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Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Report: Cannabis Use in Bipolar Disorder and Major Depressive Disorder

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Abstract:	BACKGROUND: In view of changes in the social acceptability and

	legalization of cannabis in some jurisdictions, clinicians need to better understand the effect of cannabis use (CU) on mood disorders. OBJECTIVE: The purpose of this task force report is to examine the effect of CU on the incidence, presentation, course, and treatment of bipolar disorder (BD) and major depressive disorder (MDD), as well as treatment response in these illnesses in the presence of comorbid cannabis use disorder (CUD). METHODS: We followed PRISMA guidelines to systematically the literature. PUBMED, EMBASE, PsycINFO, CINAHL and Cochrane Central Register of Controlled Trials were searched from inception to October 2020 focusing on: CU and BD or MDD, and treatment of co-morbid CUD. RESULTS: The database search yielded 12,691 publications. After excluding articles that did not meet criteria, 23 studies remained in BD, 22 in MDD, 10 in both diagnoses, and 1 in the treatment of comorbid CUD and MDD. CU is highly prevalent in mood disorders with a lifetime prevalence of 52-71% and 6-50% in BD and MDD, respectively. CU is associated with earlier onset and increased suicidal risk in BD, and a worsened course and functioning of both BD and MDD, although the data pertaining to depression are more equivocal. A single randomized controlled study of the addition of fluoxetine to CBT showed no improvement over placebo and CBT. CONCLUSION: The results strongly suggest that CU is associated with a deleterious effect on the course of MDD and BD as well as on functioning. These effects are supported by more consistent data in BD than in MDD. Given the prevalence of CU and the limitations of the data, it is essential that its impact on mood disorders be evaluated through well-designed studies, which control for the type, amount, and frequency of CU. 2021_7_12_Cannabis_CANMAT_12june2021_abstract_f.docx

Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Report: A systematic review and recommendations of Cannabis Use in Bipolar Disorder and Major Depressive Disorder

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Abstract

BACKGROUND: Given the increasing acceptability and legalization of cannabis in some jurisdictions, clinicians need to improve their understanding of the effect of cannabis use (CU) on mood disorders.

OBJECTIVE: The purpose of this task force report is to examine the effect of CU on the incidence, presentation, course, and treatment of bipolar disorder (BD) and major depressive disorder (MDD), and the treatment of comorbid cannabis use disorder (CUD).

METHODS: We conducted a systematic literature review using PRISMA guidelines. We searched PUBMED, EMBASE, PsycINFO, CINAHL and Cochrane Central Register of Controlled Trials from inception to October 2020 focusing on CU and BD or MDD, and treatment of comorbid CUD. Randomized controlled trials (RCT), designs involving repeated measures or a comparison group were included. We excluded diagnoses based on scales. The GRADE approach was used to evaluate bias and results presented in a summary of findings table.

RESULTS: The search yielded 12,691 publications, 56 meeting criteria: 23 of BD, 21 of MDD, 11 of both diagnoses, and 1 of treatment of comorbid CUD and MDD. Of 2479640 participants, 73891 had BD and 408223 MDD without CU. Of those with CU, 2761 had BD and 5044 MDD. The studies included 12502 comparison participants, 1977219 individuals at risk and 196022 pregnancies. The lifetime prevalence of CU is 52-71% and 6-50% in BD and MDD, respectively. CU is associated with earlier onset and increased suicidal risk in BD, and aggravated course and functioning of both BD and MDD.

CONCLUSION: The data indicate that CU is associated with worsened course and functioning of MDD and BD. The data are more consistent in BD than in MDD. Given the prevalence of CU, its impact on mood disorders should be evaluated through well-designed studies, which control for the type, amount, and frequency of CU.

1 | Introduction

BD and MDD are common and persistent conditions, with a Canadian lifetime prevalence of 11.3% for major depressive episodes [1], 0.87% for bipolar I disorder and 0.57% for bipolar II disorder [2]. There are complex interactions between CU and mood disorders; CU may contribute to psychopathology, which may in turn lead to CU. In addition, underlying factors may contribute to both mood disorder psychopathology and CU [3, 4]. In the United States, past-year CU by adults more than doubled between 1991-2 and 2001-2 (4.4% and 9.5% respectively) and increased in more recent studies [5]. In Europe, lifetime CU varies from 0.7% in Turkey to 40.9% in France [6].

In view of the prevalence of CU, the Canadian Network for Mood and Anxiety Treatments (CANMAT) constituted a Task Force to review the literature and summarize current evidence regarding the impact of cannabis on BD and MDD. To this end, we sought to review all controlled trials and observational studies that reported on CU and BD and/or MDD and randomized controlled trials (RCT) of the treatment of comorbid CUD and BD or MDD, with the aim of providing recommendations regarding CU for people with mood disorders.

2 | Methods

2.1 | Data Sources

The PRISMA 2009 guidelines [7] were followed to conduct a systematic review of the impact of CU in individuals diagnosed with either BD or MDD (Figure 1). We specifically wished to assess the association between CU and its potential impact on illness progression (age of onset, number of episodes, rates of relapse), illness manifestation (suicidality, severity of symptoms, types of symptoms) and different aspects of functioning (quality of life, employment, cognition). The Task Force developed selection criteria prior to the database search. A documentation professional (MD) assisted with operationalizing the criteria and conducted a search of PubMed, Embase, PsycINFO, CINAHL and the Cochrane databases from inception to October 2020. The detailed search strategy is available upon request. In addition, we manually searched reference lists of published reviews for relevant articles.

Insert Figure 1 about here.

2.2 | Study Selection

We included all original clinical observational studies and trials, excluding case reports, studying the use of cannabis in BD and/or MDD. Definitions of use, dependence and abuse varied between publications. Studies that used mixed populations (i.e., inclusion of participants with schizophrenia, MDD, BD) were only included if they reported data separately by diagnosis. Studies were required to have a clinical measure of interest (e.g., age of onset, severity of symptoms, risk of suicide) for which the population of interest was either compared to a comparison population or was followed over time. Articles written in a language other than English or French were

excluded. In the section evaluating treatment of mood disorders and CUD, only randomized controlled trials were considered. Two authors (VT and GB) independently reviewed the abstracts and disagreements between reviewers were resolved by consensus.

2.3 | Data Extraction and Synthesis

A database review yielded 12,691 potentially relevant articles. After excluding duplicates, 6,501 titles remained. After screening the abstracts 6,331 articles were excluded, leaving 170 eligible articles. A further 114 studies were excluded after reading the full text. The remaining 56 studies were independently evaluated by two authors (VT and GB) for data related to patients' demographic information (age and sex), diagnosis, number of patients in each study, inclusion and exclusion criteria, and outcome measures. A senior investigator (SB) resolved disagreements among reviewers. Supplementary Tables II and III detail the characteristics of included studies. The 56 studies included 1 RCT, 3 prospective studies, 26 longitudinal or cohort studies and 26 cross-sectional studies. The studies on BD included 73 891 participants, 2 761 of whom had CU or CUD. The studies of MDD included 408 223 participants of whom 5 044 had CU or CUD. The comparator groups comprised 12 502 participants. Studies evaluating populations at risk of developing CU, MDD, or BD included 1 977 219 participants. A single study examined 196 022 pregnancies but did not report the number of participants involved. A meta-analysis was not deemed appropriate given the heterogeneity of the studies retrieved.

2.4 | Grading of Evidence and Recommendations

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method [8] was used to rate the quality of evidence for each individual study included in the review, as well as for the overall certainty of the evidence for each outcome measure (see Table 1). Briefly, the GRADE method proposes four levels for expressing the quality of evidence (high, moderate, low, and very low) based on eight criteria that can either increase or decrease confidence in estimates of outcomes of a systematic review (Table 2). Recommendations were graded as Strong or Qualified. A strong recommendation reflects more certainty in evidence and greater consensus that most people should follow the recommendation. A qualified recommendation reflects lower certainty in evidence and suggests greater variation in the decision-making process, including individual assessment of values and preferences.

Insert Tables 1 and 2 about here.

3 | Findings and Discussion

3.1 | What is the prevalence of CU and CUD in individuals with BD or MDD?

Our review found 16 studies [9-24] that documented prevalence rates of CU or CUD in BD. Lifetime CU (LT-CU) is high in this population, ranging from half [9, 10] to two thirds [11] using cannabis over their lifetime. This rate of LT-CU is as much as seven-fold higher in individuals with BD than in comparison participants without BD (71.3%, OR 6.8 CI 5.41-8.52) [11]. The cross-sectional prevalence rates of CU vary from a low of 3.3% [13, 14, 23] to a high of approximately 18 % [15, 16], while one study found past-year prevalence to be 14.7% [18] .

CUD is also increased in those with BD as compared to the general population (7.2% versus 1.2%, respectively) [17] and ranges from 7,2% to 30%[11, 12, 17, 18] . The prevalence of CU, cannabis abuse (CA) and CD is generally higher in BD-I as compared to BD-II [19, 25]. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), consisting of a representative population of 43 093 participants [19], found the prevalence of CU in BD-I and BD-II to be respectively 23.6% and 10.2% for cannabis dependence (CD), 9.7% and 4.9% for CA and 11.8% and 5.7% for CUD [19].

Other factors may influence the prevalence of CU in BD. For example, the use of cigarettes is associated with a higher prevalence of CU compared to non-smokers (55.7% vs 18.1%) [20] and heavy cigarette smokers used cannabis more often each week [21]. In a population of individuals with BD and a risk of violence, the prevalence of CU in the 30 days prior to hospitalization was 27.0% [24].

Ten studies addressed the question of CU prevalence in MDD [12-14, 18, 19, 24, 26-29], and found prevalence ranges for CU from 7.5% [26] to 18.9% [28]. This compares to a population rate of 8.67% yielding an adjusted odds ratio (AOR) of 2.17 (CI 1.92–2.45) [28]. The prevalence range for CUD varies from 2.0% to a high of 16.3% [12-14, 19, 26], representing a four-fold increase of CUD prevalence in MDD (2.0%) compared to a population rate of 0.5% [13]. As in the general population, CUD prevalence is higher in men than in women (BD: 3.7% vs 1.0%, general population: 0.8% vs 0.2% respectively) [13]. In a study of a population of MDD at risk of violence, the prevalence of CU was 32% in the month prior to hospitalization [24]. Individuals with MDD have lower levels of CU than those with BD with 8.9% of individuals using cannabis in the past year and with 39.4% meeting criteria for CUD (compared to 14.7% and 51.8% respectively in BD p=0.05) [18]. A twin study found CUD prevalence to be 24.3% in individuals with MDD compared to

12.3% in those without MDD (OR 2.66, CI 2.10–3.37) and determined that the best-fitting model is that of CUD leading to MDD [29]. Further, compared to individuals without MDD, those with MDD have a much greater risk of using cannabis during pregnancy (12.7 % vs 3.7 %; OR 3.8, CI 2.8–5.0) [27]. Overall, individuals with depression are twice as likely to use cannabis and are at four times the risk of having CUD.

3.2 | Is CU associated with increased use of other substances in individuals with mood disorder?

Eleven studies presented data that allowed examination of the use of substances other than cannabis in individuals with BD and CU [10, 17, 20-22, 25, 30-34]. Daily tobacco use is significantly more prevalent in individuals with BD who used cannabis in the past 6 months (80.5%) compared to those who did not (45.5%) [30] although another study, including only smokers with BD, found no significant difference in pack-years in those with CUD compared to those without[25]. Adolescents with BD and CU also have high rates of cigarette use (49%) and lifetime nicotine dependence (70%) [21]. Other studies confirm increased odds of nicotine dependence in this population to be 2.31 to 3.8 [17, 22] while CUD confers a four-fold risk of nicotine dependence (3.83, CI 2.21-6.66) [31]. A gradient of prevalence of daily tobacco use ranging from 46.9 % in individuals with BD without CU, 73.4% in those with intermediate levels of CU and 83.9% in those with CUD (P=0.001) [32]. This may a bidirectional relationship since, in individuals with BD, CU is significantly more frequent (55.7%) in those with nicotine use compared to those without nicotine use (18.1%) [20] and heavy smokers with BD used more cannabis than those who did not smoke or were light smokers [21].

Alcohol use is more common in individuals with BD who use cannabis (12-month prevalence: 55.6%) compared to those who do not (23.7%) [33]. In contrast to individuals with BD without CUD, those with CUD are more likely to misuse alcohol ($p<0.001$)[34]. Alcohol use disorder (AUD) is also significantly higher in those with BD and CUD compared to those without CUD [22, 25, 31]. Although not statistically significant, the prevalence of AUD in individuals with BD, increases along a gradient from lower to higher levels of CU, ranging from 14.1% in those without CU, 18.8% in those with intermediate CU and 27.3% in those with CUD [32]. Only one study found an absence of influence of CU on alcohol use or dependence [30].

Substance use disorder (SUD) is also more frequent in BD with comorbid CU [33] and increases with increasing intensity of use, along a gradient of prevalence of SUD ranging from 3.1 % in those without CU, 17.2% in those with intermediate CU, and 39.4% in those with CUD ($P=0.001$) [32]. SUD is significantly more frequent (25,5%-71.9%) in those with CUD than in those without CUD (3.2%-19%) [25, 31]. The same study that failed to find a difference in AUD in individuals with BD and CU failed to find a significant influence of CU on cocaine or amphetamine use or on dependence [30]. An interesting finding suggested that the prevalence of AUD and other SUD varies with order of onset of BD and CU [10]. When CU preceded the emergence of BD, alcohol abuse was less frequent than when BD onset preceded CU onset [10]. Curiously, the opposite was true for dependence, which was more common in those individuals with BD in whom CU preceded BD onset [10]. Other SUDs were more common in those who used cannabis before BD onset ($P<0.001$) [10].

Two studies permitted comparisons of comorbid substance use in MDD with CU compared to MDD without CU [26, 35]. Individuals with MDD and CUD are significantly more likely to smoke daily (67.0%) compared to those without comorbid CUD (13.0%)[35]. They are also more likely to misuse alcohol (43.0%) in comparison to those without CUD (3.0%) [35]. As in BD, MDD is associated with a higher prevalence of SUD in those who use cannabis (3.0-43.14%) compared to those who do not (0.0-14.29%) [26, 35]. This prevalence is even higher (59.54%)[26] in those with MDD and comorbid CUD [35].

3.3 | Is CU associated with alterations in the symptomatic manifestations of BD or MDD?

Ten studies included in this review contributed to an exploration of this question in BD [10, 11, 15, 21, 22, 24, 33, 36-38]. The use of cannabis influences the severity, type and frequency of episodes in BD. CU increases the likelihood of mixed episodes [10], with Agrawal and colleagues finding an OR of 1.52 (CI 1.02-2.27) [11].

Continued CU is associated with an increased severity of manic symptoms [33, 39], and global illness severity [24, 33]. Individuals whose onset of BD occurred before the beginning of CU had an increase in subsyndromal manic symptoms compared to those who did not use cannabis [10].

Increased severity of depressive [37] and psychotic symptoms [22, 33] is seen in individuals with BD who use cannabis and manic symptoms even more so with the added use of nicotine [21]. Nicotine use is associated with adverse outcomes in BD [40] and may

signal the presence of other comorbidities, such as attention deficit hyperactivity disorder [41], which are also associated with a poor prognosis in BD [41].

A study, using contemporaneous measures of the chronological relationship between CU and symptomatology, found that CU is associated with the emergence of manic and hypomanic but not depressive symptoms [15]. A decrease in symptoms of anxiety, tension, depression, and an increase in 'vigor' followed the use of cannabis in individuals with BD [15]. In contrast, another study found an increase in depressive symptoms, despite confirming the increase in positive affect and of manic symptoms [38]. It is possible that CU is associated with acute improvements in mood but also with subsequent depressive symptoms. Thus, individuals more easily associate CU with its proximal positive effects on mood than its distal negative ones.

Five studies in our review contained data that allowed an examination of the interaction between CU and MDD symptoms [24, 26, 42-44]. In MDD as in BD, CU is associated with an increase in illness severity as measured by the BPRS [24]. A longitudinal study revealed correlations between the level of CU and an increase in depressive symptoms, anhedonia, weight changes, insomnia and hypersomnia, as well as in psychomotor agitation [26]. Another study found CU in MDD to be associated with increased negative symptoms [42]. Sex may influence the effects of CU in MDD. Occasional CU was associated with greater psychological distress in females as opposed to males [43] while in an adolescent population, anhedonia, psychomotor changes, guilt, low self-esteem, and poor concentration were associated with CU in boys with MDD but not in girls [44]. It is possible that the effects of CU may vary with the manner of use of cannabis since higher doses have been shown to depress and lower doses to enhance serotoninergic transmission while

acute administration of cannabis increased dopamine release and chronic use is associated with blunting of the dopaminergic responsivity [45].

In summary, what limited data exists suggests that CU is also associated with worsening of mood disorder symptoms.

3.4 | Is CU associated with alterations of the illness course of BD or MDD?

The course of BD with co-occurring CU was described in 19 studies [9-11, 15-17, 22, 23, 25, 32, 33, 38, 46-52]. CU has been linked to an increased incidence of a first episode of BD [46, 47]. The age of BD onset is earlier in cannabis users [16, 48] by as much as 9 years [16]. Age of onset is also earlier in those who use higher quantities of cannabis (greater than 10 times during one month, lifetime) compared to those who use lower quantities (less than 10 times during one month, lifetime) [32]. Similarly, CUD is also correlated with an earlier age of onset of BD [11, 17, 25]. Furthermore, individuals with BD and CUD tend to be younger [22]. The effect of recent CU on age of onset may differentially affect the type of episodes, lowering the age of onset of psychotic and manic episodes but having little effect on the onset of depressive episodes [49].

Rapid cycling [10] is more common in individuals with BD who use cannabis, and in those with CU and have a history of childhood abuse [50]. In the same vein, a history of lifetime CU is associated with earlier hospitalization [51] and CUD with more frequent hospitalizations [25]. Finally, BD with current CU is associated with an increased recurrence rate compared to nonusers; while those with a history of previous use that has ceased have similar levels compared to those who have never used cannabis [23].

CU in BD is associated with a subsequent increase in positive affect, as well as with manic and depressive symptoms [38] while recent CU is associated with hypomania and mania, but not depression [15]. Individuals with BD and CU display increased severities of mania, hallucinations, delusions, and overall illness at one-year follow-up [33]. They also spend more time in manic and mixed episodes [10]. More frequent episodes [17], mixed states [11], manic episodes [25], and psychotic symptoms [22] also appear more common in BD with CUD. On the other hand, Kvitland and colleagues found that individuals with excessive use preceding the onset of BD did not differ from those without CU; however, they observed a longer duration of untreated mania in individuals with excessive CU compared to those without such use [9]. In the same study, CU was not associated with the duration of untreated illness [9]. Another population study also did not find increased incidence of BD over a period of 35 years in those with CU compared to those without CU, highlighting the further work that needs to be done in this area [52].

Eleven studies addressed the course of depression [26, 44, 46, 47, 52-58]. CU is associated with increased emergence of MDD in some studies [46, 47, 53, 54], but not in others [26, 52, 55]. Further, a prospective study found that both high and low frequency of CU before age 18 was associated with an increased risk of developing MDD [54] while cross-sectional studies identify an increased likelihood of depression in cannabis users [57, 58] compared to nonusers, with greater odds in heavy users [58]. In contrast, one study failed to find an effect of CU on the age of onset of MDD [56]. In an adolescent population, the prevalence of a major depressive episode was higher in boys with CU although not for non-substance related episodes [44].

Information about the effect of CU on the age of onset of MDD is more equivocal than in BD. Some preliminary data signals a higher prevalence of depression in cannabis users, and in particular with heavy use [57, 58], but further research is necessary to clarify this relationship.

3.5 | Is CU associated with an increase of suicidal thoughts and behaviours in MDD and BD?

Six studies addressed the effect of CU on suicide in BD [11, 12, 43, 49, 50, 59] and three in MDD [26, 57, 59]. Habitual CU by individuals with BD is associated with suicidal ideation [43] and attempts [11, 43], while current CU is correlated with increased suicidal completion (HR 1.86, CI 1.15–2.99) [12]. Recent CU is significantly correlated with increased lifetime suicide attempts [49]. CUD, as determined through registers of treatment for substance abuse, is not associated with increased mortality by suicide [59] suggesting that treatment of CUD may have a beneficial effect. Occasional CU is linked with suicidal ideation and attempts in women with BD, but not men (OR 2.45, CI 1.79-3.36) [43]. In adolescents with BD, CU is associated with increased odds of suicidality (AOR 1.74, CI 1.28–2.35) [60]. The combination of CU and childhood abuse in individuals with BD is also associated with increased likelihood of a suicide attempt [50].

Adolescents with MDD and a history of CU have a higher risk of suicide attempts in the past year (ORs 2.06–2.53, $p < 0.001$), with frequency of CU having no influence on the risk [61]. In a twin study of depression, early and frequent CU was significantly associated with both MDD and suicidal ideation [57]. One study of depression found no difference in suicidality in those with CU or CUD compared

to those without CU [26] while in another mortality from suicide is decreased in MDD with CUD [59], leading the authors to speculate that the use of cannabis as self-treatment may have alleviated distress and thus suicide. In this study, CUD was identified by registration in treatment centers or use of pharmacological treatments for SUD; thus, an equally likely hypothesis may be that treatment offsets the risks of CUD.

Globally, CU contributes to increased suicidality in both BD and MDD; although the literature in MDD is sparse and more inconsistent than that in BD.

3.6 | Is CU associated with alterations of functioning in BD and MDD?

Seven studies explored functioning in BD with CU [11, 21, 23, 24, 33, 39, 51]. BD with CU is associated with decreased global functioning [24] and CUD with increased disability (OR 2.19, CI 1.45-3.31) [11]. A history of CU in individuals with BD is associated with increased work impairment and decreased likelihood of living with a partner [23]. The reason for this is unclear but may be a consequence of the burden imposed on relationships by increased severity of symptoms, worsened course and greater functional impairment associated with CU in BD. Despite greater engagement in social activities, individuals with BD and CU are less likely to have a relationship [33]. They experience less satisfaction with life, but this effect seems to be mediated by other SUDs [33]. Continued CU is associated with both elevated mood and decreased global functioning at one-year follow-up [39]. Sex may influence the impact of CU; for example, CU is associated with greater ‘financial issues’ and decreased quality of life in women but not men [51]. The

combination of cannabis abuse or dependence with heavy cigarette use is associated with decreased functioning in adolescents with BD [21].

Three studies permitted the evaluation of the impact of CU on functioning in depression [24, 26, 61] showing associations with decreased functioning in some studies [24, 61] but not others [26].

In sum, in both BD and MDD, CU and CUD are associated with greater disability and decreased functioning.

3.7 | Is CU associated with alterations of cognition in BD & MDD?

We found only two studies addressing the effect of CU on cognition in BD [30, 62] and none in MDD. Braga and colleagues selected individuals with BD and CUD; most had a history of CUD and a minority (9/50) had current CUD [62]. Those individuals with BD and past or current CU or CUD performed better on several neuropsychological tasks (Digits Forward, Trails B, Digits Backward) than the comparator group of BD without CU or CUD [62]**.** The second study [30] included a subgroup of 133 individuals with BD, 18 of whom had used cannabis in the past 6 months. Compared to those without, those with a history of CU performed better on semantic fluency [30].

It is difficult to glean a signal from these data because of the very small number of studies and sample sizes, as well as the observation that very few of the participants were current users of cannabis.

3.8 | Is CU associated with alterations of response to treatment in BD and MDD?

We found little data that directly addressed the relationship between CU and response to treatment although it can be argued that the worsened course of illness may be related to diminished treatment response [23, 25]. It is possible that the worsened illness course may be related to CU may also affect treatment response by decreasing treatment adherence [33].

3.9 | Are there efficacious treatments for comorbid CU and mood disorders?

After careful consideration, we found no studies meeting our criteria that examined the treatment of comorbid BD and CUD. We identified one RCT examining the treatment of CUD and MDD with cognitive behavioral therapy (CBT) and add-on fluoxetine or placebo in 70 adolescents and young adults [63]. Both groups improved in both depression and substance use outcomes but there was no significant difference between CBT plus fluoxetine and CBT plus placebo.

4 | Practical considerations

Box 1 shows take home messages from this review. Table 3 summarizes the consensus recommendations for CU in BD and MDD, with a strong recommendation for individuals with BD to avoid CU, and a qualified recommendation to avoid CU for individuals with MDD.

Insert Box 1 and Table 3 about here.

Given the clear signal that CU is associated with alterations in the course and outcome of mood disorders, it is important that clinicians inquire about CU. The use of a questionnaire improves the identification of CU and CUD [64] and useful questions and images can improve the estimation of quantity and type of CU [65]. Patients often have difficulty being precise about quantity and type of cannabis and the use of images may facilitate ascertainment of use [66]. Clinicians can adapt questions to the needs of their practice. Although, there is limited knowledge of the differential effects of the different constituents of cannabis, documentation of the changes in the composition of cannabis may allow clinician and patient to understand potential associations between such alterations and clinical symptomatology. Clinicians should explore three different dimensions:

1. Course of use- age of onset, and frequency of use.
2. Quantity- amount and concentrations of the different component of cannabis.
3. Context of use- physical, social and psychological context of use as well as use of other substances. Examples of contextual elements are the use of cannabis to reduce symptoms such as anxiety, agitation or pain (sometimes presented as self-medication) or to enhance social interactions or induce a sense of well-being in individuals with no pre-existing distress (recreational use) or pregnancy.

A discussion of current information regarding CU in mood disorders should include an understanding of the dimensions of CU in that particular patient and a nuanced communication of the impact of CU on course and clinical outcome. The use of CU during pregnancy is an increasing phenomenon [67] and is associated with the presence of MDD [27, 68]. The clinician should communicate

the preliminary nature of the data concerning the potential impact of such use on the fetus and the signal of possible harmful effects [69-71]. Should the patient desire to reduce or stop CU psychosocial interventions, in particular motivational enhancement therapy and CBT, have been shown to be associated with a reduction of use [72].

5 | Conclusion

There is a clear signal that CU, and in particular heavy CU, is associated with a worsened course of illness, decreased functionality and increased mortality through suicide in BD. The data is less consistent in MDD; nevertheless, age of MDD onset does not appear to be earlier in those who use CU as it is in BD, nor is there an increase in mortality through suicide. The impact of CU on functioning in MDD is uncertain but tends to be associated with impairment.

This review summarizes the literature of the impact of CU in BD and MDD. Importantly, the studies included were required to have mood disorders meeting diagnostic criteria of either MDD or BD rather than proxies of these diagnoses. The resulting findings are thus more applicable to clinical populations. It is clear that more data is necessary but that the data, such as it is, points to clear potential of harm in BD and a more modest deleterious effect in depression. It is important for clinicians to gain an understanding of the reasons for CU in the individual patient and to share the potential impact of CU on illness course and quality of life, as well as the limitations of the information available. Certainly, clinicians can caution against the use of cannabis firmly in the case of BD and with more reservation in the case of MDD.

5 | Limitations

Despite the greater consistency of results concerning CU and BD as compared to CU and MDD, the quality of the data does not allow for robust conclusions regarding the impact of cannabis on the course and presentation of mood disorders. Although this review was rigorous and systematic, the data available was highly variable and of mostly low quality. The amount of cannabis used was variably quantified, often relying on retrospective recall. Studies differed as to the cut-off points used to determine frequent or infrequent use, low or high quantity of use. In addition, the content of tetrahydrocannabinol (THC) and cannabidiol (CBD) were not determined although THC is considered to mediate the psychoactive effect of cannabis[73] and thus may potentially mediate the more negative effects of cannabis. Very few studies confirmed use of cannabis through quantitative methods such as urine concentration. Past and current use were also often amalgamated, and participants were recruited from different population groups among studies, and sometimes even within the same study, further contributing to the variability of results. It is possible that some of the variability in the findings could be related to the effect of cannabis on comorbid anxiety disorder or other comorbidities that were variably examined in the studies included in this review[74] .

While it is necessary for future studies to address the short-comings in the literature, it is also important to acknowledge the challenges of studying and treating individuals with comorbid substance use as well as conducting research on cannabis, a heterogeneous compound with pleotropic actions on multiple biological systems.

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Table 1. Summary of Findings for Main Outcomes in BD and MDD

Outcomes	# of Studies		Risk with CU		Certainty of the Evidence (GRADE) with Explanation	
	BD	MDD	BD	MDD	BD	MDD
Prevalence of CU/CUD						
CU lifetime prevalence	13	5	**52-71%**	**6-50%**	⊕⊕⊕⊖ moderate	⊕⊕⊕⊖ moderate
CUD lifetime prevalence	4	6	**3.3-7.2%**	**2.1-6.3%**	⊕⊕⊕⊖ moderate	⊕⊕⊕⊖ moderate
SUD Comorbidities						
Nicotine	5	1	↑	↑	⊕⊖⊖⊖ very low	⊕⊖⊖⊖ very low
AUD	7	1	↑	↑	⊕⊖⊖⊖ very low	⊕⊖⊖⊖ very low
SUD	7	2	↑	↑	⊕⊖⊖⊖ very low	⊕⊖⊖⊖ very low
Severity & Symptoms						
Phenomenology	10	5	↑ mania & mixed episodes ↑ rapid cycling ↑ psychotic features	↑ depressive symptoms ↔ episodes	⊕⊕⊖⊖ low	⊕⊖⊖⊖ very low
Illness Course						
Age of onset	8	4	↓	↔	⊕⊕⊖⊖ low	⊕⊕⊖⊖ low
Remission/relapse	1	0	↓ remission / ↑ recurrence	-	⊕⊖⊖⊖ very low	⊕⊖⊖⊖ very low
Suicidality	6	3	↑ attempt & completion	↔ ideation & attempt	⊕⊕⊖⊖ low	⊕⊕⊖⊖ low
Functioning/Cognition						
Functioning	7	3	↓	↓ or ↔	⊕⊖⊖⊖ very low	⊕⊖⊖⊖ very low
Cognition	2	0	↑ or ↔	-	⊕⊖⊖⊖ very low	-
Treatments						
Pharmacological	-	1	-	↔	-	⊕⊖⊖⊖

						very low

Abbreviations: AUD=Alcohol Use Disorder, BD= Bipolar Disorder, CU= Cannabis Use, CUD=Cannabis Use Disorder, SUD= substance use disorder.

Table 2. Quality of Evidence Ratings with GRADE Approach

Rating	Definition
High	High confidence in the effect estimate, i.e., the true effect is likely close to that of the estimate of the effect.
Moderate	Moderate confidence in the effect estimate. The true effect is probably close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Low confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	Very low confidence in the effect estimate: The true effect is probably substantially different from the estimate of effect.

Table 3. CANMAT recommendations for cannabis use by individuals with mood disorders

Recommendation	Certainty of evidence	Strength of recommendation
Individuals with bipolar disorder should avoid the use of cannabis	Moderate	Strong
Individuals with major depressive disorder should avoid the use of cannabis	Low-Moderate	Qualified

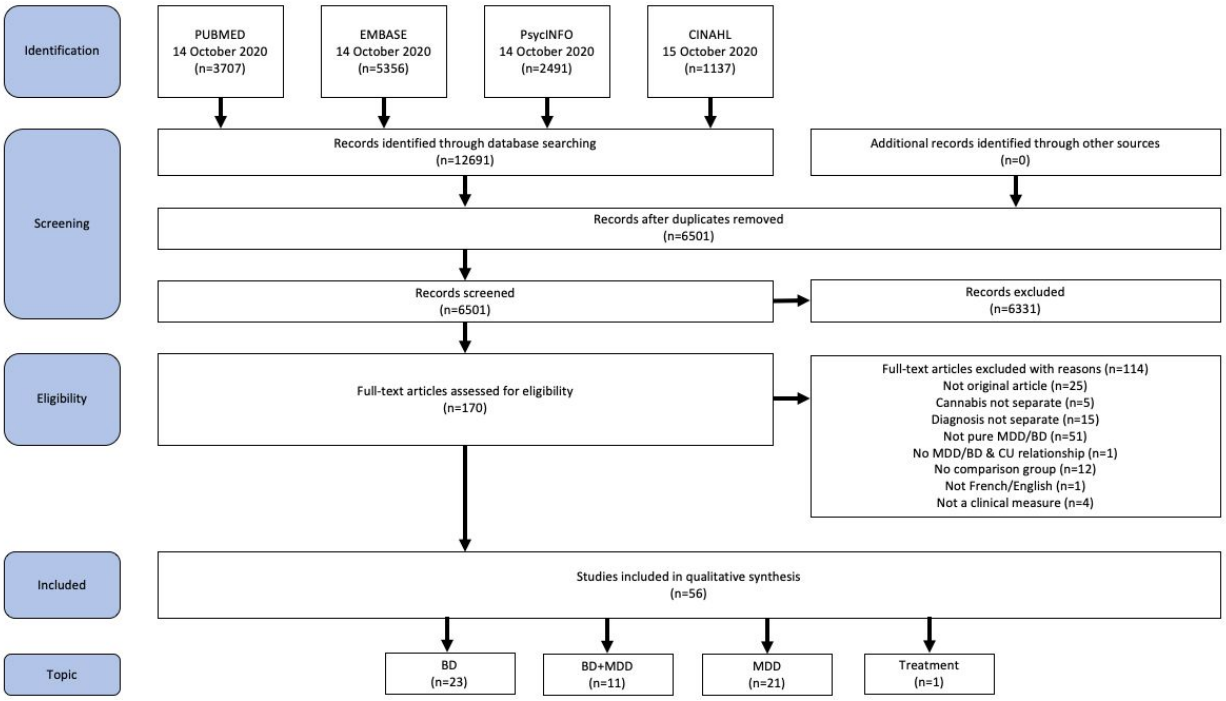
Identification
PUBMED
14 October 2020
(n=3707)
EMBASE
14 October 2020
(n=5356)
PsycINFO
14 October 2020
(n=2491)
CINAHL
15 October 2020
(n=1137)
Screening
Records identified through database searching
(n=12691)
Additional records identified through other sources
(n=0)
Records after duplicates removed
(n=6501)
Records screened
(n=6501)
Records excluded
(n=6331)
Eligibility
Full-text articles assessed for eligibility
(n=170)
Full-text articles excluded with reasons (n=114)
Not original article (n=25)
Cannabis not separate (n=5)
Diagnosis not separate (n=15)
Not pure MDD/BD (n=51)
No MDD/BD & CU relationship (n=1)
No comparison group (n=12)
Not French/English (n=1)
Not a clinical measure (n=4)
Included
Studies included in qualitative synthesis
(n=56)
Topic
BD
(n=23)
BD+MDD
(n=11)
MDD
(n=21)
Treatment
(n=1)

Table Supplementary I. Comparison of Substance Use Disorder Classification

	DSM-IV	DSM-5	ICD-10
Cannabis Dependence (CD)	**Three or more of the following criteria within a 12-month period:** - Tolerance - Used in larger amounts/longer - Repeated attempts to quit/control use - Much time spent using - Physical/psychological problems related to use - Activities given up to use	N/A	**Three or more of the following criteria within a 12-month period:** - Strong desire / sense of compulsion to take substance - Difficulties controlling use (onset, termination, levels of use) - Withdrawal - Tolerance - Neglect of alternative pleasures / interests due to use - Persisting use despite evidence of harmful consequences
Cannabis Abuse (CA)	**One or more of the following criteria within a 12-month period and no dependence diagnosis:** - Hazardous use - Social/interpersonal problems related to use - Neglected major roles to use - Legal problems	N/A	**One or more of the following criteria within a 12-month period and no dependence diagnosis:** - Harmful use - Nature of harm clearly identifiable - Pattern of use persisting for at least 1 month
Cannabis Use Disorder (CUD)	N/A	**Two or more of the following criteria within a 12-month period:** - Hazardous use - Social/interpersonal problems related to use - Neglected major roles to use - Withdrawal - Tolerance - Used in larger amounts/longer - Repeated attempts to quit/control use - Much time spent using	N/A

	Physical/psychological problems related to use Activities given up to use Craving

Supplementary Table II. Summary of Findings for Main Outcomes in BD and MDD, GRADE with explanation

Outcomes	# of Studies		Risk with CU		Certainty of the Evidence (GRADE) with Explanation			
	BD	MDD	BD	MDD	BD		MDD	
Prevalence of CU/CUD								
CU lifetime prevalence	13	5	52-71%	6-50%	⊕⊕⊕⊖ moderate	Downgraded due to imprecision (wide definition of CU)	⊕⊕⊕⊖ moderate	Downgraded due to imprecision (wide definition of CU)
CUD lifetime prevalence	4	6	3.3-7.2%	2.1-6.3%	⊕⊕⊕⊖ moderate	Downgraded due to imprecision (varying definitions of CUD)	⊕⊕⊕⊖ moderate	Downgraded due to imprecision (varying definitions of CUD)
SUD Comorbidities								
Nicotine	5	1	↑	↑	⊕⊖⊖⊖ very low	Downgraded due to imprecision (wide definition of nicotine use)	⊕⊖⊖⊖ very low	-
AUD	7	1	↑	↑	⊕⊖⊖⊖ very low	Downgraded due to imprecision (order of onset of comorbid conditions not assessed)	⊕⊖⊖⊖ very low	Downgraded due to imprecision (order of onset of comorbid conditions not assessed)
SUD	7	2	↑	↑	⊕⊖⊖⊖ very low	Downgraded due to imprecision (confounds not controlled for)	⊕⊖⊖⊖ very low	Downgraded due to risk of bias (only diagnosed SUDs assessed)
Severity & Symptoms								
Phenomenology	10	5	↑ mania & mixed episodes ↑ rapid cycling ↑ psychotic features	↑ depressive symptoms ↔ episodes	⊕⊕⊖⊖ low	Downgraded due to imprecision (wide definition of CU)	⊕⊖⊖⊖ very low	Downgraded due to inconsistency of results
Illness Course								
Age of onset	8	4	↓	↔	⊕⊕⊖⊖ low	Downgraded due to study design (retrospective)	⊕⊕⊖⊖ low	Downgraded due to study design (retrospective)
Remission/relapse	1	0	↓ remission / ↑ recurrence	-	⊕⊖⊖⊖ very low	Downgraded due to lack of evidence (only 1 study)	⊕⊖⊖⊖ very low	Downgraded due to lack of evidence (only 1 study)
Suicidality	6	3	↑ attempt & completion	↔ ideation & attempt	⊕⊕⊖⊖ low	Downgraded due to study design (retrospective)	⊕⊕⊖⊖ low	Downgraded due to study design (retrospective)
Functioning/Cognition								
Functioning	7	3	↓	↓ or ↔	⊕⊖⊖⊖ very low	Downgraded due to imprecision (confounds not controlled for)	⊕⊖⊖⊖ very low	Downgraded due to inconsistency of results

Cognition	2	0	↑ or ↔	-	⊕⊖⊖⊖ very low	Downgraded due to inconsistency of results	-	-
Treatments								
Pharmacological	-	1	-	↔	-	-	⊕⊖⊖⊖ very low	Downgraded due to lack of evidence (only 1 study)

Abbreviations: AUD=Alcohol Use Disorder, BD= Bipolar Disorder, CU= Cannabis Use, CUD=Cannabis Use Disorder, SUD= substance use disorder.

Supplementary Table III. Characteristics of Included Studies with GRADE Rating

Study	# Subjects (M/F); Prevalence of Mood Disorder (where reported)	Patient Inclusion Criteria	Main Outcomes	Main Results, OR (95% CI)			Limitations	Conclusion	GRADE Rating
				Prevalence of CU/CUD	Illness Course	Functioning & Cognition			
Bipolar Disorder (BD)									
Aas et al. 2013	587 BD (234 M/ 353 F)	BD-I/II/NOS	BD-AO; rapid cycling; mixed episodes; suicide attempt		**CU+childhood abuse**: ↓ BD AO***, ↑ rapid cycling (sexual abuse: OR 1.63, CI 1.11–2.38; emotional abuse: OR 1.61, CI 1.13–2.30), ↑ suicide attempt (sexual abuse: OR 2.13, CI 1.49–3.14; emotional abuse: OR 1.88, CI 1.34–2.63)		Retrospective assessment of childhood abuse	Additive effects of CA + childhood abuse on frequency of rapid cycling & suicide attempt	⊕⊕⊖⊖ low
Agrawal et al. 2011	471 BD, 1761 ctl (sex not reported)	BD	LT CU & CUD; BD sxs; suicide attempt; disability	**LT CU:** 6.8x ↑ BD vs ctl (71.3% vs 26.8%, CI 5.41-8.52); **CUD:** 30% BD	**BD+CUD:** ↑ suicide attempt (OR 1.51, CI 1.01-2.26); mood sxs precede CU in 53% BD; ↑ mixed episodes (OR 1.52, CI 1.02-2.27)	**BD+CUD:** ↑ disability (OR 2.19, CI 1.45-3.31)	CU data not available in ctl; retrospective design	CUD more prevalent in BD vs ctl & associated w/ greater disability in BD	⊕⊖⊖⊖ very low

Baethge et al. 2008	166 BD (90 males, 76 females)	18+ yrs, first-LT manic or mixed episode BD-I	CU	**CU:** 18.1%	**BD:** hypo/mania associated w/ CU during preceding (RC 0.111, CI 0.054–0.168) or same quarter (RC 0.116, CI 0.053–0.178); depression unrelated to CU		Type & frequency of CU not assessed	CU precedes & coincides w/ mania	⊕⊖⊖⊖ very low
Braga et al. 2012	50 BD+CUD (31 males, 19 females), 150 BD-I (65 males, 85 females)	BD-I, 18-65 yrs, no history of neurological disorders, no major CNS trauma, IQ > 70	CVLT, COWAT, Animal Naming, WAIS-R-Digit Span, Trail Making Parts A & B, IQ, AO, psychosis history, GAF			**BD+CUD:** ↑ Digits forward*, Trails B*, Digits Backward*	Retrospective analysis; CU history categorical; antipsychotic drug use & illness duration not assessed	↑ cognition in BD+CUD vs BD	⊕⊖⊖⊖ very low
De Hert et al. 2010	90 BD (32 males, 58 females), 676 SZ (440 males, 236 females)	Outpatients & inpatients w/ BD or SZ	CU, AO	**CU:** ↑ SZ vs BD***	**CU:** ↓ AO by 9 yrs in BD & 1.5 yrs in SZ*		Age at 1st admission proxy for AO; small BD sample	CU associated w/ greater reduction in AO in BD vs SZ	⊕⊖⊖⊖ very low
de la Fuente-Tomás et al. 2020	224 BD+LT CU (21 males, 15 females), BD (57 males, 131 females)	BD, 17+ yrs, receiving outpatient treatment	FAST, GAF, QoL		**BD+LT-CU:** earlier hospitalization**	**Females BD+LT CU:** ↓ financial issues**, ↓ QoL**; **Males BD+LT CU:** no	Self-report CU; small subsamples (secondary analysis); cross-sectional design	LT CU associated w/ earlier age at first hospitalization in males &	⊕⊖⊖⊖ very low

						difference in financial issues		females, and worse QoL in females only	
Gruber et al. 2012	12 BD+CU, 20 CU only, 11 BD only (sex not reported)	BD+CU & CU: CU ≥ 2,500 times in their lives, CU ≥ last 5/7 days, test positive for urinary cannabinoids, meet CA/CD criteria	HAMA-A, MADRS, YMRS, POMS		**After CU, BD+CU (vs CU only):** ↓ HAM-A*, ↓ MADRS**, ↑ POMS-vigor**, ↓ POMS-tension***, ↓ POMS-depression*, ↓ POMS total score**; **Before CU, BD+CU (vs BD only):** ↓ POMS-vigor*, ↑ PMOS-confusion**, ↑ PMOS-tension*, ↑ PMOS-fatigue**, ↑ PMOS-depression**, ↑ MADRS***, ↑ YMRS***		Small sample size; long-term effects not assessed; sex not reported	CU attenuates BD sxs	⊕⊖⊖⊖ very low
Heffner et al. 2013	80 BD+CA/CD (42 males, 38 females)	13-22 yrs, BD-I+CA/CD, reported ever trying a cigarette	Heavy smoking, nicotine dependence, BD sxs	**Heavy vs light- & no cig use:** ↑ weekly CU; **Current heavy cig use:** 49%; **LT nicotine dependence:** 92% of heavy cig use & 49% of	**Nicotine dependence:** ↑ YMRS	**Heavy cig use vs light cig use & non cig use**: ↓ functioning	Exploratory analyses not controlling for multiple comparisons	Heavy smoking and nicotine dependence highly prevalent in BD+CA/CD & associated w/ greater	⊕⊖⊖⊖ very low

				current non-cig use				illness severity	
Heffner et al. 2008	134 BD + cig use (37 males, 36 females), BD + non-cig use (30 males, 31 females)	BD-I inpatients hospitalized for first manic episode w/ < 1-month psychotropic medication for BD prior to hospitalization	Cig use; AO CU	**BD + cig use:** 55.7% CU (versus 18.1% CU in non-cig use); **Cig use at first hospitalization**: 45.5%	**BD + cig use:** earlier AO CU**		Homogenous sample	Smoking status in BD related to current and past CU	⊕⊖⊖⊖ very low
Kvitland et al. 2016	101 BD + recent CU (14 males, 10 females), BD + no recent CU (26 males, 51 females)	BD-I, w/in 1st year of inpatient or outpatient treatment for manic episode, 17-65 yrs	AO first manic, depressive, psychotic episodes; LT suicide attempt		**Recent CU:** ↓ AO manic & psychotic* but not depressive episode, ↑ LT suicide attempt**		Retrospective reporting of AO symptoms; cross-sectional design	CU associated w/ more severe illness course	⊕⊖⊖⊖ very low
Kvitland et al. 2016	62 BD (25 males, 37 females)	Receiving first treatment for BD-I, 17-65 yrs	GAF, LT suicide attempt, IDS, YMRS, PANSS	**LT CU:** 52%	No associations between duration untreated BD & LT suicide attempt, IDS, YMRS, PANSS at baseline or 1-year-FUP	No associations between DUB & GAF baseline or 1-year-FUP	Small sample; retrospective assessment of CU; limited assessment of functioning (GAF)	No associations between features of previous illness episodes &	⊕⊖⊖⊖ very low

Kvitland et al. 2015	62 BD (25 males, 37 females)	BD-I, within 1st year of receiving treatment for manic episode, 17-65 yrs	GAF, YMRS	**Continued CU:** ↑ YMRS at 1-year-FUP***	**Continued CU:** ↓ GAF at 1-year-FUP*	Small sample size; cross-sectional design	clinical outcomes BD+CU during first year of treatment at higher risk for elevated mood and worse global functioning	⊕⊖⊖⊖ very low
Lagerberg et al. 2016	529 BD no CUD (232 males, 297 females), 113 BD+CUD (64 males, 49 females)	France site: 18+ yrs, BD-I/II, euthymic at inclusion; Norway site: 18-65 yrs, BD-I/-II	AO, LT frequency of depressive/manic episodes, # hospitalizations, functioning, neurocognition, suicidality, psychotic sxs	**CUD:** ↓ BD-AO (CI -7.65 to -3.64), ↑ manic episodes (OR 1.93, CI 1.15–3.23), ↑ hospitalizations (OR 2.93, CI 1.85–4.64)		CU & mood episodes collected retrospectively	CUD exacerbates illness severity	⊕⊕⊕⊖ moderate
Lagerberg et al. 2014	227 BD + no/low CU (76 males, 151 females), 64 BD + intermediate CU (28 males, 36 females), 33 BD+CUD (14	18-65 yrs, BD	AO (hypo)manic, mixed, & depressive episodes	**CU:** ↓ AO (highest CU vs. lowest CU*), ↓ AO in patients w/ LT psychosis*		Cross-sectional design; categorical 3-level classification of CU not based on	Increasing doses of CU associated w/ ↓ BD-AO	⊕⊖⊖⊖ very low

	males, 19 females)						empirical evidence		
Lagerberg et al. 2011	151 BD (59 males, 92 females)	BD-I/II, 18-65 yrs, fluent in Scandinavian language	BD-AO		**CU:** ↓ BD-AO***		Retrospective assessments	CU associated w/ ↓ BD-AO independent of CU preceding or following BD onset	⊕⊕⊖⊖low
Lev-Ran et al. 2012	1,905 BD (sex nr)	18+ yrs	AO, median # mood episodes, nicotine dependence, AUD, SUD, antisocial personality disorder	**BD:** ↑ CUD prevalence (10.1 M/4.1 F) vs general population (1.2%); **BD+CUD:** ↑ nicotine dependence (AOR=3.8), ↑ AUD (AOR=6.6), ↑ SUD (AOR=11.9)	**BD+CUD:** ↑ antisocial personality disorder (AOR=2.8); **BD+CUD:** ↓ BD-AO, ↑ median # mood episodes per year		Cross-sectional design; under-reporting due to social desirability effects	CUD associated w/ significant co-morbidities & more severe illness course in BD	⊕⊕⊕⊖ moderate
Ringen et al. 2009	133 BD (55 males, 78 females), 140 SZ (73 males, 63 females)	18-65 yrs, SZ, schizophreniform disorder, schizo-affective, BD-I/II/NOS, fluent in Scandinavi	Psychomotor speed, attention, working memory, executive functioning, verbal learning & memory			**CU+BD:** ↑ performed on semantic fluency subtest of verbal fluency*	Cross-sectional design; small BD+CU sample; wide criteria for CU (any use in past 6 months); details of CU (amount smoked, duration of use, THC content)	CU related to improved cognition in BD	⊕⊖⊖⊖ very low

		an language					not assessed; previous medication not assessed (influence on neurocognition); self-report CU		
Sagar et al. 2016	12 BD+CU (11 males, 1 female), 18 BD only (8 males, 10 females), 23 CU only (16 males, 7 females), 21 ctl (8 males, 13 females)	Native English speakers, no psychopathology (other than BD-I & CA/CD), no neurological disorder or medical problems, no head injury w/ loss of consciousness, ≤ 15 LT uses of illicit drugs (except CU), no recreational use of prescripti	WCST, Stroop, Trail Making Test, COWAT, Digit Span, ROCF, CVLT, HVOT, TMD, HAM-A, MADRS, YMRS		**BD+CU vs BD:** ↑ MADRS*	**BD+CU vs BD:** ↔ on neurocognition	Small sample size across groups; higher than average IQs	No additive negative impact of BD+CU on cognition	⊕⊖⊖⊖ very low

		on or OTC medications, no ECT						
Strakowski et al. 2007	75 BD no CU (31 males, 44 females), 36 BD before CU (22 males, 14 females), 33 CU before BD (22 males, 11 females)	BD-I (manic or mixed), 12-45 yrs, no previous psychiatric hospitalizations, < 1-month LT previous thymoleptic or antipsychotic drug exposure, English speaking, able to return for FUP visits	BD sxs	**BD+CUD:** 47.9% (BD before CU: 25.0% & CU before BD: 22.9%)	**CU:** ↑ time in manic/mixed episodes*, ↑ rapid cycling*; **BD onset before CU (vs. no CU):** ↑ subsyndromal manic sxs*	Small sample sizes in subgroup analyses; sxs ratings & CU self-reported	CU associated with more frequent relapse	⊕⊖⊖⊖ very low
Tyler et al. 2015	24 BD (16 males, 8 females)	18+ yrs; euthymic BD-I/-II; CU ≥ 2 occasions per week (in ≥ half the weeks	CU, affect (positive & negative), mania, depression		**Positive affect:** ↑ CU (OR 1.25, CI 1.06–1.47**); **CU:** subsequent ↑ in positive affect (CI 0.20–0.51***), ↑ manic sxs (CI 0.05–0.34**), ↑	Small sample size; self-reported CU; CU amount not assessed	CU associated with changes in positive affect & BD symptoms	⊕⊖⊖⊖ very low

		in 3 months prior to assessment); no organic brain disease or moderate/severe learning disability		depressive sxs (CI 0.04–0.29**)				
van Rossum et al. 2009	3459 BD (1528 males, 1898 females)	BD inpatients & outpatients, 18+ yrs, CGI-BP mania ≥ 3	CGI-BP overall illness, mania, depression, CGI hallucinations/delusions, medication compliance, AUD, SUD, independent living, work impairment, relationship, frequency	**CU:** ↑ CGI-BP overall illness at 1-year-FUP (CI 0.04–0.22**), ↑ CGI-BP mania (CI 0.06–0.24**), ↑ CGI hallucinations/delusions (CI 0.03–0.19**), ↓ treatment compliance (CI 1.12–1.72**), ↑ AU/AUD (CI 0.07-0.13***), ↑ SUD (CI 0.09-0.13***)	**CU:** ↓ satisfaction w/ life (CI 0.05-0.24**), no difference in other social outcome variables	Self-reported CU	Unfavorable association between CU & BD symptoms at 1-year-FUP	⊕⊕⊖⊖low

			of social activities, satisfaction w/ life, # dependents to care for						
Weinstock et al. 2016	36 BD+CUD (18 males, 18 females), 194 BD no CUD (78 males, 116 females)	18+ yrs; primary diagnosis of BD-I at hospital admission & discharge	BD sxs, demographic variables	**Comorbid CUD:** 16%; **BD+CUD:** comorbid nicotine dependence (OR 2.31, CI 1.08–4.94), ↓ anxiety disorders (OR 0.13, CI 0.11–0.82)	**BD+CUD:** ↓ age (OR 0.97, CI 0.93–1.00), ↑ psychotic features (OR 2.75, CI 1.24–6.11)		Retrospective chart review; missing data on AO sxs, overall illness severity, history of mixed episodes/rapid cycling, history of trauma, treatment history/adherence)	BD+CUD associated w/ greater clinical severity	⊕⊖⊖⊖ very low
Zorrilla et al. 2015	1701 BD never CU (720 males, 981 females), 89 BD + previous CU (62 males, 27 females), 132 BD + current CU (90 males, 42 females)	BD (manic/mixed episode)	Work impairment, relationship status, living situation, sxs remission & relapse	**Previous CU:** 4.6% BD**; Never CU**: 88.5% BD	**Previous CU (4.6% BD):** ↑ remission, ↓ relapse; **Current CU (6.9% BD):** ↓ remission**, ↑ recurrence*	**Previous CU (4.6% BD):** ↑ work impairment*, ↑ not to be living w/ partner**	Medication effects not considered; CU self-reported; confounding effects of AU not adjusted for	Continued CU associated w/ greater risk of recurrence & poorer functioning	⊕⊖⊖⊖ very low
Bipolar Disorder (BD) & Major Depressive Disorder (MDD)									
Bahorik et al. 2013	137 BD (77 males, 60 females), 460 MDD (237 males, 223 females), 204	English speaker, 18-40 yrs, SZ, BD,	BPRS, GAF		**CU:** ↑ BPRS (CI = 0.83–2.47***)	**CU:** ↓ GAF (CI = -3.67 to -0.99**) across all diagnoses	CU self-reported; CU non-quantified; GAF measure	CU associated w/ ↑ sxs & ↓	⊕⊖⊖⊖ very low

	SZ (127 males, 77 females)	MDD, at-risk for future violence (based on patient self-report, collateral informants' reports & official records (i.e., hospital & arrest records)			limited by global focus & incorporation of sxs into measurement; treatment & medication compliance not systematically collected	functioning in BD across diagnoses	
Conway et al. 2006	43,093 participants (MDD: 11.8% males/20.9% females; BD-I: 3.2% males/3.4% females; BD-II: 2.5% males/2.2% females)	18+ yrs	CUD/CA/CD prevalence, MDD, BD	**MDD**: CUD 16.3%, CA 12.6%, CD 3.7%; **BD-I:** CUD (30.2%), CA (21.0%), CD (9.3%); **BD-II:** CUD (20.6%), CA (14.9%), CD (5.7%); MDD & CD in females > males (OR 7.2*)	Order of onset of comorbid conditions & AUD not assessed	↑ association between mood disorders & CD vs CA; ↑ prevalence of CU/CA/CUD in BD vs MDD	⊕⊕⊕⊖ moderate
Feingold et al. 2015	Sample w/o prior LT MDD: 853 CU (571 males, 282 females), 27,777 non-CU (12,158	LT or PY MDD or BD-I/II	Incidence of mood disorder, initiation	**Daily CU:** ↑ MDD incidence (AOR 0.58, CI 0.22–1.51); **Baseline MDD:**	CU frequency at FUP in baseline MDD/BD not reported; confounding	Baseline MDD but not BD associated w/ future	⊕⊖⊖⊖ very low

	males, 15,592 females); Sample w/o prior LT BD: 1029 CU (635 males, 393 females), 31,577 non-CU (13,082 males, 18,495 females)		of CU, CU frequency	initiation of CU (AOR 1.72, CI 1.1–2.69); **Weekly to almost daily CU:** ↑ BD incidence (AOR 2.47, CI 1.03–5.92)		variables not reported	initiation of CU	
Hjorthoj et al. 2015	41,470 SZ (24,127 males, 17,343 females), 11,739 BD (5,092 males, 6,647 females), 88,270 MDD (33,127 males, 55,143 females)	SZ, MDD, BD	All-cause mortality, suicide completion, deaths from accidents		**CUD only:** ↓ suicide risk (MDD: SHR 0.14, CI 0.03–0.55**); **AUD+CUD mortality:** ↑ all-cause (BD: HR 1.63, CI 1.09–2.43*; MD: HR 2.36, CI 1.87–2.98***), ↑ accidents (MDD: SHR 6.01, CI 3.62–9.97***); **HD+CUD mortality:** ↑ all-cause (BD: HR 1.81, CI 1.06–3.11*; MD: HR 2.71, CI 2.04–3.60***), ↑ accidents (MDD: SHR 10.63, CI 6.71–16.84***); **AUD+HD+CUD**	Analyses limited to diagnosed SUDs	CUD does not individually increase risk of mortality in BD or MDD; CUD w/ AUD and/or HD confers additional	⊕⊕⊕⊖ moderate

					mortality: ↑ all-cause (BD: HR 3.03, CI 2.99–3.91***; MDD: HR 3.44, CI 2.34–3.96***), ↑ accidents (BD: SHR 9.41, CI 5.34–16.58***; MD: SHR 11.85, CI 8.71–16.13***)			
Manrique-Garcia et al. 2012	45,087 males	Swedish males w/ survey data on CU, no psychiatric diagnosis at baseline	MDD, BD + affective psychosis, schizoaffective disorder		No association between frequency of CU & risk of MDD or BD	Diagnoses of MDD limited to inpatients; no females assessed	No increased risk of mood disorders following CU	⊕⊖⊖⊖ very low
Nesvag et al. 2015	BD (6,306 males, 9,234 females), MDD (32.104 males, 55,436 females), SZ (5,842 males, 3,160 females)	BD, MDD, SZ	CUD	**BD:** 3.3% CUD (5.2% males, 2.0% females); **MDD:** 2.0% CUD (3.7% males, 1.0% females); **Population:** 0.5% (0.8% males, 0.2% females)		Sample restricted to those in contact w/ specialist health-care services	CUDs highly prevalent in BDD & (less so) in MDD	⊕⊕⊖⊖low
Østergaard et al, 2017	35,625 SZ (20,862 males, 14,763 females), 9,279	13-56 yrs old w/ diagnosis	Suicide completio	**CUD:** 10.53% BD, 6.39% MDD	**Current CU+BD:** ↑ suicide	Older adults (+56 yrs old) omitted due to	CU associated w/ ↑ risk for	⊕⊕⊕⊖ moderate

	BD (4,034 males, 5,245 females), 72,530 MDD (27,224 males, 45,306 females), 63,958 PD (25,693 males, 38,265 females)	of SZ, BD, MDD, or PD	n, suicide attempt		completion (HR 1.86, CI 1.15–2.99)	time-span of registers; order & combination of multiple SUDs not assessed; only information on diagnosed SUDs available; confounding variables (e.g., trauma, social networks) not assessed	suicide completion in BD; risk of suicide attempt more associated w/ AUD than CUD (across all study populations)	
Taub et al. 2018	217 MDD (122 males, 95 females), 168 BD (99 males, 69 females)	MDD, BD, CU	Frequency & daily dose of CU, rates	**MDD:** PY-CU 8.9% (of these 39.4% CUD); **BD:** PY-CU 14.7% (of these 51.8% CUD); **BD+CU:** ↑ joints per day during most intensive use vs. BD alone*		Retrospective self-reports of CU & psychiatric evaluation; adolescents excluded from NESARC sample	↑ CU in BD vs MDD	⊕⊖⊖⊖ very low
Toftdahl et al. 2016	463,003 pts (sex not reported)	Patients w/ registered psychiatric disorders in Danish Psychiatric Central Register	SUD (including CUD) prevalence	**CUD:** 3.3% BD, 2.1% MDD		Patients w/ multiple diagnoses represented by dominating disorder (risk of diagnostic misclassification); sex not reported	↑ CUD prevalence in BD vs MDD	⊕⊖⊖⊖ very low

van Laar et al. 2007	3,881 w/o LT BD or MDD (2,096 males, 1,785 females), 3,854 w/o LT anxiety disorders (2,120 males, 1,734 females)	18-64 yrs, MDD, BD or anxiety disorders	Incidence of MDD & BD		**Baseline CU:** ↑ first MDD (OR 1.62, CI 1.06–2.48), ↑ first BD (OR 4.98, CI 1.80–13.81)	Self-reported CU; cannabis THC potency less during study execution (1996-9); sample w/ relatively late onset MDD, BD & anxiety disorders	Associations between CU & first incidence of MDD & BD	⊕⊖⊖⊖ very low
Wittchen et al. 2007	1,324 participants (cross-sectional; sex not reported) & 1,310 participants (longitudinal; sex not reported)	14-17 yrs at baseline	CU/CUD	**LT CU**: 19.3%; **CUD** 2.6%; **Cumulative incidence rates at 10-year-FUP CU / CUD**: 54.3% / 13.7%; **MDD:** ↑ incident CU (OR 1.9) & incident CUD (OR 2.5); **BD:** ↑ incident CU (OR 2.5) & incident CUD (OR 2.7)	**CU:** ↑ incident MDD (OR 2.7, CI 1.6–4.4) & incident BD (OR 4.7, CI 2.2–10.0)	Confounding effects of treatment not considered	MDD & BD associated w/ incident CU & progression to CUD	⊕⊕⊖⊖low
Major Depressive Disorder (MDD)								
Abraham et al. 1999	375 MDD (129 males, 246 females)	MDD, HADRS >/= 16	AO MDD, AO CA		AO MDD = AO CA (18.6 ± 0.8 yrs)	Variability in dose, route of administration, adulteration of cannabis w/ other	Cannabis & depression co-occur	⊕⊖⊖⊖ very low

						substances not controlled for		
Agrawal et al. 2017	13,986 twins (5,573 males, 8,413 females)	MZ & same-sex DZ twins from Australian Twin Registry	CU frequency, AO CU, suicidal ideation (ever & persistent), suicide attempt	**CU:** 30.44%–69·0%; **MDD:** 20.3%–28.5%	**Mean AO CU:** 17.9 yrs –21.1 yrs; **Suicidal ideation:** 24.9%–26.3%; **MZ w/ more vs less frequent CU:** ↑ MDD (OR 1.98, CI 1.11–3.53), ↑ suicidal ideation (2.47, 1.19–5.10); **DZ:** early CU → MDD & suicidal ideation (OR 2.23–6.50) vs MZ (OR 1.17–2.00)	CU self-reported; CU descriptors limited to frequency of use & age AO	Early & frequent cannabis use associated w/ MDD & suicidal ideation	⊕⊕⊕⊖ moderate
Bersani et al. 2016	51 MDD+CUD (37 males, 14 females, 51 MDD only (33 males, 18 females)	18+ yrs, MDD+CUD or MDD	HDRS, PANSS negative sxs		**MDD+CU:** ↑ negative sxs**	Cross-sectional design	Concomitant CUD+MDD increases negative sxs severity	⊕⊕⊖⊖low
Carrà et al. 2019	167,338 young people (85,677 males, 85,661 females), 360,108 adults (176,813 males, 183,295 females)	PY MDE	MDE & CU prevalence rates, CU		**Young people (12-17 yrs):** ↑ likelihood of PY-MDE in CU (occasional: OR 2.50, CI 1.79–2.28; weekly: OR 1.61, CI 1.34–1.92; heavy: OR 1.38, CI 1.12–1.69) vs. non-users (OR 2.32, CI 2.08–2.59;	PY CU & MDE self-reported; cross-sectional observations	CU associated w/ ↑ MDE prevalence in CU vs non-users	⊕⊕⊖⊖low

					Adults (18-64 yrs): ↑ PY MDE in CU (occasional: OR 2.45, CI 2.26–2.72; weekly: OR 2.59, CI 2.25–2.97; heavy: OR 2.65, CI 2.30–3.05) vs. non-users (OR 1.79, CI 1.64–1.96)				
Chen et al. 2002	1,232 MDE (455 males, 777 females), 5,560 no MDE (2,829 males, 2,731 females)	15-45 yrs, MDE	MDE		**CU:** 1.6 times ↑ risk of MDE (CI 1.1–2.2)		AO MDE collected retrospectively	Association between CU & subsequent risk of MDE	⊕⊕⊖⊖low
Degenhardt et al. 2013	1,756 participants (825 males, 931 females)	Adolescent & young adult residents of Victoria, Australia	MDE, AD		No association between CU in adolescence & MDD at age 29 (AOR 2.01, CI 1.0–4.6)		Different assessment approaches used at each wave; confounding treatment effects not considered	Adolescent CU not associated w/ MDD in adolescence/ late young adulthood	⊕⊖⊖⊖ very low
Feingold et al. 2017	853 CU (571 males, 282 females), 27,777 non-CU (12,158 males, 15,592 females)	Non-institutionalized, 18+ yrs, PY MDD	Recurrence vs. remission, number of depressive sxs, suicidality, impairment in	**MDD:** 7.5% reported CU w/o CUD & 4.7% CUD	**Non-CU vs CU w/o CUD & CU w/ CUD:** ↑ AO MDD***, no difference in # of LT MDD episodes; **Level of CU:** ↑ depressive sxs at follow-up***;	**CUD vs non-CU:** no difference in functioning or QoL	Short FUP; rates of CU lower than parallel surveys from other regions	CU not associated w/ increased clinical severity in MDD (i.e., suicidality, functionality & QoL)	⊕⊕⊖⊖low

			social, occupational & educational functioning, treatment utilization rates, QoL		**CUD:** ↑ anhedonia (AOR 2.62, CI 1.36–5.08**), change in body weight (AOR 2.30, CI 1.33–3.99**), insomnia/hypersomnia (AOR 2.30, CI 1.29–4.12**), psychomotor agitation (AOR 3.51, CI 1.95–6.30***); **CUD vs non-CU:** no difference in suicidality			
Gilder et al. 2012	202 participants (98 males, 104 females)	Living on or near 8 Southwest California American Indian reservations, at least 1/16th Native American Heritage, 13-17 yrs, able to be transported from	MDE/MDD & CD comorbidity	**CD:** ↑ MDE in boys (OR 4.87, CI 1.43–16.59) but not girls (OR 1.77, CI 0.71–4.38); **CD:** ↑ MDD in boys (OR 0.37, CI 0.10–1.39) & girls (OR 0.92, CI 0.37–2.30)	**MDD+CU:** median AO MDE same between boys & girls		Analyses performed separately for boys and girls	Association between depression & CD more significant in male vs female adolescents	⊕⊕⊖⊖low

		home to research institute						
Goodwin et al. 2020	11,623 females	Female, 12-49 yrs, pregnant at time of interview	CU	**MDE (vs no MDE):** ↑ CU during pregnancy (12.7 % vs 3.7 %; OR 3.8, CI 2.8–5.0)		CU self-reported	Females w/ MDD more likely to use cannabis during pregnancy	⊕⊖⊖⊖ very low
Gukasyan et al. 2020	14,873 adolescents w/ CU (7,793 males, 7,080 females), 73,079 adolescents w/o CU (37,124 males, 35,955 females)	12-17 yrs, respondents of CU & MDD surveys	LT & PY MDD (w/ & w/o severe role impairment), PY suicide attempt	**LT CU (vs never-use):** ↑ LT & PY MDD; **CU:** ↓ prevalence of LT MDD in heavy vs light users & non-use in PY (OR 0.17, CI 0.16–0.19 vs OR 0.22, CI 0.21–0.24 vs OR 0.24, CI 0.22–0.27)	**LT CU (vs never-use):** ↑ PY suicide attempt; **History of CU:** ↑ PY suicide attempt (ORs 2.06–2.53)	**LT CU (vs never-use):** ↑ MDD w/ severe role impairment***	Broad grouping of CU severity; confounding effects of treatment	CU history associated w/ ↑ MDD in adolescents; yet ↑ CU frequency associated with ↓ MDD	⊕⊖⊖⊖ very low
Halladay et al. 2019	43,466 participants (21,690 males, 21,776 females)	15+ yrs	PY MDE, psychological distress, suicidal ideation/suicide attempt	**Occasional vs non-CU:** ↑ MDE (males: OR 2.37, CI 1.79–3.36; females: OR 2.45, CI 1.79–3.36); **Regular vs non-CU**: ↑ MDE (males: OR 4.16, CI 3.15–5.50; females: OR 3.67, CI 2.63–5.12)	**Occasional CU:** ↑ psychological distress in females (OR 2.84, CI 2.15–3.53) vs males (OR 1.57, CI 1.14–2.01); **Occasional CU:** ↑ suicidal ideation/suicide attempt in females (OR 2.45, CI 1.79-3.36)		Cross-sectional design	Associations between CU & suicidal ideation/suicide attempt & psychological distress stronger for females vs males; no sex differences for associations	⊕⊕⊕⊖ moderate

							between CU & MDE	
Halladay et al. 2020	43,466 participants (21,686 males, 21,780 females)	15-60 yrs	MDE, suicidal ideation	**CU:** ↑ MDE (OR 1.55, CI 1.12–2.13)	**CU:** ↑ suicidal ideation (OR 1.59, CI 1.11–2.27)	Cross-sectional design; self-report measures; CU operationalized as frequency only (i.e., did not include AO, previous SUDs, frequency of daily use)	Monthly CU related to suicidal ideation & MDE	⊕⊕⊖⊖low
Harder et al. 2008	1,494 participants (672 males, 822 females)	Data on adolescent CU or young adult MDD	MDE	**CU vs non-CU:** no difference in MDD risk for females (OR 0.7, CI 0.2–2.3) or males (OR 1.7, CI 0.8–3.6)		AO CU reported retrospectively	Adolescent-onset CU not associated w/ young adult MDD	⊕⊕⊖⊖low
Hengartner et al. 2020	591 participants (292 males, 299 females)	Subjects screened with SCL-90-R at age 19/20 yrs	MDD, suicidality, anxiety disorders	**Adolescent CU:** ↑ MDD (AOR 1.36, CI 1.10–1.69**); **Frequency of CU in adolescence:** ↑ MDD risk in adult life**	**Adolescent CU:** ↑ suicidality (AOR 1.74, CI 1.28–2.35***), no difference in anxiety disorders	Retrospective report of CU; adolescent CU not quantified; mental health problems in adolescence not assessed	Early age CU ↑ risk of depression in adulthood	⊕⊖⊖⊖ very low
Marmorstein et al. 2012	566 adopted adolescents (245 males, 321 females), 432 non-adopted	Adopted & non-adopted adolescent siblings,	MDD, SUDs	**Parental MDD:** ↑ MDD in adopted*** & non-adopted** adolescents;		Information on prenatal environment of adopted youth not available	Parental MDD & CUD both contribute to MDD in	⊕⊖⊖⊖ very low

	adolescents (187 males, 245 females)	11-20 yrs (≤ 5 yrs apart)		**Parental CUD:** ↑ MDD in adolescents (OR 2.17, CI 1.34–3.52**)			adolescent offspring	
Pacek et al. 2013	20,845 ctl (7,486 males, 13,359 females), 5,943 AUD (4,008 males, 1,926 females), 395 CUD (219 males, 176 females), 1,475 AUD+CUD (1,053 males, 422 females)	AUD w/o LT CUD, LT CUD w/o LT AUD, LT AUD+CUD	MDD, CUD, CA	**CUDs/CA alone:** ↑ MDD at FUP (OR 2.01, CI 1.09–3.68 / OR 2.67, CI 1.35–5.28); **Baseline MDD:** ↑ CUD (OR 2.01, CI 1.09–3.68), ↑ CA (OR 2.67, CI 1.35–5.28)		Self-report, recall bias (LT questions)	Bidirectional associations between CUD & MDD	⊕⊕⊕⊖ moderate
Pacek et al. 2019	728,691 individuals (no PY MDE: 11.09 males/6.28 females; PY MDE: 22.61 males/16.98 females)	12+ yrs	CU, perception of risk w/ CU	**MDD vs non-MDD:** ↑ prevalence of CU (18.94% vs 8.67%; AOR 2.17, CI 1.92–2.45)	**Perception of risk of CU:** ↓ in MDD vs non-MDD***	CU specifiers (e.g., route of administration, potency, type of cannabis, reason for use) not reported; self-reports	Prevalence of CU more common in MDD + perceived as ↓ risk	⊕⊕⊖⊖low
Rhew et al. 2017	521 youth (269 males, 252 females)	13–15 yrs	CUD, AUD	**PY CU at age 18:** 20.9%; **MDD in early adolescence:** ↑ CUD (PR 1.50, CI 1.07–2.10*) but not AUD		Self-report	MDD during early adolescence associated w/ ↑ likelihood of CUD in later adolescence	⊕⊕⊖⊖low

Schoeler et al. 2018	285 males	Males, born in 1961/62, attending 1 of 6 primary schools in deprived area of London	MDD	**Early onset (< 18 yrs) high / low frequency CU vs non-CU:** ↑ risk for MDD (OR 8.83, CI 1.29–70.79* / OR 2.41, CI 1.22–4.76*; **↑ CU frequency in adolescence:** ↑ MDD in early / later adulthood (CI 1.03–1.12*** / CI 1.10–1.31***); **MDD in early adulthood:** ↓ frequency of CU in later adulthood (CI 0.57–0.92**)	**High / low frequency early-onset CU:** ↓ time to MDD onset (HR 8.69, CI 2.07–36.52** / HR 2.09, CI 1.16–3.74*)		Restricted to males; self-report CU; MDD only assessed at last follow-up (age 48 yrs); THC levels in cannabis have increased since study execution	Early- but not late-onset CU is a risk factor for later MDD	⊕⊖⊖⊖ very low
Smolkina et al. 2017	565 MZ twins (169 male, 396 female), 640 DZ twins (118 male-male, 298 female-female, 224 male-female)	Twin (MZ or DZ), complete data on CUD & MDD	CUD & MDD comorbidity	**MDD vs non-MDD:** CUD 24.3% vs 12.3 (OR 2.66, CI 2.10–3.37); **MZ twins w/ vs w/o CUD:** ↑ MDD (46.0% vs 28.12%, OR 2.83, CI 1.12–7.19)			Confounding factors (e.g., AO) not included; retrospective data	CUD risk factors contribute to MDD specifically in high-risk individuals	⊕⊕⊖⊖low

Young-Wolff et al. 2020	196,022 females (11,681 prenatal CU, 184,341 no prenatal CU)	Pregnant females, completed self-report questionnaire on prenatal SU & urine toxicology test at first prenatal visit	MDD, anxiety, trauma	**Prenatal CU:** ↑ maternal MDD (10.6% vs 4.3%**); **Maternal MDD:** ↑ CU (AOR 2.25, CI 2.11–2.41)	CU screening limited to pregnant females at 8 weeks' gestation	MDD associated w/ CU in pregnant females	⊕⊖⊖⊖ very low

Note. AOR = adjusted odds ratio; AO = age of onset; AU = alcohol use; AUD = alcohol use disorder; BD = Bipolar Disorder; BD-I = Bipolar Disorder – Type I; BD-II = Bipolar Disorder – Type II; BD-NOS = Bipolar Disorder – Not Otherwise Specified; BPRS = Brief Psychiatric Rating Scale; CA = cannabis abuse; CD = cannabis dependence; CGI-BP = Clinical Global Impressions Scale for use in BP; CI = confidence interval; CNS = Central Nervous System; COWAT = Controlled Oral Word Association Test; ctl = control; CVLT = California Verbal Learning Test; CU = cannabis use; CUD = cannabis use disorder; DUB = Duration of Untreated Bipolar Disorder; DZ = dizygotic; FAST = Functioning Assessment Short Test; FUP = follow-up; GAF = Global Assessment of Functioning; HD = hard drugs; HDRS = Hamilton Depression Rating Scale; HR = hazard ratio; IDS = Inventory of Depressive Symptomatology; LT = lifetime; MADRS = Montgomery–Asberg Depression Rating Scale; MDD = Major Depressive Disorder; MDE = Major Depressive Episode; MZ = monozygotic; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions; OR = odds ratio; OTC = over-the-counter; PANSS = Positive and Negative Syndrome Scale; PD = Personality Disorder; POMS = Profile of Mood States; PR = Prevalence Ratio; PY = past-year; QoL = quality of life; RC = regression coefficients; SCL-90-R = Symptom Checklist 90-Revised; SHR = subhazard ratio; SU = substance use; SUD = substance use disorders; sxs = symptoms; SZ = schizophrenia; WAIS-R = Wechsler Adult Intelligence Test-Revised; WCST = Wisconsin Card Sorting Test; YMRS = Young Mania Rating Scale; yrs = years; *p < 0.05; **p < 0.01; ***p < 0.001.

Supplementary Table IV. Characteristics of Included Treatment Response Study with GRADE Rating

Study	# Subjects	Inclusion Criteria	Main Drug/Treatment	Comparator Treatment(s)	Placebo Treatment	Main Outcomes	Main Results, OR (95% CI)	Limitations	Conclusion	GRADE Rating
Major Depressive Disorder (MDD)										
Cornelius, 2010	36 placebo group (23 males, 13 females), 34 fluoxetine group (20 males, 14 females)	14-25 yrs, CUD+MDD, current CU (use w/in prior 30 days), baseline HAM-D score $\geq$ 15	Fluoxetine (10mg increased to 20mg at 2-weeks) w/ CBT & MET	-	Placebo	HAM-D, BDI, AU, CU	**Fluoxetine vs placebo:** no difference on BDI or CUD (both groups improved on BDI)	Moderate sample size, restricted age group	Fluoxetine did not demonstrate greater efficacy vs placebo for treating MDD or CU sxs	⊕⊕⊕⊖moderate

Note. AU = alcohol use; BDI = Beck Depressive Inventory; CBT = Cognitive Behavioral Therapy; CD = cannabis dependence; CU = cannabis use; CUD = cannabis use disorder; HAM-D = Hamilton Rating Scale for Depression; MDD = Major Depressive Disorder; MET = Motivational Enhancement Therapy; sxs = symptoms; yrs = years.

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	~~X~~Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	~~X~~Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	~~X~~Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	~~X~~Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	~~X~~Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	~~X~~Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	~~X~~Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes~~X~~
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes~~X~~
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes~~x~~
OTHER			
Funding	11	Specify the primary source of funding for the review.	~~NA~~Not applicable
Registration	12	Provide the register name and registration number.	~~NA~~Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	S32
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P9-20
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	S Table III
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	S Table III
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P9, Table I
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	S Table III
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P8
Study characteristics	17	Cite each included study and present its characteristics.	S Ttable III, P9-20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	S Ttable III
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	S Ttable III
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9-20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not done
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table I: Summary of ~~fondings~~Findings ~~table~~
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P9-20
	23b	Discuss any limitations of the evidence included in the review.	P23-24
	23c	Discuss any limitations of the review processes used.	P24
	23d	Discuss implications of the results for practice, policy, and future research.	P22-23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	A protocol was not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	COI provided
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	S Table III

PRISMA 2020 Checklist

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