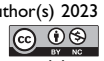
Canadian Psychiatric Association
Association des psychiatres du Canada

Systematic Review

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
2023, Vol. 68(8) 557-571



DOI: 10.1177/07067437231183525
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Cannabidiol as a Harm Reduction Strategy for People Who Use Drugs: A Rapid Review

Le cannabidiol comme stratégie de réduction des méfaits pour les personnes qui utilisent des drogues : une revue rapide et des aperçus cliniques

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Abstract

Objective: The drug poisoning crisis throughout North America necessitates novel harm reduction approaches. Emerging evidence suggests that cannabidiol (CBD) may have some utility as a harm reduction modality for those with problematic substance use. This rapid review aimed to synthesize available evidence on CBD as a potential harm reduction tool for people who use drugs while providing clinical and research insights.

Method: A systematic search in EMBASE, MEDLINE, CENTRAL, and CINAHL was completed in July 2022. For inclusion, studies had to meet the following criteria: (1) drawn from an adult population of people who use drugs; (2) investigates CBD as an intervention for problematic substance use or harm reduction–related outcomes; (3) be published after the year 2000 and in English; and (4) be primary research or a review article. A narrative synthesis was used to group outcomes relevant to harm reduction and provide clinical and research insights.

Results: We screened 3,134 records, of which 27 studies (5 randomized trials) were included. The evidence remains limited, but available studies support the potential utility of CBD to reduce drug-induced craving and anxiety in opioid use disorder. There were low-quality studies suggesting that CBD may improve mood and general well-being of people who use drugs. Evidence suggests that CBD monotherapy may not be an adequate harm reduction strategy for problematic substance use but rather an adjunct to the standard of care.

Conclusion: Low-quality evidence suggests that CBD may reduce drug cravings and other addiction-related symptoms and that CBD may have utility as an adjunct harm reduction strategy for people who use drugs. However, there is a significant need for more research that accurately reflects CBD dosing and administration regimens used in a real-world context.

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Résumé

Objectif : La crise d'empoisonnement à la drogue dans toute l'Amérique du Nord nécessite de nouvelles approches de réduction des méfaits. Les données probantes émergentes suggèrent que le cannabidiol (CBD) peut être d'une certaine utilité comme modalité de réduction des méfaits aux personnes ayant une utilisation de drogues problématique. La présente revue rapide visait à synthétiser les données probantes disponibles sur le CBD à titre d'outil potentiel de réduction des méfaits pour les personnes qui utilisent des drogues tout en procurant des aperçus cliniques et de recherche.

Méthode : Une recherche systématique dans EMBASE, MEDLINE, CENTRAL, et CINAHL a été effectuée en juillet 2022. Pour être incluses, les études devaient satisfaire aux critères suivants : (1) tirées d'une population adulte de personnes utilisant des drogues; (2) recherche le CBD comme intervention pour l'usage problématique de substances ou des résultats liés à la réduction des méfaits; (3) publiés après l'an 2000 en anglais; et (4) recherche primaire ou article de synthèse. Une synthèse narrative a servi à grouper les résultats liés à la réduction des méfaits et offrant des aperçus de recherche.

Résultats : Nous avons examiné 3,134 dossiers, dont 27 études (5 essais randomisés) ont été incluses. Les données probantes demeurent limitées mais les études disponibles soutiennent l'utilité potentielle du CBD pour réduire l'état de manque induit par la drogue et l'anxiété dans les troubles liés à l'utilisation d'opioïdes. Des études de faible qualité suggéraient que le CBD peut améliorer l'humeur et le bien-être général des personnes qui utilisent des drogues. Les données probantes suggèrent que la monothérapie au CBD n'est peut-être pas une stratégie adéquate de réduction des méfaits pour l'utilisation de substances problématique, mais plutôt un complément à la norme de soins.

Conclusion : Des données probantes de faible qualité suggèrent que le CBD peut réduire l'état de manque de drogues et d'autres symptômes liés à la dépendance et que le CBD peut avoir une utilité comme complément d'une stratégie de réduction des méfaits pour les personnes qui utilisent des drogues. Cependant, il y a un besoin significatif de plus de recherche qui reflète précisément le dosage et le régime d'administration utilisés en situation réelle.

Keywords

cannabidiol, CBD, harm reduction, addiction, drug craving, drug substitution

Introduction

The worsening drug poisoning crisis throughout the USA and Canada has necessitated exploring novel harm reduction approaches. There is growing evidence that cannabis may be a promising harm reduction strategy for people who use drugs (PWUD). Cannabis use has been associated with reducing the use of or substituting other drugs.[1-4] Additionally, it has been associated with alleviating symptoms such as nausea, anxiety, and insomnia, commonly present in substance use disorders.[5,6] Recent cohort studies revealed that individuals at high risk of overdose commonly substitute cannabis for more harmful drugs (e.g., stimulants and opioids) as a harm reduction strategy.[7] Further, individuals reporting difficulty accessing addiction treatment or who used substances with limited treatment options, such as methamphetamines, had a higher likelihood of using cannabis as a harm reduction strategy.[8] These findings highlight the potential harm-reducing impacts of cannabis among PWUD.

The 2 primary cannabinoids in cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). The vast majority of evidence for cannabis as a harm reduction strategy is focused on THC-dominant products or does not distinguish between cannabinoids. However, preclinical and emerging clinical evidence has shown that CBD may act as an anxiolytic, antidepressant, and antipsychotic, as well as having procognitive and neuroprotective effects.[9] Given the close connection that problematic substance use has on mood and cognition,[10,11] there may be a role for CBD in problematic substance use. Further, preclinical and some clinical evidence suggests that CBD may have a role in regulating reinforcement, motivation, and withdrawal-related effects of various addictive substances.[9]

CBD is non-intoxicating and has a significantly reduced side effect profile compared to THC.[12,13] The lower risk of abuse and severe adverse psychiatric events,[14,15] such as psychosis, is particularly desirable as the negative impact of high-dose THC is a common concern regarding the use of cannabis within this population. As such, there has been growing interest in how CBD, specifically, can be utilized as a harm reduction tool.

The COVID-19 pandemic and measures meant to mitigate the pandemic, such as self-isolation and border closures, worsened the opioid poisoning crisis by disrupting the drug supply and increasing the number of people using drugs in isolation.[16,17] Between April and December 2020, 5,148 apparent opioid toxicity deaths occurred in Canada alone, representing an 89% increase from the same time frame in 2019.[18] This highlights the apparent need to urgently scale up existing evidence-based responses to overdose, such as opioid agonist therapies for people living with opioid use disorders and supervised drug consumption sites, as well as develop and evaluate innovative harm reduction strategies. Although there is widespread popular interest in the therapeutic use of CBD, there remains a paucity of information on the potential utility of CBD for harm reduction in PWUD. Thus, this rapid review sought to synthesize

available evidence on CBD as a harm reduction modality for PWUD. We aimed to (1) assess the potential benefits and risks of CBD for PWUD related to harm reduction and (2) assess gaps in research.

Method

The rapid review process was guided by the methodology presented by the Cochrane Rapid Reviews Methods Group[19] and PRISMA reporting guidelines.[20] Research aims, eligibility, and search strategies were collaboratively agreed upon by a multidisciplinary group of authors, including clinicians, academic researchers, and community harm reduction counsellors. A systematic search in EMBASE, MEDLINE, CENTRAL, and CINAHL was completed capturing literature from 1 January 2000 to 10 March 2023. Search terms for CBD were combined with search terms for harm reduction, substance use disorder, or substance use treatment using Boolean operators. Complete search strategies are presented in Supplemental Appendix 1.

Inclusion Criteria and Study Selection

For inclusion, studies had to meet the following criteria: (1) be drawn from an adult population of PWUD, (2) evaluates CBD as an intervention for problematic substance use or harm reduction–related outcomes, (3) be published after the year 2000 and in English, and (4) be primary research or a review article. Given the dearth of literature on this topic, there were no restrictions on study design. Non-peer-reviewed articles (e.g., op-eds, commentaries, and editorials) and articles investigating cannabis use without specific investigation or discussion of CBD were excluded. Author LL assessed study eligibility, while KN and CM verified the results.

Data Extraction and Synthesis

Data were extracted and synthesized by LL, with verification by KN and CM. A narrative synthesis was used to group outcomes into themes and considerations relevant to harm reduction by LL and CM. Following this, all research team members provided feedback to produce the final results.

Assessment of Bias

The quality of systematic reviews was assessed by AMSTAR.[21] The quality of narrative reviews was assessed using SANRA.[22] The quality of randomized controlled trials (RCTs) was assessed using RoB2.[23]

Results

We identified 3,968 potential records from databases. After the removal of duplicates, 3,134 studies were screened, from which 129 full-text documents were reviewed, and 27 studies were included (Figure 1).[9,24-46]

Study Characteristics

Study characteristics are displayed in Tables 1 to 3. Of the included studies, there were 3 RCTs reported across 5 (18.52%) studies,[29,34,36,37,41] 1 (3.7%) pilot clinical trial,[28] 1 (3.7%) open-label pilot study,[47] 1 (3.7%) cross-sectional survey study,[48] 1 (3.7%) qualitative study,[45] 2 (8.33%) case reports,[35,42] and 16 (59.26%) reviews.[9,24-27,30-33,38-40,43,44,46,49] Evidence was primarily available for the use of CBD adjunctively to opioids and cocaine. Two studies focused on polydrug-using samples.[45,48] Within the 16 reviews, the same 5 relevant studies were cited.[28,29,34,36,37] Seven studies used oral isolate CBD products ranging from 400 to 800 mg of CBD,[29,34,36,37,41,47] 1 case report used a sublingual isolate CBD tincture of 600 mg/day,[42] 1 case report used whole-plant CBD-rich cigarettes at a dose of ~400 mg/day,[35] and 2 observational studies involved participants using a combination of whole-spectrum CBD products with variable dosing.[45,48] All of the RCTs used a once-per-day dosing regimen.

Summary of Findings

There remains limited available evidence in humans for using CBD as a harm reduction strategy in PWUD. Available studies support the utility of CBD for reducing drug-induced craving and anxiety in opioid use disorder and the potential attenuation of the drug-cue-induced stress response. Potential benefits were not observed in higher-quality studies for cocaine use disorder. Similar conclusions were reported in all 16 reviews. CBD was safe and well tolerated within the included RCTs. Evidence is insufficient to draw definitive conclusions on other outcomes relevant to harm reduction such as mood, mental health, or withdrawal management. Detailed study findings are presented in Table 1.

Opioids. One RCT reported that acute CBD administration of 400 and 800 mg oral CBD significantly reduced cue-induced craving and anxiety compared to placebo.[29] Differences were most pronounced within 24 h post-CBD ingestion. However, differences in placebo were also detected 7 days post-dose. Two pilot studies similarly reported success in the reduction of drug-cue-induced craving.[28,47] Evidence is insufficient to assess other relevant outcomes such as managing withdrawal[42] and anxiety or depression,[28,47] as evidence for these outcomes was only available from pilot studies and 1 case report, with mixed findings being reported.

Cocaine. One RCT reported across 3 manuscripts examined 800 mg/day of CBD in individuals with cocaine use disorder and found no evidence that CBD was more efficacious compared to placebo in improving cognitive outcomes,

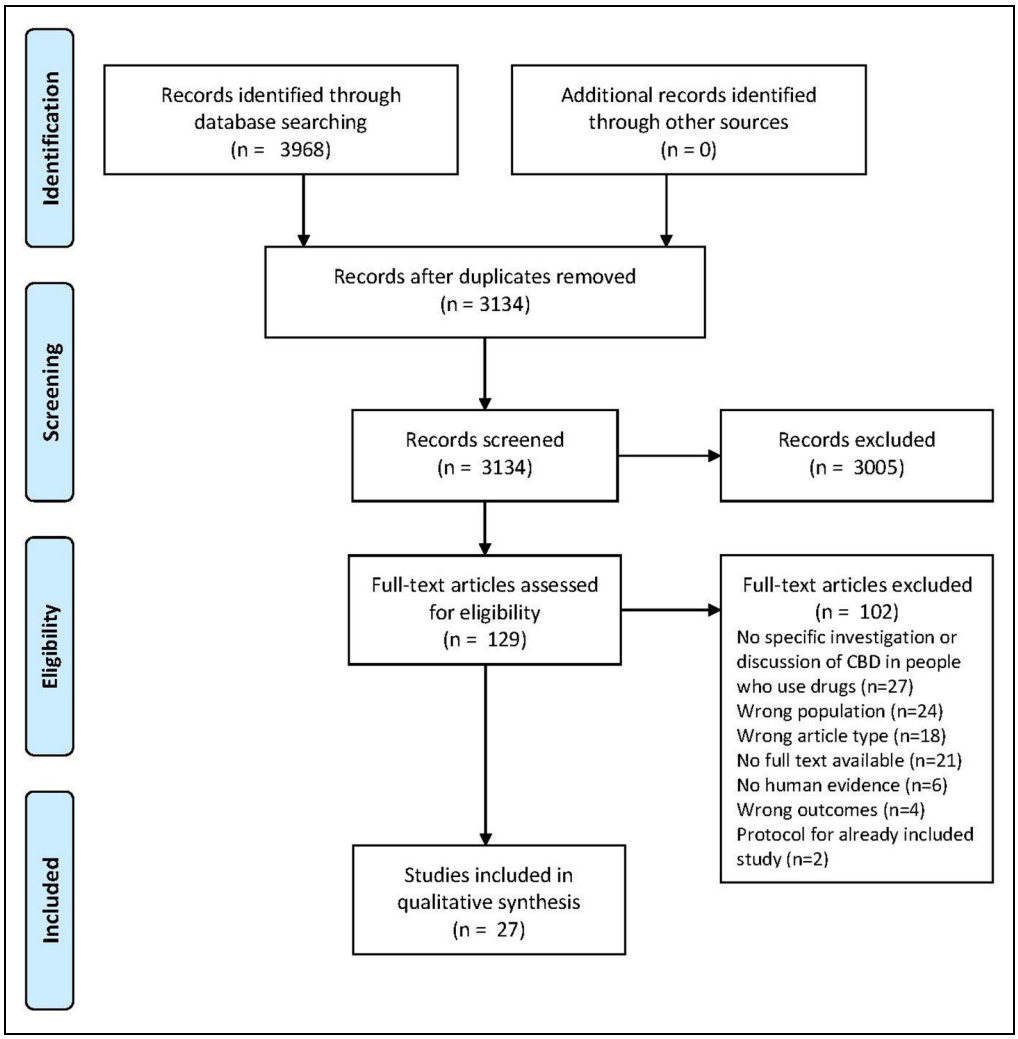

Figure 1. Flow diagram for study selection of studies for CBD for harm reduction in PWUD review. CBD = cannabidiol; PWUD = people who use drugs.

modulating anxiety symptoms or cortisol levels, reducing cravings and withdrawal symptoms, or preventing the resumption of cocaine use.[36,37,41] Similarly, another RCT investigating 300 mg/day of oral CBD cocaine-dependent individuals found no difference in craving levels, anxiety, depression, or sleep compared to the placebo.[34] One case report reported a cessation of cocaine use and improved mental health following the use of high-dose CBD cigarettes (400 mg/day); however, given the low quality of evidence, no conclusions can be drawn.[35]

Polydrug use. Two studies, 1 qualitative and 1 cross-sectional survey, examined CBD in samples composed of polydrug use.[45,48] The qualitative study examining experiences of PWUD accessing a cannabis distribution program reported high popularity of CBD use in their sample.[45] Participants reported improved pain, reduced cravings, better sleep, more energy, and general feelings of wellness.[45] The cross-sectional study reported a low prevalence of frequent CBD use overall (9%), with self-reported benefits in frequent CBD consumers, including improved relaxation, anxiety, sleep, and pain.[48] The quality of this evidence does not permit definitive conclusions to be drawn.

Gaps in Evidence

All studies noted the need for more human research, particularly larger-scale clinical trials. Several reviews highlighted the need to expand research using varied CBD dosing and administration tactics.[27,40] Specifically, the lack of efficacy seen in the cocaine studies was noted to potentially be impacted by the once-per-day dosing regimen used within the trials. However, this may be relevant for all of the included RCTs. It was noted that research examining CBD as an adjunctive treatment, in addition to an alternative treatment, for problematic substance use was a worthwhile

Table 1. Study Characteristics.

Primary research Study	Study type	Drug	Sample	Intervention	Primary outcomes	Key results
Hurd et al.[29]	RCT	Opioid	Abstinent individuals with heroin use disorder ($N = 42$)	Oral CBD 400 mg, 1×/day for 3 days ($n = 14$) Oral CBD 800 mg, 1×/day for 3 days ($n = 13$) Placebo, 1×/day for 3 days ($n = 15$)	Drug-cue-induced craving and anxiety	CBD 400 mg (mean diff = 0.44) and 800 mg (mean diff = 0.23) had significantly reduced cue-induced craving scores compared to placebo (mean diff = 0.93) The CBD 800 mg group retained significantly reduced craving scores (mean diff = 0.39) compared to placebo (mean diff = 0.94) up to 7 days post-dose ($P = 0.017$) The CBD 400 mg group (mean diff = −0.14) and 800 mg group (mean diff = −0.03) had significantly reduced drug-induced anxiety scores compared to placebo (mean diff = 0.53) up to 7 days post-dose Most significant reduction in craving and anxiety within 24 h post-CBD ingestion No effect of CBD on the out-of-clinic heroin craving questionnaire compared to placebo at any time CBD is well tolerated with no serious adverse events
Meneses-Gaya et al.[34]	RCT	Cocaine	Cocaine-dependent men ($N = 31$)	Oral CBD 300 mg, 1×/day for 10 days ($n = 14$) Placebo, 1×/day for 10 days ($n = 17$)	Craving intensity, anxiety, depression, sleep, adverse events	No difference in the reduction of cocaine craving levels between CBD and placebo ($P = 0.116$) No difference in measures of anxiety ($P = 0.80$), depression ($P = 0.46$), and sleep ($P = 0.37$) between CBD and placebo CBD is well tolerated with no serious adverse events
Mongeau-Pérusse[a] et al.[37]	RCT	Cocaine	Individuals with moderate to severe cocaine use disorder ($N = 78$)	Oral CBD 800 mg, 1×/day for 13 weeks ($n = 40$) Placebo, 1×/day for 13 weeks ($n = 38$)	Drug-cue-induced craving, time-to-relapse	Drug-cue-induced craving (mean CBD = 4.69, mean placebo = 3.21; $P = 0.069$) and stress (mean CBD = 1.50, mean placebo = 1.46; $P = 0.887$), daily craving ($P = 0.698$), withdrawal symptoms ($P = 0.662$), sustained abstinence (CBD = 41%, placebo = 50.1%; $P = 0.089$), and time-to-relapse (hazard ratio = 1.20, $P = 0.51$) did not differ between CBD and placebo

(continued)

Table 1. Continued.

Primary research Study	Study type	Drug	Sample	Intervention	Primary outcomes	Key results
						Only 3 participants did not relapse (CBD, *n* = 1; placebo, *n* = 2) CBD was well tolerated with few serious adverse events
Mongeau-Pérusse[a] et al.[36]	RCT	Cocaine	Individuals with moderate to severe cocaine use disorder (*N* = 78)	Oral CBD 800 mg, 1×/day for 13 weeks (*n* = 40) Placebo, 1×/day for 13 weeks (*n* = 38)	Anxiety (Beck Anxiety Inventory, Visual Analogue Scale), stress response	No difference in anxiety scores via the Beck Anxiety Inventory (*P* = 0.27) or Visual Analogue Scale (*P* = 0.18) between CBD and placebo CBD did not decrease anxiety after stressful (*P* = 0.14) or cocaine (*P* = 0.885) scenarios compared with placebo There was no statistically significant difference in cortisol levels between CBD and placebo groups (*P* = 0.76)
Rizkallah[a] et al.[41]	RCT	Cocaine	Individuals with moderate to severe cocaine use disorder (*N* = 78)	Oral CBD 800 mg, 1×/day for 13 weeks (*n* = 40) Placebo, 1×/day for 13 weeks (*n* = 38)	Cognitive function (visual memory, inhibition, and risky decision-making)	CBD did not improve cognitive function compared to placebo (Pattern Recognition Memory *P* = 0.080, Stop Signal Task *P* = 0.644, Cambridge Gambling Task: quality of decision-making: *P* = 0.994; deliberation time: *P* = 0.507; delay aversion: *P* = 0.968; risk-taking: *P* = 0.914)
Hurd et al.[28]	Pilot clinical trial	Opioid	Abstinent individuals with heroin use disorder (*N* = 9)	Oral CBD 400 mg, 1×/day for 3 days (*n* = 2) Oral CBD 800mg, 1×/day for 3 days (*n* = 4) Placebo, 1×/day for 3 days (*n* = 3)	Drug-cue-induced craving and anxiety	Decreased subjective cue-induced drug craving 1 h post-dose for CBD (mean = 0.83) compared to placebo (mean = 2.67) Decreased general drug craving from baseline between CBD (mean = −16.33) and placebo (mean = −4.33) up to 7 days post-dose
Suzuki et al.[47]	Open-label pilot study	Opioid	Individuals with opioid use disorder on buprenorphine (*N* = 5)	Oral CBD 600 mg, 1×/day for 3 days (*n* = 5)	Drug-cue-induced craving	Drug-cue-induced craving was significantly lower after CBD dosing compared with baseline (0.4 vs. 3.2, paired *t*-test, *P* = 0.0046) No significant changes in secondary measures of depression, anxiety, pain, or opioid withdrawal were noted CBD was well tolerated
Roser et al.[48]	Cross-sectional survey study	Polydrug use	Individuals with substance use disorder (*N* = 495)	Smoked CBD at unspecified doses	Prevalence and motives of CBD use	34.3% of patients reported trying CBD once, with 9% reporting regular use for over a year

(continued)

Table 1. Continued.

Primary research Study	Study type	Drug	Sample	Intervention	Primary outcomes	Key results
						Of those reporting regular use, 40% self-reported improvements in relaxation and sleep and 30% reported reduction in pain and anxiety
Valleriani et al.[45]	Qualitative	Polydrug use ~50% drug of choice = stimulants ~50% drug of choice = opioids	Individuals who unregulated drugs accessing a low-barrier cannabis distribution program ($N = 23$)	Variable combination of inhalation and edible THC and CBD products	Experience in accessing a cannabis distribution program	The use of CBD was popular Reported benefits included reduced pain, reduced cravings, better sleep, more energy, and general feelings of wellness CBD viewed as generally inaccessible due to the cost
Meyer et al.[35]	Case report	Cocaine	A 30-year-old male patient diagnosed with schizophrenia, personality disorder, cannabis use disorder, cocaine use disorder	CBD-rich cigarettes, ~20 cigarettes/day for ~400 mg of CBD/day + methylphenidate	Reduction in cocaine and cannabis use improved psychiatric symptoms	Stopped cocaine and high-dose THC use Improved psychotic symptoms and general functioning No further hospitalizations
Shaw and Marcu[42]	Case report	Opioid	A 27-year-old male with 8 years of severe opioid use disorder	Sublingual CBD tincture, 200 mg 3×/day (600 mg/day) for 10 days	Withdrawal symptoms	Reduction in clinical opioid withdrawal scale scores from 14 to 5 on day 2, complete resolution by day 7 Successful transition to naltrexone-based abstinence maintenance therapy
Reviews						
Study	**Review type**		**Drug**	**Main conclusions**		**Cited evidence**
Bonaccorso et al.[25]	Systematic		Opioid	CBD may reduce drug-induced craving for opioids Need for large-scale RCTs		Hurd et al.[28]
Daldegan-Bueno et al.[27]	Systematic		Cocaine	CBD alone is not a sufficient agent to reduce cocaine craving and relapse It may have more significant therapeutic potential in alleviating comorbid symptoms associated with cocaine use Substantial need for more controlled trials with varied doses, administration protocols, and populations		Mongeau-Perusse et al.[37]; Meneses-Gaya et al.[34]
McKee et al.[33]	Systematic		Opioid	CBD may reduce drug-induced craving and anxiety for opioids Favourable safety profile Quality of evidence low to moderate, larger RCTs needed		Hurd et al.[29]
Paulus et al.[40]	Systematic		Opioids Cocaine	Evidence does not support the use of CBD in reducing cocaine craving/relapse but does support reducing cue-induced craving and anxiety for opioids		Meneses-Gaya et al. [34]; Mongeau-Pérusse et al.[37]; Hurd et al.[28]; Hurd et al.[29]

(continued)

Table 1. Continued.

Primary research Study	Study type	Drug	Sample	Intervention	Primary outcomes	Key results
				Once-daily dosing may explain the lack of efficacy for cocaine use disorder Available evidence paresis spared, need for more human research		
Tang et al.[49]	Systematic		Opioids Cocaine	CBD might not be an ideal treatment for crack cocaine withdrawal CBD could be a potential treatment for opioid abuse		Hurd et al.[29]; Meneses-Gaya et al.[34]
Babalonis and Walsh[24]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety for opioids		Hurd et al.[29]
Britch et al.[26]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety for opioids Favourable safety profile and low abuse liability		Hurd et al.[29]
Karimi-Haghighi et al.[30]	Comprehensive		Opioid Cocaine	CBD may reduce drug-induced craving and anxiety for opioids Cocaine craving, anxiety, and relapse rates unaffected by CBD Potential utility in substance use disorders as antipsychotic More trials are needed to establish the actual clinical utility		Hurd et al.[29]; Meneses-Gaya et al.[34]; Mongeau-Pérusse et al.[37]
Kudrich et al.[31]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety for opioids Favourable safety profile Growing evidence suggests that CBD may reduce symptoms commonly observed in opioid use disorder patients undergoing withdrawal (e.g., anxiety, pain, insomnia, craving, nausea, vomiting, muscle spasms, and blood pressure), but more clinical research is needed Future RCTs should investigate CBD as an adjunctive treatment in clinical settings		Hurd et al.[29]
Legare et al.[32]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety for opioids Has therapeutic potential for opioid use disorder Not an effective replacement for OUD but may serve as a valuable adjunct to traditional medication-assisted treatments		Hurd et al.[29]
Morel et al.[38]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety for opioids Need for improved outcome measures and biomarkers		Hurd et al.[29]

(continued)

Table 1. Continued.

Primary research Study	Study type	Drug	Sample	Intervention	Primary outcomes	Key results
Navarrete et al.[9]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety, reduce heart rates, and reduce cortisol levels Minimal evidence		Hurd et al.[29]
Pauli et al.[39]	Comprehensive		Opioid	CBD reduced in-and-out-of-clinic opioid cravings No serious adverse effects A larger sample size needed to form definitive conclusions		Hurd et al.[28]
Sloan et al.[43]	Comprehensive		Opioid	CBD may blunt cue-induced craving in opioid dependence following a period of abstinence May be helpful in combination with naltrexone to block the priming effects of craving and relapse Safe to administer in combination with low doses of fentanyl, lack of studies examining higher dose opioids		Hurd et al.[28]
Spanagel[44]	Comprehensive		Opioid	CBD has a good safety profile, but clinical evidence is mixed Acute CBD administration may significantly reduce cue-induced cravings with long-lasting beneficial effects on craving Need larger RCTs		Hurd et al.[29]
Wiese and Wilson-Poe[46]	Comprehensive		Opioid	CBD may reduce drug-induced craving and anxiety Promising therapeutic potential as CBD appears neither intoxicating nor rewarding and has a favourable safety profile Further research is warranted to explore as an adjunct or alternative treatment for opioid use disorder		Hurd et al.[29]

Note. CBD = cannabidiol; THC = tetrahydrocannabinol; RCT = randomized controlled trial; OUD = opioid use disorder
[a]From the same large clinical trial.

focus.[32,43,46] Additionally, there is a gap in human evidence for the impact of CBD on methamphetamine disorders. Finally, only 1 study reported the lived experience of PWUD using CBD,[45] presenting another critical gap in the literature. More broadly, reconciling the positive reports of CBD from those with lived experience and the mixed outcomes of clinical research remains a challenge.

Quality of Evidence

The quality of included studies was assessed to be low. All RCTs were assessed as having a high risk of bias (Figure 2).[29,34,36,37,41] This was primarily due to the potential for missing outcome data, a common research challenge within this population, and a lack of published study protocols. The 2 case reports, 2 pilot studies, 1 cross-sectional survey study, and 1 qualitative study were considered to also have a high risk of bias due to study design.[28,35,42,45,47,48]

The 4 systematic reviews assessed with AMSTAR-2 were rated critically low[25,40] or low[33,49] quality primarily due to no predefined protocols, no discussion on the funding source included studies, and no bias assessment (Table 2). For the remaining narrative reviews, 11/12 were assessed with SANRA as being moderate or high quality (Table 3).[9,24,26,27,30-32,38,39,43,44] However, we still considered these lower-quality evidence as they only contained evidence from RCTs judged to be a high risk of bias and would have been rated as low or critically low quality using the AMSTAR-2 criteria for systematic reviews. It should be noted that all reviews converged on similar conclusions for each of the studies regardless of quality rating.

Discussion

This rapid review sought to assess the available evidence on the utility of CBD as a harm reduction strategy for PWUD. The amount and quality of available evidence on this topic remain low. Of the limited evidence, there is some indication that CBD may help reduce opioid drug craving and anxiety. There is limited support for cocaine drug craving and relapse

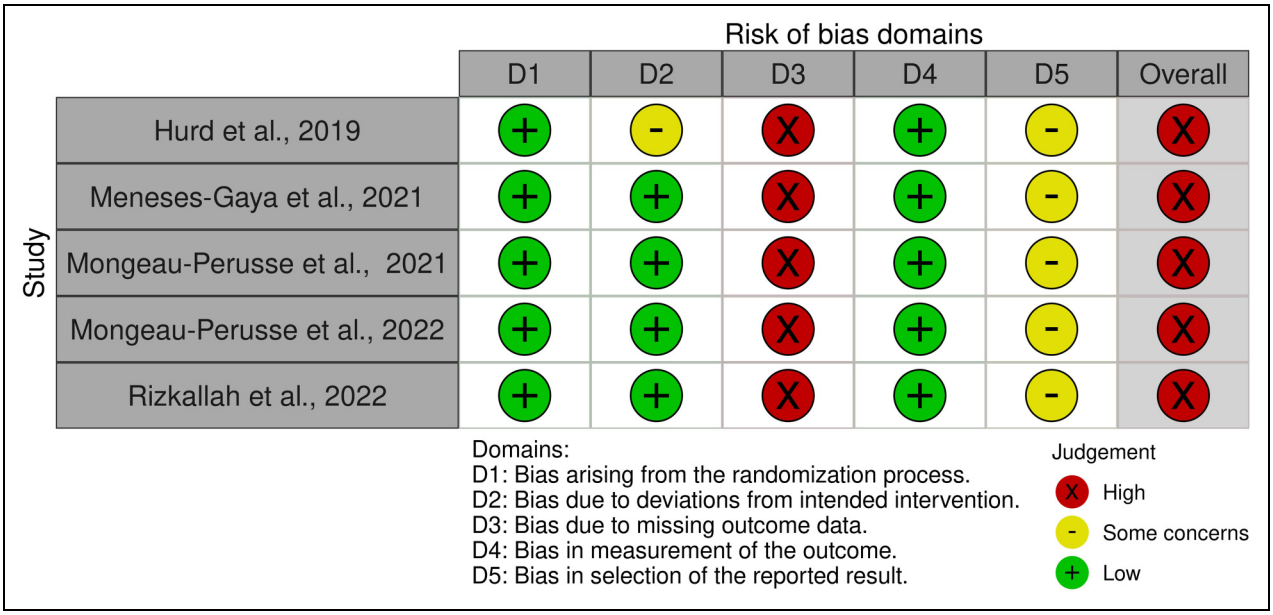

Figure 2. Risk of bias assessments for RCTs are included in this review. RCTs = randomized controlled trials.

Table 2. AMSTAR-2 Quality Assessment for Included Systematic Reviews.

	Item																
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall rating
Bonaccorso et al.[25]	Y	N	Y	Y	N	Y	PY	Y	N	N	NA	NA	N	Y	NA	Y	Critically low
McKee et al.[33]	Y	N	Y	Y	Y	Y	PY	Y	Y	N	NA	NA	Y	Y	NA	Y	Low
Paulus et al.[40]	Y	N	Y	N	N	N	PY	Y	N	N	NA	NA	N	Y	NA	Y	Critically low
Tang et al.[49]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	NA	NA	N	Y	NA	Y	Low

Note. Y = Yes, N = No, PY = Probable yes, NA = Not applicable. AMSTAR-2 items can be found in Shea et al.[21]

Table 3. SANRA Quality Assessment for Included Narrative Reviews.

Study	Item						Total	Quality
	1	2	3	4	5	6		
Babalonis and Walsh[24]	2	1	0	2	2	2	9	Moderate
Britch et al.[26]	1	1	0	2	2	2	8	Moderate
Daldegan-Bueno et al.[27]	2	2	2	2	2	2	12	High
Karimi-Haghighi et al.[30]	2	2	0	2	2	2	10	Moderate
Kudrich et al.[31]	2	2	2	2	2	2	12	High
Legare et al.[32]	2	1	1	2	2	2	10	Moderate
Morel et al.[38]	2	2	2	2	2	2	12	High
Navarrete et al.[9]	2	2	2	2	2	2	12	High
Pauli et al.[39]	2	2	0	2	2	2	10	Moderate
Sloan et al.[43]	2	2	0	2	2	2	10	Moderate
Spanagel[44]	2	1	0	2	2	2	9	Moderate
Wiese and Wilson-Poe[46]	1	0	0	2	2	2	7	Low

Note. SANRA items can be found in Baethge et al.[22]

as of now. There was some indication that CBD may be beneficial in improving mood and general well-being, which warrants further investigation. These findings largely reflect how current research focuses on CBD as a replacement for traditional medication-assisted treatments or monotherapy for problematic substance use. Several key research insights are discussed below, contributing an important extension to the literature base that allows for the contextualization of findings and guidance of future directions with real-world utility.

Considerations for Current Evidence

There are several important considerations when evaluating the results of the available studies. First, as with any pharmacotherapy, the dosing regimen of cannabis significantly impacts efficacy. The duration of action for cannabis ranges between 2–4 h for inhalation and 6–8 h for ingestion.[50] Similar to any condition causing 24-h symptomatology, ideal treatment for problematic substance use would provide relief around the clock. All of the current RCTs used once-per-day dosing, leaving a large window of the day without symptom control. Additionally, daytime versus night-time symptom management typically requires different approaches. In a real-world clinical context, it is common to use CBD to manage daytime symptoms and THC to manage night-time symptoms (e.g., sleep issues).[51,52] Using the same treatment regimen for day and night may limit the efficacy of the cannabis treatment plan.

Second, access to supportive psychosocial strategies (e.g., mental health support, group therapy, mindfulness, and cognitive behavioural therapy) should also be considered. Psychosocial interventions have been identified as an essential aspect of successfully treating opioid use disorder.[53] No opioid studies had supportive care integrated into the study protocol. While several studies investigating CBD for cocaine use did provide supportive care (detox and group therapy), they only dosed once per day, which may have diminished the overall treatment efficacy.

Finally, another concept to consider is that of the entourage effect, which refers to the concept of the sum of the whole plant, including all the cannabinoids and terpenes being synergistic and more significant as a whole versus a single CBD molecule.[54] Most of these studies used isolate CBD versus whole-plant or "full-spectrum" products. There is emerging evidence for other significant cannabinoids and terpenes that may benefit this patient population. For example, preclinical evidence shows the acid precursor cannabidiolic acid (CBDA) may be helpful for stress and anxiety,[55] while the cannabinoid cannabigerol (CBG) was self-reported to improve sleep, anxiety, depression, and pain in humans.[56] Terpenes such as myrcene, linalool, and beta-caryophyllene also may have sedative or anxiolytic effects.[57-61] Improved sleep and anxiety may help improve mood and general well-being, which may reduce harm.

Together, these factors must be considered when looking at evidence of CBD's efficacy to improve outcomes and reduce harm related to problematic substance use. There is a great need for further research that more closely replicates real-life addiction management strategies better. Research evaluating psychosocial and mental health support interventions with appropriate dosing regimens should be prioritized.

Research Gaps and Future Directions

The first clinical trial for using CBD in the context of problematic substance use was in 2015. Since that time, only a handful of other studies have been published. There is a great need for more human research, particularly larger-scale clinical trials. Considering the worsening conditions of the opioid epidemic, this strategy should have an increase in research funding. With a paucity of clinical trials, we encourage publishing case reports in which CBD is used as a harm reduction tool for problematic substance use. This may help inform clinical trial dosing and protocols. Mixed-methods evaluations will also be crucial for reconciling and contextualizing outcomes of standardized assessments with reports of those with lived experience of CBD use.

More specifically, there is a need to investigate varied dosing and administration tactics (e.g., variations in CBD full-spectrum flower products, day vs. night dosing regimens, dosing frequency, and route of administration) and strategies facilitating comprehensive management over an extended period of time. The use of CBD adjunctively to standard pharmacotherapy and psychosocial interventions, rather than a replacement or monotherapy for substance use treatment, should be the focus of future research.[31,32,46] Additionally, as there is currently no evidence on the impact of CBD on methamphetamine use and current treatments are limited in efficacy, this is also a worthwhile future direction.

Finally, the potential for CBD to improve comorbid symptoms (e.g., mood, mental health, and insomnia) is an underresearched area and may enhance understanding of the mechanisms that underlie some of the potential beneficial effects of CBD to help overcome or reduce the harms of problematic substance use. When considering harm reduction strategies for reducing negative consequences associated with drug use,[62] interventions that promote feelings of well-being, health, and improved mood may be of crucial importance. In other clinical populations, CBD has been associated with the reduction of a variety of symptoms (e.g., anxiety, low mood, pain, insomnia, nausea, and muscle spasms) that are commonly observed in individuals with problematic substance use, particularly when undergoing withdrawal or treatment.[31,63-65] Given its low abuse potential and limited side effects,[13,14] CBD may be desirable for many patients. As such, the actual utility of CBD to reduce harm may be a supportive strategy to existing treatment approaches such as traditional medication-assisted treatments (e.g., Opioid agonist therapy (OAT)) and supportive psychosocial strategies. There is a significant need to investigate this potential in well-designed studies that replicate real-world dosing protocols (e.g., multiple daily doses) over an adequate period of time to detect effects.

Conclusion

The use of CBD as a harm reduction tool for PWUD is an emerging area of interest. To date, research remains limited. There is some evidence that CBD may help reduce opioid drug craving and anxiety, which may be 1 tool in decreasing the risk of relapse and overdose. However, evidence is not sufficient to suggest that CBD alone is an adequate treatment to reduce problematic substance use. Nonetheless, the potential for improved well-being combined with a reduction in drug craving may allow for greater adherence and engagement in other treatment modalities (e.g., therapy and OAT) and should be a focus of future research. Further, there is little risk of harm associated with the use of CBD, making it a desirable adjunct pharmacotherapy option. There is a great need for more research in this area that accurately reflects treatment and dosing regimens used in a real-world context to better evaluate CBD's utility as a harm reduction tool for PWUD.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Outside of submitted work, CM is the Medical Director of Greenleaf Medical Clinic and Chief Medical Officer for Translational Life Sciences. She is on the Board of Directors for The Green Organic Dutchman. She is an advisor to PreveCeutical, Pinnacle Care, Africanna, EO Care, Andira Medicine, Active Patch Technologies, and Dosist. Additionally, she has provided medical consultation and/or received support for industry-sponsored continuing medical education from Aleafia, Aurora, Canopy, Spectrum, Tilray, Emerald Health, and Syqe Medical. MK is the director of The CannSolve Clinic. IM authorizes cannabis through The CannSolve Clinic. He has provided industry-sponsored continuing medical education and/or consulting for Tilray, Unipharm, Maricann, Shoppers Drug Mart, Lancaster House, and MDBriefCase. He has been the qualified investigator in an industry-sponsored (Tilray) study of cannabis for post traumatic stress disorder (PTSD). M-JM holds the Canopy Growth professorship in cannabis science at the University of British Columbia, a position established through arm's length gifts to the university from Canopy Growth, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. ZW has received research funding from Tilray and Doja, licensed producers of cannabis, and was a Research Director for Indigenous Bloom. The authors LL, KN, and FF declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Interior Universities Research Coalition (IURC) Ministry of Health (MoH) Research Grant awarded to authors FF and ZW on behalf of "The Maverick Cannabis Project" to the School of Nursing, Thompson Rivers University, and the Department of Psychology, University of British Columbia-Okanagan Campus (Grant number 451078).

Data Availability

Data and materials associated with this rapid review are available upon request.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Corsi K, Davis J, Kral A, Bluthenthal R, Booth R. Effects of cannabis use on opioid injection frequency. 2015. doi:10.1016/j.drugalcdep.2015.07.1052.
2. Lau N, Sales P, Averill S, Murphy F, Sato S-O, Murphy S. A safer alternative: cannabis substitution as harm reduction. Drug Alcohol Rev. 2015;34(6):654-659. doi:10.1111/dar.12275.
3. Lucas P. Rationale for cannabis-based interventions in the opioid overdose crisis. Harm Reduct J. 2017;14(1):58. doi:10.1186/s12954-017-0183-9.
4. Socías ME, Kerr T, Wood E, et al. Intentional cannabis use to reduce crack cocaine use in a Canadian setting: a longitudinal analysis. Addict Behav. 2017;72:138-143. doi:10.1016/j.addbeh.2017.04.006.

5. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. J Affect Disord. 2017;218:1-7. doi:10.1016/j.jad.2017.04.026.
6. Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Curr Neuropharmacol. 2006;4(3):239-257.
7. Mok J, Milloy M-J, Grant C, et al. Use of cannabis for harm reduction among people at high risk for overdose in Vancouver, Canada (2016–2018). Am J Public Health. 2021;111(5):969-972. doi:10.2105/AJPH.2021.306168.
8. Mok J, Milloy M-J, Grant C, et al. Use of cannabis as a harm reduction strategy among people who use drugs: a cohort study. Cannabis Cannabinoid Res. 2022 May 31 [accessed 2022 Aug 20]. https://www.liebertpub.com/doi/abs/10.1089/can.2021.0229 doi:10.1089/can.2021.0229.
9. Navarrete F, García-Gutiérrez MS, Gasparyan A, Austrich-Olivares A, Manzanares J. Role of cannabidiol in the therapeutic intervention for substance use disorders. Front Pharmacol. 2021;12:626010. doi:10.3389/fphar.2021.626010.
10. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry. 2005;162(8):1483-1493. doi:10.1176/appi.ajp.162.8.1483.
11. Wilcox CE, Pommy JM, Adinoff B. Neural circuitry of impaired emotion regulation in substance use disorders. Am J Psychiatry. 2016;173(4):344-361. doi:10.1176/appi.ajp.2015.15060710.
12. Arkell TR, Vinckenbosch F, Kevin RC, Theunissen EL, McGregor IS, Ramaekers JG. Effect of cannabidiol and Δ^{9}-tetrahydrocannabinol on driving performance: a randomized clinical trial. JAMA. 2020;324(21):2177. doi:10.1001/jama.2020.21218.
13. Dos Santos RG, Guimarães FS, Crippa JAS, et al. Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials. Expert Opin Drug Metab Toxicol. 2020;16(6):517-526. doi:10.1080/17425255.2020.1754793.
14. Schoedel KA, Szeto I, Setnik B, et al. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: a randomized, double-blind, controlled trial. Epilepsy Behav. 2018;88:162-171. doi:10.1016/j.yebeh.2018.07.027.
15. Schubart CD, Sommer IEC, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MPM. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res. 2011;130(1-3):216-221. doi:10.1016/j.schres.2011.04.017.
16. Health Canada. Apparent opioid-related deaths. aem. 2017 Sep 14 [accessed 2018 Sep 18]. https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/apparent-opioid-related-deaths.html.
17. Norton A, Kerr T. Applying the lessons of COVID-19 response to Canada's worsening opioid epidemic. eClinicalMedicine. 2020 [accessed 2022 Oct 6];29: 100633. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30377-1/fulltext doi:10.1016/j.eclinm.2020.100633.
18. Health Canada. Opioid- and stimulant-related harms in Canada. 2022 [accessed 2022 Mar 25]. https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/.
19. Garritty C, Gartlehner G, Nussbaumer-Streit B, et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. J Clin Epidemiol. 2021;130:13-22. doi:10.1016/j.jclinepi.2020.10.007.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-269, W64. doi:10.7326/0003-4819-151-4-200908180-00135.
21. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Br Med J. 2017;358:j4008. doi:10.1136/bmj.j4008.
22. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4(1):5. doi:10.1186/s41073-019-0064-8.
23. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928. doi:10.1136/bmj.d5928.
24. Babalonis S, Walsh SL. Therapeutic potential of opioid/cannabinoid combinations in humans: review of the evidence. Eur Neuropsychopharmacol. 2020 Apr 6 [accessed 2020 Apr 13];36:206-216. http://www.sciencedirect.com/science/article/pii/S0924977X20300651 doi:10.1016/j.euroneuro.2020.03.002.
25. Bonaccorso S, Ricciardi A, Zangani C, Chiappini S, Schifano F. Cannabidiol (CBD) use in psychiatric disorders: a systematic review. NeuroToxicology. 2019;74:282-298. doi:10.1016/j.neuro.2019.08.002.
26. Britch SC, Babalonis S, Walsh SL. Cannabidiol: pharmacology and therapeutic targets. Psychopharmacology. 2021;238(1):9-28. doi:10.1007/s00213-020-05712-8.
27. Daldegan-Bueno D, Maia LO, Glass M, Jutras-Aswad D, Fischer B. Co-exposure of cocaine and cannabinoids and its association with select biological, behavioural and health outcomes: a systematic scoping review of multi-disciplinary studies. Eur Neuropsychopharmacol. 2021;51:106-131. doi:10.1016/j.euroneuro.2021.06.002.
28. Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics. 2015;12(4):807-815. doi:10.1007/s13311-015-0373-7.
29. Hurd YL, Spriggs S, Alishayev J, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019;176(11):911-922. doi:10.1176/appi.ajp.2019.18101191.
30. Karimi-Haghighi S, Razavi Y, Iezzi D, Scheyer AF, Manzoni O, Haghparast A. Cannabidiol and substance use disorder: dream or reality. Neuropharmacology. 2022;207:108948. doi:10.1016/j.neuropharm.2022.108948.
31. Kudrich C, Hurd YL, Salsitz E, Wang A-L. Adjunctive management of opioid withdrawal with the nonopioid medication

cannabidiol. Cannabis Cannabinoid Res. 2021;7:569-581. doi:10.1089/can.2021.0089.
32. Legare CA, Raup-Konsavage WM, Vrana KE. Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. Pharmacology. 2022;107(3-4):131-149. doi:10.1159/000521683.
33. McKee KA, Hmidan A, Crocker CE, et al. Potential therapeutic benefits of cannabinoid products in adult psychiatric disorders: a systematic review and meta-analysis of randomised controlled trials. J Psychiatr Res. 2021;140:267-281. doi:10.1016/j.jpsychires.2021.05.044.
34. Meneses-Gaya CD, Crippa JA, Hallak JE, et al. Cannabidiol for the treatment of crack-cocaine craving: an exploratory double-blind study. Braz J Psychiatry. 2021;43(5):467-476. doi:10.1590/1516-4446-2020-1416.
35. Meyer M, Walter M, Borgwardt S, Scheidegger A, Lang E, Köck P. Case report: CBD cigarettes for harm reduction and adjunctive therapy in a patient with schizophrenia and substance use disorder. Front Psychiatry. 2021;12:712110. doi:10.3389/fpsyt.2021.712110.
36. Mongeau-Pérusse V, Rizkallah E, Morissette F, et al. Cannabidiol effect on anxiety symptoms and stress response in individuals with cocaine use disorder: exploratory results from a randomized controlled trial. J Addict Med. 2022 [accessed 2022 Aug 29];16:521-526; Publish Ahead of Print. https://journals.lww.com/10.1097/ADM.0000000000000959 doi:10.1097/ADM.0000000000000959.
37. Mongeau-Pérusse V, Brissette S, Bruneau J, et al. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. Addiction. 2021;116(9):2431-2442. doi:10.1111/add.15417.
38. Morel A, Lebard P, Dereux A, et al. Clinical trials of cannabidiol for substance use disorders: outcome measures, surrogate endpoints, and biomarkers. Front Psychiatry. 2021;12:565617. doi:10.3389/fpsyt.2021.565617.
39. Pauli CS, Conroy M, Vanden Heuvel BD, Park S-H. Cannabidiol drugs clinical trial outcomes and adverse effects. Front Pharmacol. 2020 [accessed 2020 Mar 17];11. https://www.frontiersin.org/articles/10.3389/fphar.2020.00063/full doi:10.3389/fphar.2020.00063.
40. Paulus V, Billieux J, Benyamina A, Karila L. Cannabidiol in the context of substance use disorder treatment: a systematic review. Addict Behav. 2022;132:107360. doi:10.1016/j.addbeh.2022.107360.
41. Rizkallah E, Mongeau-Pérusse V, Lamanuzzi L, et al. Cannabidiol effects on cognition in individuals with cocaine use disorder: exploratory results from a randomized controlled trial. Pharmacol Biochem Behav. 2022;216:173376. doi:10.1016/j.pbb.2022.173376.
42. Shaw C, Marcu J. Case report: cannabidiol in the management of acute opioid withdrawal. Am J Endocannabinoid Med. 2021;3:6-11.
43. Sloan ME, Gowin JL, Ramchandani VA, Hurd YL, Le Foll B. The endocannabinoid system as a target for addiction treatment: trials and tribulations. Neuropharmacology. 2017;124:73-83. doi:10.1016/j.neuropharm.2017.05.031.
44. Spanagel R. Cannabinoids and the endocannabinoid system in reward processing and addiction: from mechanisms to interventions. Dialogues Clin Neurosci. 2020;22(3):241-250. doi:10.31887/DCNS.2020.22.3/rspanagel.
45. Valleriani J, Haines-Saah R, Capler R, et al. The emergence of innovative cannabis distribution projects in the downtown eastside of Vancouver, Canada. Int J Drug Policy. 2020;79:102737. doi:10.1016/j.drugpo.2020.102737.
46. Wiese B, Wilson-Poe AR. Emerging evidence for cannabis' role in opioid use disorder. Cannabis Cannabinoid Res. 2018;3(1):179-189. doi:10.1089/can.2018.0022.
47. Suzuki J, Martin B, Prostko S, Chai PR, Weiss RD. Cannabidiol effect on cue-induced craving for individuals with opioid use disorder treated with buprenorphine: a small proof-of-concept open-label study. Integr Med Rep. 2022;1(1):157-163. doi:10.1089/imr.2022.0070.
48. Roser P, Habermeyer B, Scherbaum N, Lay B. Cannabidiol use among patients with substance use disorders. J Subst Use. 2022:1-7. doi:10.1080/14659891.2022.2120425.
49. Tang Y, Tonkovich KL, Rudisill TM. The effectiveness and safety of cannabidiol in non-seizure-related indications: a systematic review of published randomized clinical trials. Pharmaceut Med. 2022;36(6):353-385. doi:10.1007/s40290-022-00446-8.
50. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018 [accessed 2018 Sep 13];84(11):2477-2482. http://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bcp.13710 doi:10.1111/bcp.13710.
51. Bhaskar A, Bell A, Boivin M, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. J Cannabis Res. 2021;3(1):22. doi:10.1186/s42238-021-00073-1.
52. MacCallum CA, Lo LA, Boivin M. "Is medical cannabis safe for my patients?" A practical review of cannabis safety considerations. Eur J Intern Med. 2021;89:10-18. doi:10.1016/j.ejim.2021.05.002.
53. George TP, Welsh L, Franchuk SL, Vaccarino FJ. Why integrating medications and psychosocial interventions is important to successfully address the opioid crisis in Canada. Can J Psychiatry. 2022;67(3):176-178. doi:10.1177/07067437211037625.
54. Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: no "strain," no gain. Front Plant Sci. 2019 [accessed 2019 Sep 25];9. https://www.frontiersin.org/articles/10.3389/fpls.2018.01969/full?&field=&journalName=Frontiers_in_Plant_Science&id=434025 doi:10.3389/fpls.2018.01969.
55. Assareh N, Gururajan A, Zhou C, Luo JL, Kevin RC, Arnold JC. Cannabidiol disrupts conditioned fear expression and cannabidiolic acid reduces trauma-induced anxiety-related behaviour in mice. Behav Pharmacol. 2020;31(6):591-596. doi:10.1097/FBP.0000000000000565.

56. Russo EB, Cuttler C, Cooper ZD, Stueber A, Whiteley VL, Sexton M. Survey of patients employing cannabigerol-predominant cannabis preparations: perceived medical effects, adverse events, and withdrawal symptoms. Cannabis Cannabinoid Res. 2021;7:706-716. doi:10.1089/can.2021.0058.
57. Braden R, Reichow S, Halm MA. The use of the essential oil lavandin to reduce preoperative anxiety in surgical patients. J Perianesth Nurs. 2009;24(6):348-355. doi:10.1016/j.jopan.2009.10.002.
58. Fidyt K, Fiedorowicz A, Strządała L, Szumny A. β-Caryophyllene and β-caryophyllene oxide—natural compounds of anticancer and analgesic properties. Cancer Med. 2016;5(10):3007-3017. doi:10.1002/cam4.816.
59. Rabbani M, Sajjadi SE, Vaezi A. Evaluation of anxiolytic and sedative effect of essential oil and hydroalcoholic extract of *Ocimum basilicum* L. and chemical composition of its essential oil. Res Pharm Sci. 2015;10(6):535.
60. Surendran S, Qassadi F, Surendran G, Lilley D, Heinrich M. Myrcene—what are the potential health benefits of this flavouring and aroma agent? Front Nutr. 2021 [accessed 2022 Oct 12];8. https://www.frontiersin.org/articles/10.3389/fnut.2021.699666.
61. Vale TGD, Furtado EC, Santos JG, Viana GSB. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from *Lippia alba* (Mill.) N.E. Brown. Phytomedicine. 2002;9(8):709-714. doi:10.1078/094471102321621304.
62. Marlatt GA. Harm reduction: come as you are. *Addictive Behaviors*. 1996;21(6):779-788. doi:10.1016/0306-4603(96)00042-1.
63. Khan R, Naveed S, Mian N, Fida A, Raafey MA, Aedma KK. The therapeutic role of cannabidiol in mental health: a systematic review. Journal of Cannabis Research. 2020;2(1):2. doi:10.1186/s42238-019-0012-y.
64. Melas PA, Scherma M, Fratta W, Cifani C, Fadda P. Cannabidiol as a potential treatment for anxiety and mood disorders: molecular targets and epigenetic insights from preclinical research. Int J Mol Sci. 2021;22(4):1863. doi:10.3390/ijms22041863.
65. White CM. A review of human studies assessing cannabidiol's (CBD) therapeutic actions and potential. J Clin Pharmacol. 2019;59(7):923-934. doi:10.1002/jcph.1387.