal ganglia, and hippocampus (Howlett et al., 1990), where they modulate neurotransmitter release (Katona

& Freund, 2012). It was initially thought that the CB2 receptor was expressed solely in peripheral tissues and immune cells (Piomelli, 2003); however, more recently it has also been found in the cerebellum and brainstem. Other receptors have been found to be involved in endocannabinoid signaling. These include orphan G protein-coupled receptors GPR119 (expressed predominantly in the digestive tract) and GPR55 (central nervous system [CNS] and bone), as well as transient receptor potential vanilloid 1 receptors (TRPV1), which are activated by endogenous cannabinoids in the CNS (Balenga, Henstridge, Kargl, & Waldhoer, 2011; Brown, 2007; Henstridge et al., 2011; Starowicz, Cristino, & Di Marzo, 2008). CBD is capable of binding to TRPV1 (Bisogno et al., 2001), and endocannabinoids have also been shown to activate TRPV1 (Brown, 2007), which has been shown to influence both dopaminergic (Tzavara et al., 2006) and glutamatergic neurotransmission (Fawley, Hofmann, & Andresen, 2014).

THC is responsible for the “high” that users enjoy, the feelings of euphoria, increased sociability, insightfulness, and sharpening of senses. It is a partial agonist at the CB1 receptor. With continued use, its binding overwhelms the endogenous endocannabinoid system and results in downregulation of the CB1 receptor and lower levels of endogenous cannabinoids (e.g., AEA), which are synthesized in an activity-dependent manner (Ceccarini et al., 2015; D’Souza et al., 2016; Hirvonen et al., 2012).

The mechanism of action of CBD is not fully understood (Boggs, Nguyen, Morgenson, Taffe, & Ranganathan, 2018; Pertwee, 2005). CBD has little affinity for the CB1 receptor but may act antagonistically against CB1 agonists via a non-orthosteric binding site (McPartland, Duncan, Di Marzo, & Pertwee, 2015; Morales, Goya, Jagerovic, & Hernandez-Folgado, 2016). Moreover, some studies suggest that CBD interacts with serotonin 1A (5-HT1A) receptors, with similar effects as 5-HT1A agonists (Boggs et al., 2018), increases the availability of endogenous AEA (Bisogno et al., 2001), and acts as allosteric modulator of mu- and delta-opioid receptors (Kathmann, Flau, Redmer, Tränkle, & Schlicker, 2006).

There is evidence that CBD is able to block or at least ameliorate many of the effects of THC (Pertwee, 2008). For instance, in an experimental study of 48 healthy volunteers, pretreatment with 600 mg oral CBD before 1.5 mg of intravenous THC significantly reduced the occurrence of psychotic symptoms and detrimental effects of THC on memory (Englund et al., 2012). Morgan and Curran tested hair samples

for cannabinoids and showed that those cannabis users with both THC and CBD in their hair had fewer psychotic symptoms than those with THC alone detected in their hair (Morgan & Curran, 2008).

Changes in recreational cannabinoids

Cannabis for recreational use is available as either herb (marijuana, grass, weed) or resin (hashish, hash). In many parts of the world such as the United States, it is commonly smoked on its own, whereas in Europe it tends to be smoked in a “joint” with tobacco (Hindocha, Freeman, Ferris, Lynskey, & Winstock, 2016). The effects of cannabis are felt after a few minutes if smoked or inhaled (e.g., from a bong) and last 2 to 3 hours; if eaten, the effects can take 2 hours to come on and they can last up to 8 hours. Cannabis remains in the body for several weeks, and withdrawal symptoms are therefore relatively mild; craving, anxiety, irritability, insomnia, appetite disturbance, dysphoria, and depression have been reported. Approximately 10% of traditional cannabis users experience dependency (Budney, Roffman, Stephens, & Walker, 2007), with some studies suggesting that this figure could be as high as 17% in those who start using cannabis during adolescence (Volkow, Baler, Compton, & Weiss, 2014). High-potency cannabis is associated with a particularly increased risk of dependence (Freeman & Winstock, 2015). The latter may be why, according to the US NESARC study, the prevalence of cannabis use disorders (CUD) is now up to 30% among past-year cannabis users (Hasin et al., 2015).

Sinsemilla is a Spanish term that means “without seeds” and refers to a type of cannabis where the female plant is left unfertilized so that so it does not produce seeds and thus converts more of its energy into cannabinoids (in particular, increased THC); it is known by a vast number of colloquial terms but most commonly in Europe as “skunk” as it has a strong smell. In the 1960s, the average proportion of THC in herbal cannabis (marijuana) and resin (hashish) in Europe was about 2% to 3%; however, there has been a move toward high-potency cannabis and by the early 21st century this had risen to an average of 14% in England (Hardwick Leslie, 2008), 20% in Holland (Pijlman, Rigter, Hoek, Goldschmidt, & Niesink, 2005), 15% in Australia (Swift, Wong, Li, Arnold, & McGregor, 2013), and 12% in the United States (ElSohly et al., 2016). Plants bred to produce a high concentration of THC cannot simultaneously produce a lot of CBD; thus, there are two reasons for the resultant cannabis having stronger psychoactive effects

(i.e., the greater psychotogenic effect of high THC and the lack of the moderating influence of CBD). An increasing assortment of cannabis products including oils and “edibles” such as chocolates and cakes are available via the Internet.

In the late 2000s, synthetic cannabinoid compounds started to be used in Germany as “legal highs,” often referred to collectively as “Spice” or “K2.” Use rapidly increased, with more than 200 synthetic cannabinoids with slightly different molecular structures now available online. Most synthetic cannabinoids are full agonists for the CB1 receptor and consequently have more powerful effects than THC, which is a partial agonist; they therefore pose a greater health risk compared to plant cannabis (Tait, Caldicott, Mountain, Hill, & Lenton, 2016). Side effects are unpredictable; acute physical reactions include nausea and vomiting, shortness of breath, hypertension, tachycardia, chest pain, and occasionally acute renal failure. Synthetic cannabinoids are not readily detectable in routine drug screening tests, making them particularly popular among certain groups such as prisoners.

Cannabis and psychosis

Prospective epidemiological studies have consistently demonstrated that cannabis use is associated with an increased risk of subsequently experiencing psychotic symptoms and developing schizophrenia-like psychoses. In the first study to examine whether cannabis might be causally related to psychosis, Andréasson, Engström, Allebeck, and Rydberg (1987) conducted a longitudinal prospective study by following up 45,750 young men who had been questioned about their use of substances when they were conscripted into the Swedish army (Andréasson et al., 1987). Those men who had used cannabis more than 50 times were six times more likely to experience schizophrenia in the next 15 years than those who had never used it. There has since been a raft of longitudinal prospective studies. These have been extensively reviewed over time (Arseneault, Cannon, Witton, & Murray, 2004; Gage, Hickman, & Zammit, 2016; McLaren, Silins, Hutchinson, Mattick, & Hall, 2010; Moore et al., 2007; Murray, Quigley, Quattrone, Englund, & Di Forti, 2016; Murray et al., 2017), so we will not reiterate all the evidence here (see Table 1). Suffice it to say that, in the current state of knowledge, of 13 prospective longitudinal studies, 10 showed that cannabis users had a significantly increased risk of psychosis compared with nonusers, while two of the remaining three

showed a trend in the same direction (Murray et al., 2016, 2017).

There is consistent evidence of a dose–response relationship between the risk for psychosis and the amount of cannabis consumed. In a first meta-analysis of six studies, Moore et al. (2007) estimated a more than doubled risk among those with the most frequent pattern of cannabis use, but in a following meta-analysis, Marconi, Di Forti, Lewis, Murray, and Vassos (2016) found that in 10 studies, the odds ratio for risk of psychosis-related outcomes reached almost 4 among the heaviest cannabis users compared to the nonusers.

Higher-potency types of cannabis carry more risk than traditional forms. Di Forti, Marconi et al. (2015) studied 410 patients with their first episode of psychosis and 390 healthy controls and found that those using high-potency cannabis on a daily basis were five times more likely than nonusers to experience a psychotic disorder; use of cannabis resin was not related to an increased risk of psychosis, likely due to the lower THC concentration and the presence of an equivalent amount of CBD (Di Forti, Marconi et al., 2015).

Psychotic episodes have been reported secondary to use of synthetic cannabinoids. Papanti et al. carried out a systematic review and reported that agitation, anxiety, paranoia, and psychosis can result from even brief use of synthetic cannabinoids; these reactions are sometimes referred to as “spiceophrenia” (Papanti et al., 2013). Increasing evidence suggests that more chronic psychotic disorders can also occur (Deng, Verrico, Kosten, & Nielsen, 2018).

Higher rates of cannabis use and CUDs were also found among individuals at ultra high risk (Carney, Cotter, Firth, Bradshaw, & Yung, 2017; Kraan et al., 2016) and with a first episode of psychosis (Myles, Myles, & Large, 2016). Psychotic patients who use cannabis have an earlier illness onset than nonusing psychotic patients (Di Forti, Marconi et al., 2015; Large, Sharma, Compton, Slade, & Nielsen, 2011). They also have higher IQ and better neurocognition than nonusing patients, as well as higher premorbid IQ and better premorbid social function (Ferraro et al., 2013, 2019; Yücel et al., 2010); cannabis-using patients with psychosis are less likely to show neurological soft signs than nonusing patients (Ruiz-Veguilla, Callado, & Ferrin, 2012). It may be that these surprising findings reflect the fact that cannabis-using psychotic patients have less neurodevelopmental impairment than non-using psychotic patients.

Critical period of adolescence

Psychotic disorders such as schizophrenia are widely accepted as being neurodevelopmental in origin, with prodromal symptoms often emerging in adolescence and early adulthood (Murray et al., 2017; Murray & Lewis, 1987). Neurodevelopmental processes that take place during this time may be important in the expression of latent vulnerability for psychosis and may be susceptible to the influence of drugs such as cannabis. Thus, exposure to exogenous cannabinoids might permanently impair the endocannabinoid system, which plays a role in neural development and impacts adversely on brain and neurotransmitter function (Volkow, Wang et al., 2014). As already mentioned, the risk of cannabis dependence and of psychosis is especially increased if use was initiated during adolescence. In the Dunedin cohort, those who started to use cannabis at age 18 or older showed only a small, nonsignificant increase in the risk of schizophrenia-like psychosis by age 26; the risk increased fourfold, however, among those starting at age 15 or younger (Arseneault et al., 2002).

There is an association between age at onset of cannabis use and levels of striatal dopamine in adult life (Bloomfield et al., 2014; Urban et al., 2012). Some imaging studies have claimed to find structural brain changes in those who started heavy cannabis use in adolescence: global reduction in gray matter volume (Mathew, Turkington, Hawk, Coleman, & Provenza, 2000), reduced fractional anisotropy in a number of white matter tracts (Gruber, Dahlgren, Sagar, Gönenç, & Lukas, 2014), reduced parahippocampal volume (Battistella et al., 2014), and greater white matter alterations (Gruber et al., 2014). These findings are discussed in detail elsewhere in this issue.

Criticisms of the causal hypothesis

Most European and Australasian experts are now convinced that cannabis is one of a number of contributory causes of schizophrenia. However, less attention has been paid to this issue in North America, although a very recent book aimed at the general population has induced considerable discussion (Berenson, 2019). The main criticisms of the causal hypothesis are as follows:

1. **Confounding by other drug use:** A number of studies have addressed this question and not found the effect of other drugs sufficient to negate the psychotogenic impact of cannabis (Arseneault et al., 2002; Di Forti, Marconi et al., 2015; Di Forti et al., 2009).

2. “Psychological deviancy”: The Dunedin study controlled for psychotic symptoms at age 11 and still found that cannabis use increased the risk of later psychotic symptoms (Arseneault et al., 2002). Two studies using data collected as part of the Swedish Army Study controlled for so-called “disturbed behavior” (including truancy, contact with police/childcare authority, running away from home), and both found that after adjustment cannabis use still significantly increased the risk of schizophrenia (Manrique-Garcia et al., 2011; Zammit, 2002).
3. Reverse causation/self-medication: It has been hypothesized that psychotic patients may use cannabis to counteract negative symptoms in people with the illness, or even allay anxiety in the prodrome, but there are few empirical data to support this (Mustonen et al., 2018). Indeed, one study by Fergusson et al. showed that people tend to smoke less cannabis after the onset of psychotic symptoms (Fergusson, Horwood, & Ridder, 2005), and the finding was confirmed by subsequent studies (Myles et al., 2016). Also, THC has been shown experimentally to worsen positive symptoms in those with schizophrenia. Psychotic patients cite enjoyment and pleasure as reasons for using cannabis, the same as in the rest of the population (Bianconi et al., 2016).
4. It is often said that there has not been an increase in the prevalence of schizophrenia, despite an increase in cannabis use; however, there is little reliable information on temporal trends in the incidence of schizophrenia, so it is difficult to examine this question. One study using consistent diagnostic criteria for schizophrenia reported that the incidence in South London doubled between 1965 and 1999 (Boydell et al., 2006). Very recently, a large European study (the EU-GEI study) has shown an eightfold variation in the incidence of psychosis across 17 centers; the highest rates were found in London and Amsterdam, which also reported the greatest use of high-potency cannabis (Di Forti et al., 2019). Indeed in these two cities, the use of high-potency cannabis accounted for almost one-third and one-half, respectively, of all new cases of psychosis.
5. A high proportion of cannabis users smoke tobacco, either concurrently (co-use) or as a component of cannabis joints (simultaneous use; Hindocha et al., 2016), and the relationship between the two is difficult to disentangle. There is a strong association between cigarette smoking and psychotic disorders. It had been assumed that tobacco smoking was secondary to the illness itself, either through self-medication or a process of institutionalization, or could be explained by confounding. More recently, a bidirectional relationship has been implicated wherein tobacco smoking may be causally related to the risk of psychosis (Gurillo, Jauhar, Murray, & MacCabe, 2015).

Tobacco smoking increases the amount of THC inhaled per gram, thus enhancing the subjective effect of cannabis (Van Der Kooy, Pomahacova, & Verpoorte, 2008), and may mediate the relationship between cannabis use and cannabis dependence, which could be explained by the more addictive properties of nicotine (Hindocha et al., 2015). Tobacco smoking has also been shown to offset the effects of cannabis on delayed verbal recall, thereby perpetuating use (Hindocha, Freeman, Xia, Shaban, & Curran, 2017). Thus, tobacco smoking might facilitate cannabis dependence, compounding the risk of experiencing a psychotic disorder. There is also some evidence to suggest a synergistic effect whereby the combination of tobacco and cannabis gives rise to symptoms of psychosis (Jones et al., 2018).
6. Shared genetic vulnerability has been a popular explanation for the association between cannabis use and psychosis. It is now possible to examine the relationship between predisposition to psychosis, as measured by the polygenic risk score for schizophrenia (PRS-Sz), and cannabis use. The PRS-Sz was reported to be associated with increased use of cannabis (Power et al., 2014), but was responsible for only a small proportion (5%) of the variance in cannabis use. Similarly, Verweij et al. (2017) showed that the PRS-Sz explained a small proportion of the variance in lifetime cannabis use in almost 7,000 individuals (Verweij et al., 2017). Gage, Hickman et al. (2015) suggested that those who use high-potency cannabis might be genetically predisposed to psychosis (Gage, Munafò, MacLeod, Hickman, & Smith, 2015), but Di Forti, Vassos, Lynskey, Craig, and Murray (2015) examined the PRS-Sz in users of low- and high-potency cannabis and found no evidence of this (Di Forti, Marconi et al., 2015).

Gage’s Mendelian randomization (MR) study of cannabis initiation and schizophrenia risk reported evidence for causal pathways operating in both directions (Gage et al., 2017). Pasman et al. (2018) used

MR to show evidence for a causal positive influence of schizophrenia risk on cannabis use (Pasman et al., 2018). Vaucher et al. adopted the opposite approach and examined whether genetic predisposition to cannabis use increased risk of schizophrenia, conducting an MR analysis of the association of genetically determined cannabis use on risk of schizophrenia in 34,241 cases and 45,604 controls and concluding strong support for a causal association between genetically determined use of cannabis and risk of schizophrenia (Vaucher et al., 2018).

In summary, genetic predisposition to schizophrenia accounts for only a small proportion of variance in cannabis use; furthermore, this effect on cannabis use is shared with an effect on other drugs not associated with psychosis such as alcohol and heroin, indicating that although this may play a small role, it is not the major reason for the association between cannabis and psychosis.

Of course, it may be that individuals vary in their susceptibility to the psychotogenic effects of cannabis. To our knowledge, only one published study has looked at a possible interaction between the polygenic risk score for schizophrenia and cannabis in causing psychosis. This showed an additive interaction of molecular genetic risk for schizophrenia with regular cannabis use (Guloksuz et al., 2019). French et al. (2015) also examined this in relation to structural brain imaging in adolescents and showed that cannabis use before the age of 16 was associated with reduced global cortical thickness, suggesting that cannabis exposure may alter cortical morphometry, but only in males with a high schizophrenia polygenic risk score (French et al., 2015).

The interaction between cannabis use and candidate genes has also been studied. Caspi et al. (2005) reported that the Val-Met functional polymorphism of the COMT gene, which plays a role in the metabolism of dopamine in the prefrontal cortex, appeared to moderate liability to cannabis-associated psychosis, but this has not been generally replicated (Vaessen et al., 2018). A variant of AKT1 has been reported to increase the risk of psychotic illness among cannabis users in two case-control studies, and a third study has shown that those who carry this variant show a greater psychotogenic response to smoked cannabis (Di Forti et al., 2012; Morgan, Freeman, Powell, & Curran, 2016; van Winkel et al., 2011). A variant in the D2 receptor gene may also increase psychosis risk; the risk was reported to be even greater in those who carry both this variant and the AKT1 risk allele (Colizzi et al., 2015). These findings of interactions

between candidate genes and cannabis use must however be regarded as unproven until larger studies are reported.

Outcome and treatment of psychotic disorders

Psychotic patients who continue to use cannabis, especially high-potency forms, have higher relapse rates, longer hospital admissions (suggesting more severe relapses which take longer to stabilize), and more severe positive symptoms than either former users who discontinued or never-users (Schoeler et al., 2016; Zammit et al., 2008) (see Table 1). These findings emphasize the importance of addressing cannabis use in the treatment of psychosis.

A variety of interventions have been tried to address continued cannabis use by psychotic patients, including cognitive behavioral therapy, motivational interviewing/motivational enhancement, and contingency management (e.g., giving shopping coupons for urine free of cannabis). These have had little success (Hjorthoj, Baker, Fohlmann, & Nordentoft, 2014). Of antipsychotics trialed, one study has shown clozapine to have a useful effect in reducing craving (Brunette et al., 2011).

Therapeutic use of CBD in psychosis

Research on the therapeutic effects of cannabinoids is still preliminary (McLoughlin et al., 2014). A German clinical trial found that CBD had antipsychotic actions equivalent to a standard antipsychotic, amisulpride, in patients with schizophrenia (Klosterkötter et al., 2012). More recently, McGuire et al. showed that CBD has beneficial effects as an adjunct to conventional antipsychotics in patients with schizophrenia (McGuire et al., 2017). However, there are unpublished negative studies, and further evidence is required before CBD can be considered as a new treatment for schizophrenia.

Cannabis and bipolar disorder (BD)

One study estimated that 30% of individuals affected with BD have used cannabis in their life and as many as 20% have comorbid CUD (Pinto et al., 2019). A meta-analysis of the few longitudinal studies found that cannabis use was related to a nearly threefold increased risk of the onset of mania in community and high-risk samples (Gibbs et al., 2014). According to another systematic review (Marangoni, Hernandez, & Faedda, 2016) of prospective studies, the odds of BD were between 2.5 and 9 times higher among individuals who smoked cannabis at least weekly,

compared to unexposed participants (Feingold, Weiser, Rehm, & Lev-Ran, 2015; Van Laar, Van Dorsselaer, Monshouwer, & De Graaf, 2007) (see Table 1). Among the studies included, a dose-response relationship was observed in the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Van Laar et al., 2007) and the National Epidemiologic Survey on Alcohol and Related Conditions study (NESARC; Feingold et al., 2015), with nearly doubled odds of BD among weekly but oddly not daily consumers.

The relation with hypomania has been less explored in the literature (Baethge et al., 2008; Rottanburg, Ben-Arie, Robins, Teggin, & Elk, 1982; Weinstein, Rosca, Fattore, & London, 2017). But in a large sample of teenagers, Marwaha, Winsper, Bebbington, and Smith (2018) have recently found evidence of a risk increasing effect of ever use and, more strongly, of weekly cannabis use, adjusted odds ratio (OR) = 2.21, 95% confidence interval [CI] [1.49, 3.28].

Course and outcome of BD

Two systematic reviews of prospective studies with a maximum follow-up of 5 years (Gibbs et al., 2014; Mammen et al., 2018) found that continued cannabis use was associated with recurrence of manic episodes and reduced response to treatment (see Table 1). Specifically, patients with comorbid CUD showed a more rapid-cycling course than the nonusers (Strakowski et al., 2007) and cannabis smokers reported greater manic and psychotic symptoms, although no effect was observed on depressive symptoms (Baethge et al., 2008; Van Rossum, Boomsma, Tenback, Reed, & Van Os, 2009). In other studies, current and continued cannabis use was related to worse global and social functioning (Kvitland et al., 2015; Zorrilla et al., 2015), a greater risk of recurrence (Zorrilla et al., 2015), and a reduced remission rate (Kim et al., 2015).

Cannabis and depressive and anxiety disorders and suicide

The effect of cannabis use on depression (Cairns, Yap, Pilkington, & Jorm, 2014; Chadwick, Miller, & Hurd, 2013; Degenhardt, Hall, & Lynskey, 2003; Hanna, Perez, & Ghose, 2017; Hosseini & Oremus, 2018; Lev-Ran et al., 2014; Lowe, Sasiadek, Coles, & George, 2019; Moore et al., 2007) and anxiety (Hosseini & Oremus, 2018; Kedzior & Laeber, 2014; Moore et al., 2007; Twomey, 2017) has begun to receive greater attention.

Cannabis and depression

According to the first meta-analysis (Moore et al., 2007) based on eight prospective studies, the risk of depression among individuals with the most frequent cannabis use (i.e., individuals affected with CUD or smoking cannabis at least on weekly basis) was slightly greater than among nonusers (OR = 1.49, 95% CI [1.15, 1.94]), with evidence of a dose-response relationship between low- and high-frequency smokers. The findings were replicated by Lev-Ran et al. (2014), who observed a marginally significant greater risk of depression in relation to cannabis use (OR = 1.17, 95% CI [1.05, 1.30]), which was slightly increased for those with the most frequent pattern of use (OR = 1.62, 95% CI [1.21, 2.16]) (see Table 2).

Among the most recent studies, in a male cohort of children at higher risk for behavioral problems, cannabis use in childhood and adolescence was related to increased risk of major depressive disorder (MDD) by 48 years, with a fourfold risk among frequent smokers, after accounting for behavioral and mood disorders and other substance use (Schoeler et al., 2018). In the Seattle Social Developmental Project, persistent regular cannabis use in adulthood, but not in adolescence, more than doubled the risk for MDD at age 33 (Guttmanova et al., 2017). A relation between problematic cannabis use and depressive symptoms was observed also in a large Swiss prospective study (Baggio et al., 2014), with a stronger effect for early and persistent cannabis use (vs. nonuse or late onset).

In contrast with these findings, the 3-year prospective NESARC study found that cannabis use, at any frequency, was unrelated to the incidence of MDD (Feingold et al., 2015). Other prospective studies suggested that the effect of cannabis use on depression may be reduced when potential confounders (including other substance use) are taken into account. For instance, an integrative meta-analysis of three Australian cohorts reported a dose-response relationship between frequency of cannabis use and moderate to severe depression, but the trend became nonsignificant after adjusting for covariates (Silins et al., 2014). Lack of effect of lifetime cannabis use was found also in the ALSPAC study (Gage, Hickman et al., 2015) and in a Swedish prospective study (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016).

Cannabis and anxiety

According to systematic reviews, only two out of six prospective studies found evidence of a relationship between cannabis use and later anxiety (Hosseini &

Oremus, 2018; Moore et al., 2007). A meta-analysis (Kedzior & Laeber, 2014) of five cohort studies, the majority of which adjusted for demographic and clinical confounders, estimated that the odds ratio for anxiety symptoms in cannabis smokers was 1.28 (95% CI [1.06, 1.54]); the finding was substantially replicated by a larger, more recent meta-analysis (Twomey, 2017). However, the evidence became inconsistent when the analyses were limited only to studies with the categorical diagnosis of anxiety disorders (Kedzior & Laeber, 2014; Twomey, 2017), and no effect was found when only high-quality studies were examined (Twomey, 2017) (see Table 2).

Among the most recent studies, the NESARC survey found that neither cannabis use nor CUD was related to greater risk of anxiety disorders (adjusted OR = 1.12, 95% CI [0.63, 0.98]), although the effect of frequent cannabis use on social anxiety approached significance (Feingold, Weiser, Rehm, & Lev-Ran, 2016). In the Seattle Social Development Project (Guttmanova et al., 2017), adolescent and adult regular marijuana use (vs. nonuse) was associated with increased risk of generalized anxiety symptoms, but not social anxiety. A prospective Hispanic cohort study showed a relationship between baseline cannabis use and greater anxiety severity at the 1-year follow up, even after accounting for depression and use of legal drugs (Duperrouzel et al., 2018).

Course and outcome of depression and anxiety

The role of cannabis use on the outcomes of depression and anxiety is controversial (Mammen et al., 2018) (see Table 2). In the NESARC study, both cannabis use and CUD were related to an earlier onset of MDD (Feingold, Rehm, & Lev-Ran, 2017), but no effect was found on the course either of MDD (Feingold et al., 2017) or of any anxiety disorders (Feingold, Rehm, Factor, Redler, & Lev-Ran, 2018). In a substance use intervention trial on an outpatient sample with depression, cannabis use was related to increased depression and anxiety (Bahorik et al., 2017). In another medication trial for cannabis cessation, cannabis reduction predicted decreased anxiety and depressive symptoms (Hser et al., 2017).

Cannabis and suicide

Accumulating evidence suggests that cannabis use may increase the risk of suicidal ideation and behaviors. A first meta-analysis of prospective studies (Moore et al., 2007) estimated the risk increasing effect on suicidal ideation as 4.55 (95% CI [1.37, 15.11]). A more recent meta-analysis (Gobbi et al.,

2019) focusing on adolescent cannabis use, and accounting for the effect of baseline suicidal thoughts, stated that cannabis smokers have a one and a half times greater risk (OR = 1.50, 95% CI [1.11, 2.03]) of suicidal ideation and a more than three times greater risk of suicidal attempts (OR = 3.46, 95% CI [1.53, 7.84]) (see Table 2). The risk tends to be higher for those who started smoking cannabis before 15 years of age (Gobbi et al., 2019) and for heavy cannabis users (Borges, Bagge, & Orozco, 2016). Furthermore, the effect of cannabis in increasing risk for suicide was also observed among individuals with psychotic (Coentre, Talina, Góis, & Figueira, 2017) and bipolar disorders (Leite et al., 2015; Pinto et al., 2019).

Pathogenetic mechanisms

Researchers have hypothesized that cannabis use exerts a direct effect on mood throughout the action of its main ingredients (THC and CBD) on the endocannabinoid, dopamine, serotonin, and other neurotransmitter systems (Chadwick et al., 2013; Degenhardt et al., 2003; Gibbs et al., 2014; Lev-Ran et al., 2014). The small amount of evidence supporting these speculations includes clinical trials reporting increased depression following acute and chronic administration of the CB1 antagonist rimonabant (see Lev-Ran et al., 2014) and preclinical studies showing that THC administration produces anhedonia- and depressive-like symptoms in rats (see Chadwick et al., 2013). In addition, THC administration has been associated with relaxation, euphoria, and dysphoria in healthy volunteers, as well as with mood improvement and pain relief in individuals with chronic diseases, such as cancer or multiple sclerosis (Ashton, Moore, Gallagher, & Young, 2005; Ashton & Moore, 2011). THC administration produced a transient amotivational state in occasional smokers (Lawn et al., 2016) and a reduced response in the inferior parietal and temporal cortex during reward activities (van Hell et al., 2012). This preliminary evidence suggests that the effect of cannabis on mood disorders may depend on the modulation exerted by the endocannabinoid receptors on the striatal neurons involved in reward functioning (Baskin-Sommers & Foti, 2015; Berridge, Robinson, & Aldridge, 2009; Volkow, Hampson, & Baler, 2017). However, further experimental studies are needed to corroborate the hypothesis, as negative findings were also reported. In contrast to psychosis, laboratory studies suggested that the THC/CBD ratio was not related to depression scores in cannabis smokers (Schubart et al., 2011) and acute administration of THC did not trigger depressive symptoms in healthy individuals (Englund et al., 2016).

The route from cannabis use to anxiety is controversial, with animal models suggesting that, depending on the quantity, the potency, and the timing of administration, cannabis might produce either an anxiolytic or an anxiogenic effect (Boggs et al., 2018; Chadwick et al., 2013; Crippa et al., 2009). According to preclinical studies, low doses of THC or other CB1 receptor agonists, such as nabilone or CP 55,940 had anxiolytic-like effects in rodents, while higher doses triggered anxious behaviors, especially after exposure to novel and challenging environments (Crippa et al., 2009). Furthermore, chronic administration during the prepubertal period was found to have anxiogenic effects on rats exposed to situational stressors, while postpubertal administration reduced anxiety, suggesting that the anxiogenic effect may depend on the effect of cannabinoids during a critical period for brain development (Chadwick et al., 2013; Kedzior & Laeber, 2014). In addition, it is conceivable that the effect of cannabis on anxiety is partially influenced by the type of stressors, as cannabinoid agonists seemed to maintain an anxiogenic effect on social stressors even during the postpubertal period (see Chadwick et al., 2013).

Some evidence suggests that anxiety symptoms may result from the interplay between the endocannabinoid and the serotonin and noradrenaline systems. For instance, in rats early exposure to the cannabinoid receptor agonist WIN-55,212-2 was associated with hyperactivity of noradrenergic neurons in the locus coeruleus and concomitant hypoactivity of serotonergic neurons, which were predictive of affective-like symptoms (Bambico, Nguyen, Katz, & Gobbi, 2010; Page et al., 2007). Accordingly, both in rodents and primate studies, the anxiolytic effect of CBD was related to its interaction with 5-HT_{1A} receptors, with agonists of 5-HT_{1A} preventing the anxiolytic effects of CBD (Campos & Guimarães, 2008; Fogaça, Reis, Campos, & Guimarães, 2014). Less documented is the effect of cannabis on the glutamate and the GABA systems (Boggs et al., 2018; Crippa et al., 2009). As in the case of psychotogenic effects, some animal and human studies have indicated that CBD administration may counteract THC-induced anxiety, although the findings have not been consistently replicated (see Boggs et al., 2018).

Besides its direct effect on the endocannabinoid and the other neurotransmitters, cannabis use may impact mood and anxiety via its association with other risk factors, which may mediate or moderate the effect of cannabis on affective outcomes (Degenhardt et al., 2003; Lev-Ran et al., 2014). These include

gender, age (Fattore & Fratta, 2010), poor education achievement (Cerdá, 2017) and other types of social disadvantage (Daniel et al., 2009), and other substance use (De Luca et al., 2017). Compared to psychosis, the combined effect of cannabis and other exposures has been less explored in mood and anxiety. The effect of cannabis use on later depression was claimed (but not yet replicated) to be moderated by the serotonin transporter gene, with greater risk for those carrying the short allele of the 5-HTTLPR genotype (Otten & Engels, 2013), and a similar effect was found on anxiety (Otten, Huizink, Monshouwer, Creemers, & Onrust, 2017). A weak age x cannabis interaction was found in a study of four Australian cohorts, suggesting a greater risk for adolescent cannabis use (Horwood et al., 2012). Furthermore, the synergistic effect of cannabis use and childhood maltreatment increased the risk of earlier onset, rapid cycling, and suicide attempt in BD (Aas et al., 2014).

Criticism of the causal hypothesis

The systematic reviews of longitudinal studies summarized above suggest that cannabis use, particularly if frequent, has a weak or no effect on later development of depression (Lev-Ran et al., 2014; Moore et al., 2007) and anxiety (Kedzior & Laeber, 2014; Twomey, 2017), but a stronger effect on mania (Gibbs et al., 2014) and suicide (Gobbi et al., 2019; Moore et al., 2007). It is possible that the weak relationship might be partially explained by the heterogeneity of definition and level of measure of both exposure and outcome (Kedzior & Laeber, 2014; Moore et al., 2007), which is consistent with the finding of an increase in the effect size when a narrower definition of cannabis use was employed (Lev-Ran et al., 2014; Moore et al., 2007). Additional caveats in the discussion of the possible effects of cannabis on mood and anxiety include the following:

1. **Reversal causality:** There may be a bidirectional relationship between cannabis use and depression and anxiety. A recent review of the relationship between cannabis use and emotions in daily life, assessed throughout momentary assessment methods, found partial evidence in favor of the self-medication hypothesis (Wycoff, Metrik, & Trull, 2018); the most robust findings were related to a reduction of negative affect and anger/hostility among patients with psychiatric disorders, thus supporting a negative reinforcement hypothesis of cannabis use as a means to relieve negative inner states (Wycoff et al., 2018).

Table 1. Relevant Systematic Reviews or Meta-Analyses Concerning the Relationship Between Cannabis and the Onset and Course of Psychosis or Bipolar Disorder

Authors, year	Type of included studies	Number of included studies	Level of assessment of cannabis use	Level of assessment of the outcome	Main findings
Arseneault, Cannon, Witton, & Murray, 2004 Carney et al., 2017	Longitudinal, prospective Longitudinal, cross-sectional, and randomized control trials Cross-sectional, case report/case series	N = 5 N = 29 N = 42	Any cannabis use Lifetime, current cannabis use, CUDs Any synthetic cannabinoid use	Psychotic symptoms and disorders Psychotic symptoms in UHR status Onset of psychotic symptoms or psychotic relapse	Cannabis use was related to a twofold risk of later psychosis (OR = 2.34, 95% CI [1.69, 2.95]). The incidence of psychosis would be reduced by about 8% upon the elimination of cannabis use. Individuals at UHR had a greater prevalence of lifetime (52.8%) and current (26.7%) cannabis use, as well as CUDs (12.8%). The odds of psychosis among cannabis users was 2.09 (95% CI [1.04, 4.18]) and was nearly doubled among people affected with CUDs (5.49, 95% CI [1.97, 15.32]). New-onset psychotic symptoms after synthetic cannabinoid use were reported by several case reports and a few cross-sectional surveys. However, some studies suggested that the effect of synthetic cannabinoids tend to resolve after discontinuation, and studies on psychotic relapse led to inconsistent findings.
Gage et al., 2016 Gibbs et al., 2014	Longitudinal, prospective Longitudinal, prospective	N = 10 N = 12 (n = 6 in the meta-analysis)	Any cannabis use Any cannabis use	Psychotic symptoms and disorders Onset and recurrence of manic symptoms	Evidence of a relationship between cannabis use and psychosis was replicated across the studies, with a pooled OR of 1.46 (95% CI [1.24, 1.72]). Cannabis use was associated with recurrence of manic symptoms in patients with bipolar disorders. There is also evidence that cannabis increased the risk of manic symptoms in individuals without previous bipolar disorders (OR = 2.97, 95% CI [1.80, 4.90]).
Kraan et al., 2016	Longitudinal, prospective	N = 7	Lifetime cannabis use, CUDs	Transition to psychosis in UHR	CUD was associated with a nearly doubled risk for transition to psychosis (OR = 1.75, 95% CI [1.13, 2.71]). No risk was related to lifetime cannabis use (OR = 1.14, 95% CI [0.86, 1.52]).
Large et al., 2011 Mammen et al., 2018	Cohort, case-control, cross sectional Longitudinal, prospective	N = 41 N = 12 (n = 5 on bipolar disorders)	Any cannabis use Recent cannabis use	Age at onset of psychotic disorder Symptomatic course or outcome of mania	On average, the age at onset of psychosis was 2.70 years earlier (SMD -0.414) among cannabis users than among nonusers. Recent cannabis use was associated with greater symptom severity at follow-up.
Marangoni et al., 2016	Longitudinal cohort or case-control	N = 22 (n = 3 on cannabis use)	Any cannabis use	Onset of bipolar disorders	Cannabis use was associated with greater risk of bipolar disorders both in community samples and in a clinical sample of patients with major depressive disorders. ORs ranged from 2.12 (95% CI [1.10, 4.08]) to 8.93 (95% CI [2.77, 28.82]).
Marconi et al., 2016	Cohort and cross-sectional	N = 12 (n = 10 in the meta-analysis)	Heaviest pattern of cannabis use in terms of either frequency or amount used or severity Any cannabis use	Psychotic symptoms and disorders	All studies confirmed a dose-response relationship between the level of cannabis use and the risk of psychosis. The estimate of the effect was 3.90 (95% CI [2.84, 5.34]).
McLaren et al., 2010	Longitudinal, prospective	N = 10	Any cannabis use	Psychotic symptoms and disorders	Evidence of an effect of any cannabis use was found in 9/10 studies. A greater risk was reported for individuals with early cannabis use or greater frequency of cannabis use.
Moore et al., 2007	Longitudinal cohort or case-control	N = 24 (n = 11 on psychosis)	Any cannabis use, most frequent pattern of cannabis use Any cannabis use	Psychotic symptoms and disorders Psychotic symptoms and disorders	Evidence of an effect of any cannabis use was found in 4/7 studies (OR = 1.41, 95% CI [1.20, 1.65]). Five out of six studies suggested a dose-response relationship with greater risk among people who used cannabis most frequently (OR = 2.09, 95% CI [1.54, 2.84]).
Murray et al., 2017	Longitudinal, prospective	N = 13	Any cannabis use	Psychotic symptoms and disorders	Cannabis use was associated with an increased risk of psychotic symptoms or disorder in 10 studies with ORs ranging from 1.7 (95% CI [1.1, 1.5]) to 4.5 (95% CI [1.1, 18.2]). The other three studies showed a trend in the same direction.
Myles et al., 2016	Cohort, case-control, cross-sectional	N = 37	Any cannabis use	Age at onset of psychotic disorder	About one-third of individuals with a first episode of psychosis have smoked cannabis in their lifetime (33.7%, 95% CI [31, 39%]). On average, the

(Continued)

Table 1. Continued.

Authors, year	Type of included studies	Number of included studies	Level of assessment of cannabis use	Level of assessment of the outcome	Main findings
Papanti et al., 2013	Case reports/case series, retrospective toxicology surveys, laboratory studies and surveys on self-reported unwanted effects	N = 41	Any synthetic cannabinoid use	Psychotic symptoms and disorders	initiation of regular cannabis use was 6.3 years (SMD = 1.56) antecedent to the onset of psychosis. Odds for continued cannabis use within 10 years from the onset was 0.56 (95% CI [0.40, 0.79]). No longitudinal studies were found. Evidence from case reports and surveys suggest an association between synthetic cannabinoid use and acute transient psychosis and, to a lesser extent, to persistent psychotic disorders or psychotic relapse.
Schoeler et al., 2016	Longitudinal	N = 24	Continued cannabis use vs. discontinued use vs. nonuse	Hospital readmission or relapse of psychotic symptom or disorder	Continued cannabis use was associated with a higher risk of relapse of psychosis (Cohen's $d = 0.36$, 95% CI [0.22, 0.50]) and to longer hospital admissions compared to nonuse ($d = 0.36$, 95% CI [0.13, 0.58]). Continued cannabis users showed also a higher rate of relapse than discontinued users ($d = 0.28$, 95% CI [0.12, 0.44]).
Zammit et al., 2008	Longitudinal	N = 10	Any cannabis use	Outcome of psychotic disorder	Cannabis use was associated with increased relapse (4/4 studies), rehospitalization (3/3 studies), and reduced adherence to treatments (3/3 studies). Evidence was less consistent for the symptomatic outcome.

Note. CI = confidence interval; CUD = cannabis use disorder; SMD = standardized mean difference; OR = odds ratio; UHR = ultra-high risk.

These findings are consistent with large prospective studies reporting an increased risk of cannabis use and CUD in patients with MDD (Feingold et al., 2015; Wittchen et al., 2007) and depressive symptoms at age 13 to 15 predicting CUD at age 18 (Rheuw et al., 2017). By contrast, in two large U.S. cohorts, the effect of cannabis use in the peer network on frequency of youth cannabis use was attenuated by adolescent depressive symptoms, which might render them more isolated or less susceptible to peer influence (Pollard, Tucker, Green, de la Haye, & Espelage, 2018). Similar results were found by the Cambridge Study in Delinquent Development (CSDD; Schoeler et al., 2018), while no influence of mood symptoms on later cannabis use was found in other studies (Baggio et al., 2014; Danielsson et al., 2016; Womack, Shaw, Weaver, & Forbes, 2016).

As far as mania and BD are concerned, in the Early Developmental Stages of Psychopathology (ESDP) study (Wittchen et al., 2007), hypomania/mania was associated with a marginally significant greater risk for cannabis use, but other studies found no prospective relationship between manic symptoms or BD and cannabis use during follow-up (Baethge et al., 2008; Feingold et al., 2015; Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006; Strakowski et al., 2007).

Although cannabis may be used to relieve occasional or persistent feelings of anxiety (Crippa et al., 2009; Kedzior & Laeber, 2014), longitudinal studies on the overall effect of anxiety disorders on later cannabis use reported mixed findings, with evidence of effect in the Great Smoky Mountains cohort (Hill, Shanahan, Costello, & Copeland, 2017), but not in the NESARC study (Feingold et al., 2016) or in two other samples (Brook, Rosen, & Brook, 2001; Duperrouzel et al., 2018). There is some evidence regarding the effect of panic disorder on increased rate of marijuana use (Feingold et al., 2016; Wittchen et al., 2007) and generalized anxiety disorder on cannabis use (Stapinski, Montgomery, & Araya, 2016) and CUD (Wittchen et al., 2007). The role of social anxiety on later cannabis use is controversial, with one study reporting an effect on cannabis dependence but not on abuse (Buckner et al., 2008), and others suggesting even a protective role (Feingold et al., 2016; Nelemans et al., 2016).

In summary, there are some indications that the putative risk-increasing effect of cannabis on the development of mood and anxiety might be confounded by the self-medicating use of the substance. In some cases, early symptoms of depression and anxiety might even protect against cannabis use. More

Table 2. Relevant Systematic Reviews or Meta-Analyses Concerning the Relationship Between Cannabis and the Onset and Course of Depression and Anxiety Disorders

Authors, year	Type of included studies	Number of included studies	Level of assessment of cannabis use	Level of assessment of the outcome	Main findings
Gobbi et al., 2019	Longitudinal, prospective	$N = 11$ ($n = 7$ on depression, $n = 3$ on anxiety, $n = 3$ on suicidal ideation, $n = 3$ on suicidal attempts)	Any cannabis use before age 18	Depressive and anxiety disorders between 18 and 32 years of age	Cannabis smokers had a modest increase in risk for depression ($OR = 1.37$, 95% CI [1.16, 1.62]) but not for anxiety ($OR = 1.18$, 95% CI [0.84, 1.67]). Furthermore, cannabis use was associated with one and a half times greater risk ($OR = 1.50$, 95% CI [1.11, 2.03]) of suicidal ideation and a more than 3 times greater risk of suicide attempts ($OR = 3.46$, 95% CI [1.53, 7.84]).
Hosseini & Oremus, 2018	Cohort, cross-sectional, and case-control	$N = 23$ ($n = 11$ on depression and anxiety)	Any cannabis use	Depressive and anxiety symptoms and disorders	Only two out of six prospective studies found evidence of a relationship between cannabis use and later depression or anxiety. A moderate relationship with depression was found in three out of four cross-sectional or case-control studies.
Lev-Ran et al., 2014	Longitudinal, prospective	$N = 14$	Any cannabis use, most frequent pattern of cannabis use	Depressive symptoms and disorders	Any cannabis use ($OR = 1.17$, 95% CI [1.05, 1.30]) and the most frequent cannabis use ($OR = 1.62$, 95% CI [1.21, 2.16]) were related to increased risk of depression.
Kedzior & Laeber, 2014	Cohort and cross-sectional	$N = 31$	Lifetime cannabis use, past-year cannabis use, cannabis use disorders	Anxiety symptoms and disorders	Anxiety was associated with cannabis use ($OR = 1.24$, 95% CI [1.06, 1.45]) and CUD ($OR = 1.68$, 95% CI [1.23, 2.31]). A further association was found between cannabis use and comorbid anxiety and depression ($OR = 1.68$, 95% CI [1.17, 2.40]). The association between cannabis use and anxiety was replicated in the subgroup of the five prospective studies ($OR = 1.28$, 95% CI [1.06, 1.54]).
Mammen et al., 2018	Longitudinal, prospective	$N = 12$ ($n = 2$ on depressive disorder)	Recent cannabis use	Symptomatic course or outcome of depression	Recent cannabis use was associated with greater symptom severity at follow-up.
Moore et al., 2007	Longitudinal cohort or case-control	$N = 24$ ($n = 15$ on depression, $n = 7$ on anxiety, $n = 6$ on suicide)	Any cannabis use, most frequent pattern of cannabis use	Depressive and anxiety symptoms and disorders, suicidal ideation and attempt	The most frequent cannabis use was related to increased risk of depression ($OR = 1.49$, 95% CI [1.15, 1.94]). Any cannabis use was related to depression in 4/11 studies, to anxiety in 2/7 studies, and to suicidal ideation in 3/5 studies.
Twomey, 2017	Longitudinal, prospective	$N = 10$	Any cannabis use	Anxiety symptoms and disorders	Cannabis use was associated with a small increase in the risk of anxiety ($OR = 1.15$, 95% CI [1.03, 1.29]), but no association was found when the meta-analysis was restricted to high-quality studies ($OR = 1.04$, 95% CI [0.91, 1.19]).

Note. CI = confidence interval; CUD = cannabis use disorder; OR = odds ratio.

recent systematic reviews reported that a growing number of studies have attempted to take into account the possibility of reverse causality, either excluding participants with baseline affective symptoms or controlling for baseline symptom severity (Lev-Ran et al., 2014; Twomey, 2017).

2. Confounding effect of intoxication: The acute effect of cannabis may increase the impact on psychiatric symptoms (Moore et al., 2007), particularly in studies with a short length of follow-up. In order to reduce the confounding effect of intoxication, some studies (see Cairns et al., 2014; Lev-Ran et al., 2014; Moore et al., 2007) employed assessment measures that enable the investigators to disentangle affective symptoms due to substance misuse, such as the Diagnostic Interview Schedule (DIS), the Diagnostic Interview Schedule for Children (DISC), the Composite International Diagnostic Interview (CIDI), or the Hypomania Checklist (HCL-32). Another strategy involved controlling the analysis for baseline substance misuse, as was done in about one-half of the studies included in the meta-analyses of Lev-Ran et al. (2014) and Twomey (2017).
3. Shared risk factors for cannabis use and common mental disorders, BD, and suicide may attenuate the effect of cannabis use. However, previous meta-analyses showed that a weak effect was still present in most of the studies after controlling for demographic and other substance misuse (Gibbs et al., 2014; Gobbi et al., 2019; Kedzior & Laeber, 2014; Lev-Ran et al., 2014; Moore et al., 2007; Twomey, 2017), suggesting that these factors do not entirely explain the association between cannabis and these mental health outcomes. Among the most recent studies, an analysis of three large Australian twin cohorts found that the effect of frequent cannabis use on MDD and suicidal ideation was still significant after controlling for early substance misuse, childhood abuse, and conduct disorder. Furthermore, the effect was of similar size both within monozygotic and dizygotic twin pairs, suggesting that the effect of frequent cannabis use is not fully accounted by genes and early environmental exposures (Agrawal et al., 2017).

Therapeutic use of CBD for mood and anxiety disorders

Although there are numerous anecdotal reports that cannabis may benefit mood and/or anxiety disorders, there are few systematic studies. One recent

investigation of the effect on CBD on mood and anxiety symptoms reported negative results and highlighted the need for further studies (Crippa, Guimarães, Campos, & Zuardi, 2018). Another review suggests that CBD premedication might reduce the anxiety arising from public speaking, but studies on other anxiogenic tasks led to inconsistent findings, and the efficacy on anxiety disorders needs to be further assessed (White, 2019).

Conclusions

There is extensive evidence that heavy use of high-potency cannabis increases the risk of psychotic symptoms and schizophrenia-like psychosis. Fewer studies have examined mania and suicide, but reports suggest that exposure to frequent cannabis use may similarly increase the risk of these conditions. Whether there is a risk-increasing effect on depression is much less clear, and there are few longitudinal controlled studies on anxiety. Large cohort studies, carefully assessing the pattern of cannabis use, controlling for potential confounders, are required to clarify the effect of cannabis on common mental disorders and to highlight any potential dose-response relationships and possible synergism with other genetic or environmental risk factors. Furthermore, while psychotic symptoms do not appear to facilitate cannabis use, self-medication may play a role in depression and anxiety where unpleasant symptoms may encourage greater cannabis consumption. It is vital to distinguish between the effects of THC and CBD; for example, in experimental studies, the former can induce psychotic symptoms which can be blocked by the latter. Interestingly, CBD may have potential as an adjunctive treatment in psychosis and in anxiety/depression, but more studies are required before these preliminary findings can be accepted.

Disclosures

LS, HQ, and CLC report no financial relationships with commercial interests in relation to this study. RMM has attended one Canopy Health advisory board meeting on the use of CBD in pain and has received honoraria for lectures from Janssen, Otsuka, Sunovion, and Lundbeck.

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