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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

Rapport du groupe de travail du Réseau canadien pour le traitement de l'humeur et de l'anxiété (CANMAT): une revue systématique et des recommandations à l'égard de l'utilisation du cannabis dans le trouble bipolaire et le trouble dépressif majeur

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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 on mood disorders.

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Objective: The purpose of this task force report is to examine the association between cannabis use and incidence, presentation, course and treatment of bipolar disorder and major depressive disorder, and the treatment of comorbid cannabis use disorder.

Methods: We conducted a systematic literature review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searching PubMed, Embase, PsycINFO, CINAHL and Cochrane Central Register of Controlled Trials from inception to October 2020 focusing on cannabis use and bipolar disorder or major depressive disorder, and treatment of comorbid cannabis use disorder. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to evaluate the quality of evidence and clinical considerations were integrated to generate Canadian Network for Mood and Anxiety Treatments recommendations.

Results: Of 12,691 publications, 56 met the criteria: 23 on bipolar disorder, 21 on major depressive disorder, 11 on both diagnoses and 1 on treatment of comorbid cannabis use disorder and major depressive disorder. Of 2,479,640 participants, 12,502 were comparison participants, 73,891 had bipolar disorder and 408,223 major depressive disorder without cannabis use. Of those with cannabis use, 2,761 had bipolar disorder and 5,044 major depressive disorder. The lifetime prevalence of cannabis use was 52%–71% and 6%–50% in bipolar disorder and major depressive disorder, respectively. Cannabis use was associated with worsening course and symptoms of both mood disorders, with more consistent associations in bipolar disorder than major depressive disorder: increased severity of depressive, manic and psychotic symptoms in bipolar disorder and depressive symptoms in major depressive disorder. Cannabis use was associated with increased suicidality and decreased functioning in both bipolar disorder and major depressive disorder. Treatment of comorbid cannabis use disorder and major depressive disorder did not show significant results.

Conclusion: The data indicate that cannabis use is associated with worsened course and functioning of bipolar disorder and major depressive disorder. Future studies should include more accurate determinations of type, amount and frequency of cannabis use and select comparison groups which allow to control for underlying common factors.

Abrègè

Contexte: Étant donné l'acceptabilité et la légalisation croissantes du cannabis dans certaines administrations, les cliniciens doivent améliorer leur compréhension de l'effet de l'utilisation du cannabis (UC) sur les troubles de l'humeur.

Objectif: Le rapport de ce groupe de travail vise à examiner l'association entre l'UC et l'incidence, la présentation, le cours et le traitement du trouble bipolaire (TB) et du trouble dépressif majeur (TDM), et le traitement du trouble d'utilisation du cannabis (TUC) comorbide.

Méthodes: Nous avons mené une revue systématique de la littérature à l'aide des lignes directrices PRISMA et avons cherché dans PUBMED, EMBASE, PsycINFO, CINAHL et le registre central Cochrane des essais contrôlés du début à octobre 2020 en mettant l'accent sur l'UC et le TB ou le TDM, et le traitement du TUC comorbide. L'approche GRADE a servi à évaluer la qualité des données probantes et les considérations cliniques ont été intégrées pour générer des recommandations CANMAT.

Résultats: Sur les 12 691 publications, 56 satisfaisaient aux critères : 23 sur le TB, 21 sur le TDM, 11 sur les deux diagnostics, et une sur le traitement du TUC et du TDM comorbides. Sur les 2 479 640 participants, 12 502 étaient des participants de comparaison, 73 891 souffraient du TB et 408 223 du TDM sans UC. Sur ceux ayant l'UC, 2 761 souffraient du TB et 5 044, du TDM. La prévalence de durée de vie de l'UC était de 52–71% et de 6–50% dans le TB et le TDM, respectivement. L'UC était associée à un cours et à des symptômes aggravés des deux troubles de l'humeur, les associations étant plus constantes dans le TB que dans le TDM : la gravité des symptômes dépressifs, maniaques et psychotiques était accrue dans le TB et les symptômes dépressifs, dans le TDM. L'UC était associée à une suicidabilité accrue et à un fonctionnement diminué tant dans le TB que le TDM. Le traitement du TUC et du TDM comorbides n'a pas démontré de résultats significatifs.

Conclusion: Les données indiquent que l'UC est associée avec un cours et un fonctionnement aggravés du TB et du TDM. Les futures études devraient comprendre des déterminations plus précises du type, de la quantité et de la fréquence de l'UC et choisir des groupes de comparaison qui permettent de contrôler les facteurs communs sous-jacents.

Keywords

Cannabis, Canadian Network for Mood and Anxiety Treatments, systematic reviews, bipolar disorder, major depressive disorder, substance use disorders, cannabinoids, comorbidity, GRADE, evidence-based medicine

Introduction

Bipolar disorder (BD) and major depressive disorder (MDD) are common conditions, with a Canadian lifetime prevalence of 11.3% for major depressive episodes globally[1] and 0.87% for BD-I and 0.57% for BD-II.[2] Interactions between cannabis use (CU) and mood disorders are complex: 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 and 1992 and 2001 and 2002 (4.4%–9.5%) and increased in more recent studies.[5] In Europe, reported lifetime CU (LT-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 assess the association between CU and BD and/or MDD, with the aim of providing recommendations regarding CU for people with mood disorders. To this end, we sought to review all randomized controlled trials (RCTs), observational, cross-sectional and case–control studies that reported on CU and BD and/or MDD, as well as RCTs of the treatment of comorbid cannabis use disorder (CUD) and BD or MDD.

Methods

Data Sources

The PRISMA guidelines[7] were followed to conduct a systematic review of the impact of CU in individuals diagnosed with either BD or MDD (see online Supplemental Material for PRIMSA checklists). Specifically, we assessed the association between CU and 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. The results are discussed using CANMAT's question–answer format to enhance readability. 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. In addition, we manually searched reference lists of published reviews for relevant articles. See Figure 1 for PRISMA flow diagram.

Study Selection

We included all original clinical observational studies and trials, excluding case studies, reporting on the use of cannabis in BD and/or MDD. Definitions of use, dependence and abuse varied among publications. Studies that used mixed populations (e.g., 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) that was either compared to a different population or was followed over time. Articles written in languages other than English or French were excluded. In the

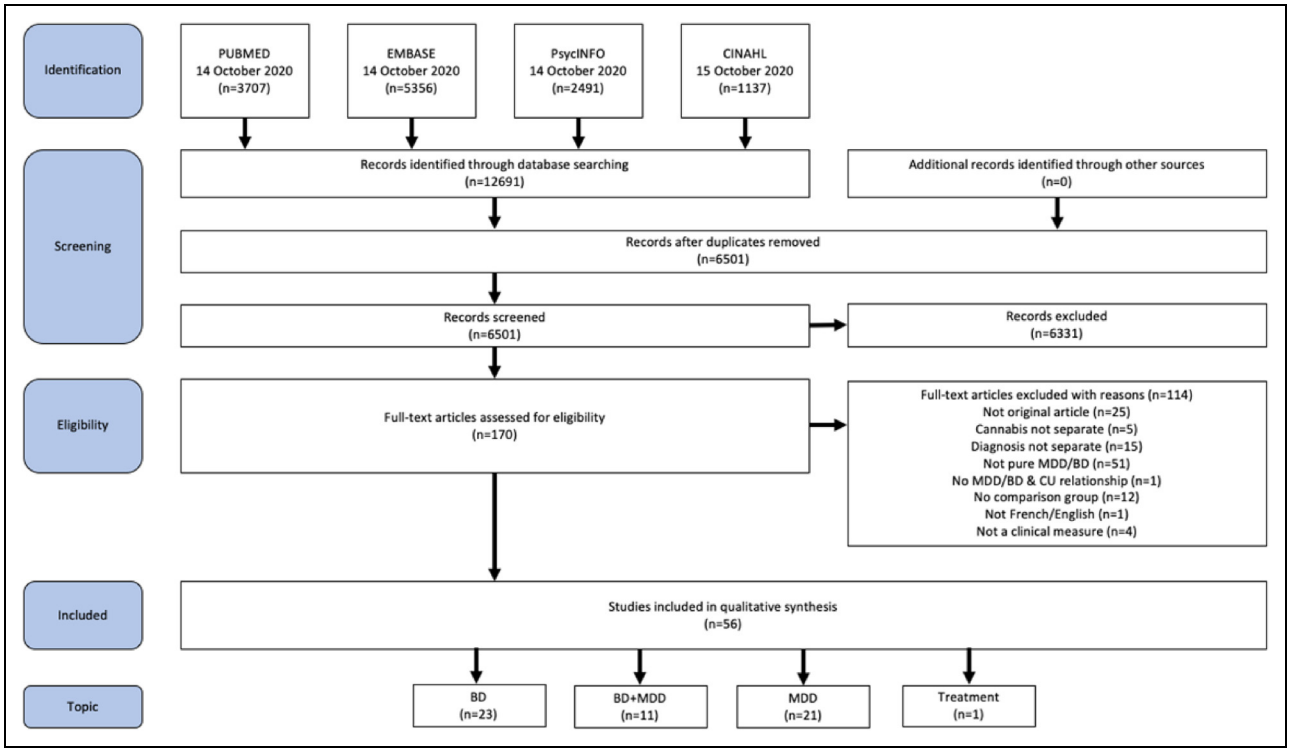

Figure 1. PRISMA flowchart.

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

Table 1. Certainty 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, i.e., 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, i.e., the true effect may be substantially different from the estimate of the effect.
Very Low	Very low confidence in the effect estimate, i.e., the true effect is probably substantially different from the estimate of effect.

Analysis of Quality of Evidence Rating and Strength of Recommendations

Two authors (VT and GB) independently assessed study quality (Supplementary Tables S3 and S4) using validated questionnaires[8,9] and resolved discrepancies through discussion. Certainty of evidence was evaluated using the GRADE framework,[10] which rates confidence in summary estimates as high, moderate, low and very low (Table 1) based on the included studies' risks of bias, directness of evidence, unexplained heterogeneity, imprecision and risk of publication bias.[11] Table 2 provides a summary of findings as well as an explanation of the major factors contributing to a lack of certainty. Due to the heterogeneity of the studies and their inconsistent results, we chose not to provide a certainty rating for each outcome. Global ratings can be found in Table 3. CANMAT guidelines integrate clinical considerations (based on the clinical experience of experts in real-world clinical settings) to the level of evidence to arrive at final recommendations. Thus, CANMAT recommendations may not always align directly with the level or strength of

Table 2. Summary of Findings for Main Outcomes in BD and MDD.

	# of Studies		Risk with CU		Explanation of potential source of lack of certainty[a]	
Outcomes	BD	MDD	BD	MDD	BD	MDD
Prevalence of CU/CUD						
CU lifetime prevalence	13	5	52%–71%	6%–50%	Varying definition of CU	Varying definition of CU
CUD lifetime prevalence	4	6	3.3%–7.2%	2.1%–6.3%	Varying definitions of CUD	Varying definitions of CUD
SUD Comorbidities						
Nicotine	5	1	↑	↑	Varying definition of nicotine use	Varying definition of nicotine use
AUD	7	1	↑	↑	Order of onset of comorbid conditions not assessed	Order of onset of comorbid conditions not assessed
SUD	7	2	↑	↑	Confounds not controlled for	Risk of bias: only diagnosed SUDs assessed
Severity and Symptoms						
Phenomenology	10	5	↑ mania and mixed episodes ↑ rapid cycling ↑ psychotic features	↑ depressive symptoms ↔ episodes	Varying definition of CU	Inconsistency of results
Illness Course						
Age of onset	8	4	↓	↔	Retrospective study design	Retrospective study design
Remission/relapse	1	0	↓ remission / ↑ recurrence	-	Lack of evidence: only one study	Lack of evidence: only 1 study
Suicidality	6	3	↑ attempt and completion	↔ ideation and attempt	Retrospective study design	Retrospective study design
Functioning/Cognition						
Functioning	7	3	↓	↓ or ↔	Confounds not controlled for	Inconsistency of results
Cognition	2	0	↑ or ↔	-	Inconsistency of results	-
Treatments						
Pharmacological	-	1	-	↔	-	Lack of evidence: only 1 study

[a]Given that the evidence summary data was not adequate to support specific recommendations, primarily due to inconsistency of results and indirectness of evidence, certainty of evidence statements for each outcome are not proposed.

AUD: alcohol use disorder; BD: bipolar disorder; CU: cannabis use; CUD: cannabis use disorder, MDD: major depressive disorder; SUD: substance use disorder.

Table 3. Canadian Network for Mood and Anxiety Treatments (CANMAT) Recommendations for Cannabis Use (CU) 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

evidence. These recommendations are reached following an iterative process of exchange of opinion and discussion until a general consensus is reached (Table 3).

Findings and Discussion

Study Inclusion and Characteristics

Our database review yielded 12,691 potentially relevant articles. After excluding duplicates, 6,501 titles remained (see online Supplemental Material for detailed search strategy). After screening the abstracts, a further 6,331 articles were excluded, leaving 170 eligible articles: of these, 114 studies were excluded after reading the full text. The remaining 56 studies were independently evaluated by two of the authors (VT and GB) for data related to patients' demographic information (age, sex), diagnosis, number of patients in each study, inclusion and exclusion criteria and outcome measures. A senior investigator (SB) resolved disagreements among reviewers. See Supplementary Tables S5 and S6 for detailed 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 of whom 2,761 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 contained 1,977,219 participants. A meta-analysis was not deemed appropriate given the heterogeneity of the studies retrieved.

Independent study quality ratings demonstrated excellent agreement across raters for total scores (intra-class correlation coefficient [ICC], 0.98), with consensus reached for 100% of discrepancies. Mean quality scores were just above average (8.1 on a 14-point scale). See Supplementary Tables S3 and S4. However, given that the evidence summary data was not adequate to support specific recommendations, primarily due to inconsistency of results and indirectness of evidence, certainty of evidence statements for each outcome will not be proposed.

What is the Prevalence of CU and CUD in Individuals With BD or MDD?

LT-CU was high in BD, ranging from half[12,13] to two-thirds[14] using cannabis over their lifetime. This rate of LT-CU is as much as sevenfold higher in individuals with BD compared to participants without BD (71.3%, OR 6.8, CI, 5.41 to 8.52),[14] where cross-sectional prevalence rates of CU varied from a low of 3.3%[15–17] to a high of approximately 18%.[18,19]

CUD was also increased in those with BD when compared to the general population (7.2% vs. 1.2%, respectively),[20] ranging from 7.2% to 30%.[14,20–22] Prevalence rates of CU, cannabis abuse (CA) and cannabis dependence (CD) are generally higher in BD-I (CD: 23.6%, CA: 9.7%, CUD: 11.8%) versus BD-II (CD: 10.2%, CD: 4.9%, CUD: 5.7%).[23]

Other factors may influence the prevalence of CU in BD. For example, the use of cigarettes was associated with a higher prevalence of CU compared to non-smokers (55.7% vs. 18.1%)[24] and heavy cigarette smokers used cannabis more often each week.[25] In the only study evaluating CU and the risk of violence in individuals with BD, the prevalence of CU in the 30 days prior to hospitalization was 27.0%.[26]

CU prevalence in MDD ranged between 7.5%[27] and 18.9%.[28] This compared to a population rate of 8.7% yielding an adjusted odds ratio (AOR) of 2.17 (CI, 1.92 to 2.45).[28] The prevalence range for CUD varied from 2.0% to 16.3%,[15,16,21,23,27] representing at least a fourfold increase of CUD prevalence in MDD (2.0%) compared to a population rate of 0.5%.[15] As in the general population, CUD prevalence was higher in men than in women (MDD: 3.7% vs. 1.0%, general population: 0.8% vs. 0.2%).[15] Individuals with MDD had lower levels of CU than those with BD, with 8.9% of individuals using cannabis in the past year and with 39.4% meeting the criteria for CUD (compared to 14.7% and 51.8%, respectively, in BD $P = 0.05$).[22] 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 to 3.37) and determined that the best-fitting model is that of CUD leading to MDD.[29] Further, MDD during pregnancy was associated with a greater risk of using cannabis (12.7% vs. 3.7%; OR 3.8, CI. 2.8 to 5.0).[30] Overall, MDD is associated with a twofold likelihood of CU and a fourfold likelihood of CUD.

The inconsistencies in reported prevalence rates of both mood disorders likely reflect differences in the historical timeframe being assessed and the population being examined, both of which varied considerably across studies included in the present review.

Is CU Associated With Increased use of Other Substances in Individuals With Mood Disorder?

Daily tobacco use was 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%)[31]; however, another study did not find such differences.[32] Adolescents with BD and CU also had high rates of cigarette use (49%) and lifetime nicotine dependence (70%).[25] In BD, CUD was associated with a fourfold risk of nicotine dependence (3.83, CI, 2.21 to 6.66)[33] and increased odds of nicotine dependence itself (2.31 to 3.8).[20,34] There was a gradient of prevalence of daily tobacco use ranging from 46.9% in individuals with BD without CU to 73.4% in those with intermediate levels of CU and 83.9% in those with CUD ($P = 0.001$).[35] This may represent a bidirectional relationship since, in individuals with BD, CU was significantly more frequent (55.7%) in those with nicotine use compared to those without nicotine use (18.1%),[24] and heavy smokers with BD used more cannabis than those who did not smoke or were light smokers.[25]

Alcohol use was more common in individuals with BD who use cannabis (12-month prevalence: 55.6%) compared to those who do not (23.7%).[36] CUD in BD was correlated with a higher risk of alcohol misuse ($P < 0.001$).[37] Alcohol use disorder (AUD) was also significantly higher in those with BD and CUD compared to those without CUD.[32–34] Although not statistically significant, the prevalence of AUD in individuals with BD increased 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.[35] Only one study found no association between CU and alcohol use or dependence.[31]

BD with comorbid CU[36] was correlated with increased frequency of substance use disorder (SUD). Increasing intensity of SUD was associated with CU along a gradient ranging from 3.1% in those without CU, 17.2% in those with intermediate CU, and 39.4% in those with CUD ($P = 0.001$).[35] SUD was significantly more frequent (25.5%–71.9%) in those with CUD than in those without CUD (3.2%–19%).[32,33] The same study that failed to find a difference in AUD in individuals with BD and CU also failed to find a significant association between CU and use or dependence of cocaine or amphetamines.[31] An interesting finding suggested that the prevalence of AUD and other SUDs varies with an order of onset of BD and CU.[13] When CU preceded the emergence of BD, alcohol abuse was less frequent than when BD onset preceded CU onset.[13] Curiously, the opposite was true for dependence, which was more common in those individuals with BD in whom CU preceded BD onset.[13] Other SUDs were more common in those who used cannabis before BD onset ($P < 0.001$).[13]

Individuals with MDD and CUD were significantly more likely to smoke daily (67.0%) compared to those without comorbid CUD (13.0%).[38] They were also more likely to misuse alcohol (43.0%) versus those without CUD (3.0%).[38] As in BD, MDD was associated with a higher prevalence of SUDs in those with CU (3.0%–43.14%) compared to those without (0.0%–14.29%).[27,38] This prevalence was even higher (59.54%)[27] in those with MDD and comorbid CUD.[38]

CU appears to be associated with the use of various substances, suggesting that the propensity for use and/or dependence may be an underlying factor and, in certain cases, may correlate with adverse outcomes of the pathology resulting from either direct or indirect causes.

Is CU Associated With Alterations in the Symptomatic Manifestations of BD or MDD?

CU was associated with differences in severity, type and frequency of episodes in BD, including an increased likelihood of mixed episodes[13,14] (OR 1.52, CI, 1.02 to 2.27).[14] Continued CU was associated with increased severity of manic symptoms[36,39] and global illness severity.[26,36] Individuals whose onset of BD occurred before the beginning of CU had an increase in subsyndromal manic symptoms compared to those without CU.[13] Increased severity of both depressive[40] and psychotic symptoms[34,36] was seen in individuals with BD and CU. Increased severity of manic symptoms was also observed, and to a greater extent with the added use of nicotine.[25] Nicotine use was correlated with adverse outcomes in BD,[41] although such use may signal the presence of other comorbidities associated with a poor prognosis in BD,[42] such as attention deficit hyperactivity disorder (ADHD).[42]

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.[18] In the same study of individuals with BD, CU at a specific time point was also associated with a subsequent decrease in symptoms of anxiety, tension, depression and an increase in "vigor".[18] In contrast, another study found an increase in depressive symptoms, in addition to the increase in positive affect and manic symptoms.[43] It is possible that individuals may more easily identify the positive effects of CU on mood rather than its negative impact.

In MDD as in BD, CU was associated with an increase in illness severity.[26] A longitudinal study revealed correlations between the level of CU and an increase in the following depressive symptoms: anhedonia, weight changes, insomnia and hypersomnia and psychomotor agitation.[27] Another study found that CU in MDD was associated with increased negative symptoms.[44] Sex may influence the effects of CU in MDD; for example, occasional CU was associated with greater psychological distress in females,[45] while, in an adolescent population, anhedonia, psychomotor changes, guilt, low self-esteem and poor concentration were associated with CU in boys but not girls with MDD.[46] The effects of CU may vary with the manner of use since higher doses have been shown to depress and lower doses to enhance serotoninergic transmission, while acute administration of cannabis can increase dopamine release, and chronic use has been associated with blunting of dopaminergic responsivity.[47]

There are data suggesting that CU, particularly during vulnerable periods such as adolescence, can alter cerebral functioning and lead to changes in brain structure.[48] It is possible that the effects of CU may overlap or contribute to prominent mood symptoms (e.g., anhedonia and apathy), leading to their exacerbation or potentially confounding the diagnosis of BD or MDD.[48] In summary, what limited data exist suggest that CU is associated with a worsening of mood disorder symptoms. Furthermore, these associations appear more consistent and clearer in BD versus MDD.

Is CU Associated With Alterations of the Illness Course of BD or MDD?

CU was associated with an increased incidence of the first episode of BD.[49,50] The age of BD onset was earlier in cannabis users[19,51] by as much as 9 years,[19] and was also earlier in those who use higher quantities of cannabis (greater than 10 times during 1 month, lifetime) compared to those who use lower quantities (less than 10 times during 1 month, lifetime).[35] Similarly, CUD was also correlated with an earlier age of onset of BD.[14,20,32] Furthermore, individuals with BD and CUD tend to be younger.[34] 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.[52]

BD with CU was associated with more frequent rapid cycling[13]; this was also the case in BD with CU and a history of childhood abuse.[53] In the same vein, a history of LT-CU was associated with earlier hospitalization[54] and CUD with more frequent hospitalizations.[32] Finally, compared to BD without CU, BD with current CU was associated with an increased recurrence rate.[17] Reassuringly, in individuals with BD who cease CU, recurrence levels were comparable to those who had never used cannabis.[17]

CU in BD was associated with hypomania and mania, but not depression.[18] Individuals with BD and CU displayed increased severities of mania, hallucinations, delusions and overall illness at 1-year follow-up.[36] They also spent more time in manic and mixed episodes.[13] More frequent episodes,[20] mixed states,[14] manic episodes[32] and psychotic symptoms[34] were also more prevalent in BD with CUD. In contrast, Kvitland and colleagues noted that individuals with excessive CU 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.[12] In the same study, CU was not associated with the duration of untreated illness.[12] Elsewhere, in a population study, there was no increase in the incidence of BD over a period of 35 years in those with CU compared to those without CU, highlighting that further work needs to be done in this area.[55]

CU was associated with increased emergence of MDD in some studies,[49,50,56,57] but not in others.[27,55,58] Further, in a prospective study, both high and low frequency of CU before the age of 18 years were associated with an increased risk of developing MDD,[57] while cross-sectional studies identified an increased likelihood of depression in cannabis users[59,60] compared to nonusers, with greater odds in heavy users.[60] One study failed to find an effect of CU on the age of onset of MDD.[61]

Information about the effect of CU on the age of onset of MDD is more equivocal than in BD. Some preliminary data signal a higher prevalence of depression in cannabis users, in particular with heavy use.[59,60] Given the intruding effects of cannabis on neurotransmission,[47] CU may contribute to alterations not only in symptomatic manifestations but also in the disease course. Importantly, pre-clinical data suggests that CU quantity may differentially alter the substance's effects on mood disorder pathology, with low and high levels of CU having opposing effects on neurotransmission.[48] This may at least partially explain the variability in findings reported here. Further research is necessary to clarify this relationship.

Is CU Associated With an Increase of Suicidal Thoughts and Behaviours in MDD and BD?

Habitual CU by individuals with BD was associated with increased suicidal ideation[45] and attempts,[14,45] while current CU was correlated with increased suicidal completion (hazard ratio (HR) 1.86, CI, 1.15 to 2.99).[21] Recent CU was significantly correlated with an increase in lifetime suicide attempts.[52] CUD, as determined through registers of treatment for substance abuse, was not associated with increased mortality by suicide,[62] suggesting that treatment of CUD may have a beneficial effect. Occasional CU was linked with suicidal ideation and attempts specifically in women with BD (odds ratio (OR) 2.45, CI, 1.79 to 3.36).[45] In adolescents with BD, CU was correlated with increased odds of suicidality (AOR 1.74, CI, 1.28 to 2.35).[63] The combination of CU and childhood abuse in individuals with BD was also associated with increased likelihood of a suicide attempt.[53]

Adolescents with MDD and a history of CU were at a higher risk of suicide attempt in the past year (ORs 2.06–2.53, $P < 0.001$), with frequency of CU having no influence on the risk.[64] In a study of depression, early and frequent CU was significantly associated with MDD as well as suicidal ideation in both monozygotic and dizygotic twins.[59] In other studies of depression, no difference in suicidality was found in those with CU or CUD compared to those without CU,[27] or mortality from suicide was decreased in MDD with CUD,[62] leading the authors to speculate that CU as self-treatment may have alleviated distress and thus suicide. In this study, CUD was identified by registration in a treatment centre or use of pharmacological treatments for SUDs; thus, an equally likely hypothesis may be that treatment of CUD offsets its risks.

Globally, CU is associated with increased suicidality in both BD and MDD; although the literature in MDD is sparse and less consistent than that in BD. These associations may represent a correlation of CU with suicidality as revealed in a recent meta-analysis of adolescents and young adults,[65] but may also reflect the deleterious effects of cannabis on mood disorders or underlying factors that may contribute to both CU and suicidality.

Is CU Associated With Alterations of Functioning in BD and MDD?

BD with CU was associated with decreased global functioning[26] and CUD with increased disability (OR 2.19, CI, 1.45 to 3.31).[14] A history of CU in individuals with BD was correlated with increased work impairment and decreased likelihood of living with a partner.[17] 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 were less likely to have a relationship.[36] There was an association with decreased life satisfaction, but this effect seems to be mediated by other SUDs.[36] Continued CU was associated with both elevated mood and decreased global functioning at 1-year follow-up.[39] Sex may also differentially affect functioning; for example, CU was associated with greater "financial issues" and decreased quality of life in women but not men.[54] Finally, the combination of CA or CD with heavy cigarette use was associated with decreased functioning in adolescents with BD.[25]

MDD with CU was associated with decreased functioning in some studies[26,64] but not others.[27]

In sum, in both BD and MDD, CU and CUD are associated with greater disability and decreased functioning. There is evidence to suggest that cannabis in itself is associated with poorer psychosocial functioning, which can vary by cumulative cannabis exposure.[66] It is unclear whether the associations highlighted in the reviewed studies represent additive effects of declines in psychosocial functioning related to mood disorders, CU or interactions of both. It is possible that other factors common to both BD, MDD and CU/CUD underly the observed associations.

Is CU Associated With Altered Cognition in BD and MDD?

Only two studies addressed the effect of CU on cognition in BD[31,37] and none in MDD. Both studies showed improved cognitive performance in certain dimensions. Such results are counterintuitive, however, both studies had serious methodological issues, including small sample sizes as well as the observation that very few of the participants were current users of cannabis. The paucity of data on this topic renders speculation regarding the associations between CU and cognition in mood disorders premature.

Is CU Associated With Altered Response to Treatment in BD and MDD?

We found few data that directly addressed the relationship between CU and response to treatment, although it can be argued that a worsened course of illness may be related to diminished treatment effect.[17,32] It is also possible that the worsened illness course with CU may in effect reduce treatment response by decreasing adherence.[36]

Are There Efficacious Treatments for Comorbid CU and Mood Disorders?

After careful review, we found no studies meeting our criteria that examined the treatment of comorbid BD and CUD. We identified one RCT in participants with both CUD and MDD (n = 70) in which cognitive behavioural therapy (CBT) with add-on fluoxetine was compared to placebo.[67] Although both groups improved in both depression and substance use outcomes, there was no significant difference between treatment groups.

Recommendations

Despite average study quality scores, GRADE ratings for all outcomes, other than prevalence, were generally low, reflecting the variability of results. However, considering the consistent signal for the deleterious effects of cannabis in BD and based on the clinical experience of experts, CANMAT provides a strong recommendation against CU use in this disorder. On the other hand, the inconsistency of the signal regarding the effects of cannabis in MDD contributes to a qualified level of recommendation against its use in this disorder (Table 3).

Given the 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,[68] and more precise questioning can improve the estimation of quantity and type of CU.[69] Patients often have difficulty being precise about quantity and type of cannabis, and the use of images may improve reporting accuracy.[69,70] Clinicians may also adapt questions to the needs of their practice. Although there is limited knowledge about the differential effects of cannabis constituents, documentation of the changes in CU may allow clinicians and patients 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. Content – amount and concentration of different cannabis constituents;
3. Context of use – physical, social and psychological context of use, as well as use of other substances. Examples of contextual elements are 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 outcomes. The growing use of cannabis during pregnancy is an emerging phenomenon[71] and is associated with the presence of MDD.[30,72] The clinician should communicate the preliminary nature of data on the potential impact of CU on the fetus and the signal of possible harmful effects.[73–75] The cannabis hyperemesis syndrome may also complicate the clinical presentation in pregnancy as well as in other situations.[76] Should the patient desire to reduce or stop CU, psychosocial interventions and in particular motivational enhancement therapy and CBT have been associated with a reduction in use.[77]

Conclusion

This review summarizes the literature on the impact of CU in BD and MDD. Importantly, all studies included were required to meet diagnostic criteria for either MDD or BD rather than proxies of these diagnoses. The resulting findings are thus more applicable to clinical populations. Although it is clear that more data are necessary, findings from the studies reviewed point to potential harm in BD and a more modest deleterious effect in MDD. In BD, CU and in particular heavy CU, may be associated with a worsened illness course, decreased functionality and increased mortality through suicide. The data are less consistent in MDD; nevertheless, age of MDD onset does not appear to be earlier in those who use cannabis 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. 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 firmly caution against the use of cannabis in the case of BD and with some reservations in the case of MDD.

Limitations

Despite the greater consistency of results concerning CU in BD when compared to CU in 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, with different cut-off points to determine frequency of use, and often relied on retrospective recall. Evolving definitions of use, dependence and abuse further contributed to the variability of results. Moreover, studies sometimes contrasted LT-CU with no use, grouping heterogeneous patterns of use together. In addition, the content of tetrahydrocannabinol (THC) and cannabidiol (CBD) were not determined, although THC is considered to mediate the psychoactive effect of cannabis[78] and thus may potentially mediate its more harmful effects. Very few studies confirmed the use of cannabis through quantitative methods such as urine concentrations. 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. 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.[79] In turn, conditions comorbid with MDD or BD (e.g., ADHD) may themselves predispose the individual to both CU and a poorer outcome. Other factors, such as early adversity and childhood trauma, may also contribute to both CU and worsened trajectories. It is also possible, and in some cases likely, that some of the associations observed are related to common underlying causes, both biological and psychosocial, that predispose the individual to MDD or BD, as well as to CU or CUD.

While it is necessary for future studies to address the shortcomings 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 pleiotropic actions on multiple biological systems.

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Supplemental material

Supplemental material for this article is available online.

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