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Review

Alleviation of opioid withdrawal by cannabis and delta-9-tetrahydrocannabinol: A systematic review of observational and experimental human studies

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ABSTRACT

Background: While six U.S. states have already officially authorized cannabinoids to substitute opioids and treat opioid use disorder, the therapeutic benefits of cannabinoids remain unclear, especially when weighted against their adverse effects.

Methods: We conducted a systematic review of studies examining the association between opioid withdrawal and cannabis use or delta-9-tetrahydrocannabinol (THC) administration. We searched multiple databases from inception to July 30, 2022, and assessed study quality.

Results: Eleven studies were identified, with a total of 5330 participants, of whom 64 % were male. Nine observational studies examined the association between cannabis use and opioid withdrawal. Two randomized, placebo-controlled clinical trials (RCTs) investigated the withdrawal-alleviating effects of dronabinol, a synthetic form of THC. Four observational studies found an association between cannabis use and the alleviation of opioid withdrawal; one reported exacerbation of opioid withdrawal symptoms; and four reported no association. RCTs reported that THC alleviated opioid withdrawal, albeit with dose-dependent increases in measures of abuse liability, dysphoria, and tachycardia. There was high heterogeneity in measurements of opioid withdrawal and the type and dose of opioid at baseline.

Conclusions: Although there is preliminary evidence that cannabis and its main psychoactive constituent, THC, may alleviate opioid withdrawal, these effects are likely to have a narrow therapeutic window. Further, the potential of cannabinoids to alleviate opioid withdrawal is determined by complex interactions between patient characteristics and pharmacological factors. Collectively, these findings have clinical, methodological, and mechanistic implications for treating opioid withdrawal during cannabinoid use, and for efforts to alleviate opioid withdrawal using non-opioid therapeutics.

1. Introduction

The United States is still in the grip of an opioid crisis (Dennis et al., 2015; Rice et al., 2016; van Rijswijk et al., 2019). Thus far, this crisis has caused an economic burden of approximately $ 1 trillion, in addition to the incalculable suffering and grief that individuals and families endure (Hagemeier, 2018). Every day, over 100 Americans die from opioid overdose, surpassing 200,000 in the last two decades alone (Rudd et al., 2016). Such harrowing consequences have prompted healthcare professionals, policymakers, and the public to seek new solutions, such as novel therapeutics for opioid use disorder (OUD).

One of the foundational goals of OUD pharmacotherapy is to alleviate opioid withdrawal, a debilitating constellation of physical and affective symptoms that follows either the abrupt discontinuation or dose reduction of an exogenous opioid (Dole and Nyswander, 1965). The physical symptoms of opioid withdrawal include gastrointestinal

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discomfort, chills, and heightened pain sensitivity; the affective symptoms, in turn, include dysphoria, anhedonia, and irritability (Kanof et al., 1992). Among persons with OUD, the standard of care for opioid withdrawal is to administer methadone or buprenorphine — the latter typically administered in combination with naloxone, in the United States. Methadone and buprenorphine increase the opioid tone by acting either as a full agonist or partial agonist at the mu-opioid receptor (MOR), respectively (Sofuoglu et al., 2019). However, people with OUD who experience opioid withdrawal may not have access to methadone or buprenorphine, limiting treatment options during periods of acute opioid withdrawal (Evans et al., 2019; Marsh et al., 2021). Further, although methadone and buprenorphine alleviate opioid withdrawal, breakthrough withdrawal symptoms often re-emerge when precipitated by anxiety, pain, or drug cues (Langleben et al., 2008; Sinha et al., 2007; Spahn et al., 2013).

Clinicians use several ancillary medications to alleviate opioid withdrawal, including non-steroidal anti-inflammatory drugs for pain; promethazine for nausea and vomiting; loperamide for diarrhea; and trazodone for sleep disturbance. Thus far, the only *non-opioid* medication approved by the Food and Drug Administration (FDA) to alleviate opioid withdrawal is lofexidine, an alpha-adrenergic antagonist that suppresses sympathetic tone, but found limited use due to its adverse events including hypotension (Kuszmaul et al., 2020). Unfortunately, all these ancillary medications tend to have modest effects in alleviating opioid withdrawal, underscoring the need to develop other therapeutic options.

Alongside recognizing the risks of opioids, there has been growing interest in cannabinoids as potential therapeutics for OUD — including as a strategy to alleviate opioid withdrawal. This strategy is dovetailed by a wealth of evidence showing crosstalk between the opioid and cannabinoid receptor systems, which overlap at the anatomical, neurochemical, and behavioral levels (Scavone et al., 2013a). Several preclinical studies demonstrate that exogenous delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, reduces opioid withdrawal in opioid-dependent animals (Bhargava, 1976a, 1976b; Cichewicz and Welch, 2003; Gamage et al., 2015; Hine et al., 1975a, 1975b; Lichtman et al., 2001); and, that, conversely, cannabinoid receptor antagonists/inverse agonizts (e.g., rimonabant) precipitate opioid withdrawal (Dunn et al., 2019; Scavone et al., 2013a). Convergent lines of evidence also show that cannabinoid agonizts may alleviate pain (Finn et al., 2021; Wang et al., 2021), an important feature of opioid withdrawal — especially when OUD and chronic pain co-occur (Coloma-Carmona et al., 2019; Rodriguez-Espinosa et al., 2021).

At the time of this writing, 37 U.S. states and the District of Columbia have authorized the medicinal use of cannabis and its constituent cannabinoids. In addition, many states have officially authorized cannabis and its constituent cannabinoids to "replace prescription opioid medications", including pharmacotherapies for OUD; for "all conditions for which opioids could be prescribed to treat"; and as "alternatives to opioid treatment" (Voelker, 2018). Though the speed of cannabinoid policy changes has far outpaced the availability of systematic evidence (De Aquino et al., 2021; Suzuki and Weiss, 2021), several observational studies reported withdrawal alleviation by cannabis among persons with OUD at different stages of methadone and buprenorphine treatment (e.g., induction vs. maintenance) (Hermann et al., 2005; Rosic et al., 2021; Scavone et al., 2013b). Moreover, experimental studies have used randomized, placebo-controlled designs to investigate cannabinoid-based medications (e.g., dronabinol, a synthetic oral form of THC) as an opioid withdrawal alleviation strategy among clinical samples — including persons receiving long-term opioid therapy undergoing a controlled taper, as well as persons with OUD undergoing induction onto intramuscular (IM) extended-release (XR) naltrexone — two clinical circumstances that require experiencing opioid withdrawal (Bisaga et al., 2015; Jicha et al., 2015; Lofwall et al., 2016).

In this systematic review, we sought to synthesize and appraise the observational and experimental studies investigating cannabis and its main psychoactive constituent, THC, to alleviate opioid withdrawal. Recent reviews have summarized the relationship between cannabis use and clinical outcomes among persons receiving medications for OUD (Lake and Pierre, 2020); and compiled preclinical and human studies probing non-opioid receptor systems — including the cannabinoid system — to improve opioid withdrawal-related outcomes (Dunn et al., 2019). In this paper, we extend findings from such prior work, by conducting a systematic review of observational and experimental human studies investigating opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent persons, regardless of OUD treatment status. After synthesizing findings from these studies, we discuss their clinical, mechanistic, and methodological implications — identifying gaps in knowledge and offering insights to guide future research.

2. Methods

2.1. Search strategy and study selection

We searched the literature per recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Rethlefsen et al., 2021). In addition, an objective search strategy was designed in consultation with a health professional with experience in information retrieval (OG) (Hausner et al., 2015, 2016). Subject headings (MeSH and EMTREE) and free terms were selected from the PubMed, EMBASE, and PsycNet-controlled vocabulary thesauruses. Additional terms were identified using the online tools PubReMiner (Koster, 2004) and MeSH on Demand (U.S. National Library of Medicine, 2021), as well as by reviewing abstracts of relevant papers.

The following databases were searched without language or date restrictions: MEDLINE (Ovid); Cochrane Central Register of Controlled Trials (Ovid); EMBASE; CINAHL; PsycArticles and Open Dissertations (EBSCO). In addition, conference proceedings abstracts were searched within the EMBASE database. The search terms included ([cannabis, dronabinol, nabilone, cannabinoids] and [opioid withdrawal suppression]. The full search strategies for the Ovid and EMBASE interfaces are reported in the supplementary material (Appendix 1). The EMBASE search was limited to the results available only in this database to avoid duplicating results with the MEDLINE (Ovid) search. Searches were conducted up until July 2022. The search strategy for MEDLINE was validated with a sensitivity of 100 % since all relevant studies previously known to the authors were identified.

Eligible studies included observational and experimental reports, including human participants exposed to cannabis or THC, while experiencing opioid withdrawal. Studies considered for inclusion reported an association between cannabis or THC exposure and the severity of opioid withdrawal symptoms. We excluded studies in which participants were not receiving opioid agonizts during exposure to cannabis or THC. Two authors (JPD and OG) independently screened the title and abstract of each article for full-text retrieval. The same authors screened the full-text articles for inclusion. All disagreements were resolved by discussion with a third author (AB), until a consensus was reached. The clinicaltrials.gov registries for eligible studies were excluded if they did not provide relevant results beyond the ones reported in published manuscripts. Finally, entries for eligible ongoing and finished studies were excluded if no results had yet been reported.

2.2. Outcome measures

The primary outcome of interest was opioid withdrawal in response to exposure to cannabis or THC, indexed by either participant- and/or observer-rated instruments for observational and experimental studies, respectively. Data collected included: 1) The sample size of each study; 2) The dose and duration of the exposure to cannabis or THC, when

available; 3) The presence of withdrawal and/or its severity, indexed by the reported outcome. In addition, when available in the included studies, we also examined secondary outcomes related to specific adverse effects of acute exposure to cannabis or THC, including: 1) Abuse potential, indexed by semi-structured questionnaires and visual analog scales (VAS); and 2) Cardiovascular effects, indexed by heart rate and blood pressure. When data was only available in plot format, efforts were made to contact the authors of primary studies. However, since significant study heterogeneity existed concerning study procedures, it was decided, a priori, that quantitative data pooling was inappropriate.

2.3. Quality rating of studies

To appraise the quality of the evidence, we used tools that were well-validated for each study design. To measure the risk of bias in observational studies, two independent reviewers (JPD, OG) applied the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (Sterne et al., 2016), which includes the following domains: confounding; selection of participants; classification of interventions (if applicable); deviations from intended interventions (if applicable); missing data; measurement of outcomes; and selection of the reported results. To measure the risk of bias in experimental studies, the same two authors (JPD, OG) applied the Revised Cochrane Tool for Assessing Risk of Bias in Randomized Trials (RoB 2) (Sterne et al., 2019), which includes the following domains: randomization process; deviations from the intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. Differences in the judgment of the risk of bias were resolved by discussion and consensus. Finally, the Recommendations, Assessment, Development, and Evaluations (GRADE) criteria were applied to both the observational and the experimental studies (Guyatt et al., 2008).

3. Results

Our search strategy generated 1542 citations, which were retrieved and imported into the reference management software EndNote (Gotschall, 2021). Duplicates were manually removed before entry into Covidence, a workflow platform for a collaborative systematic review

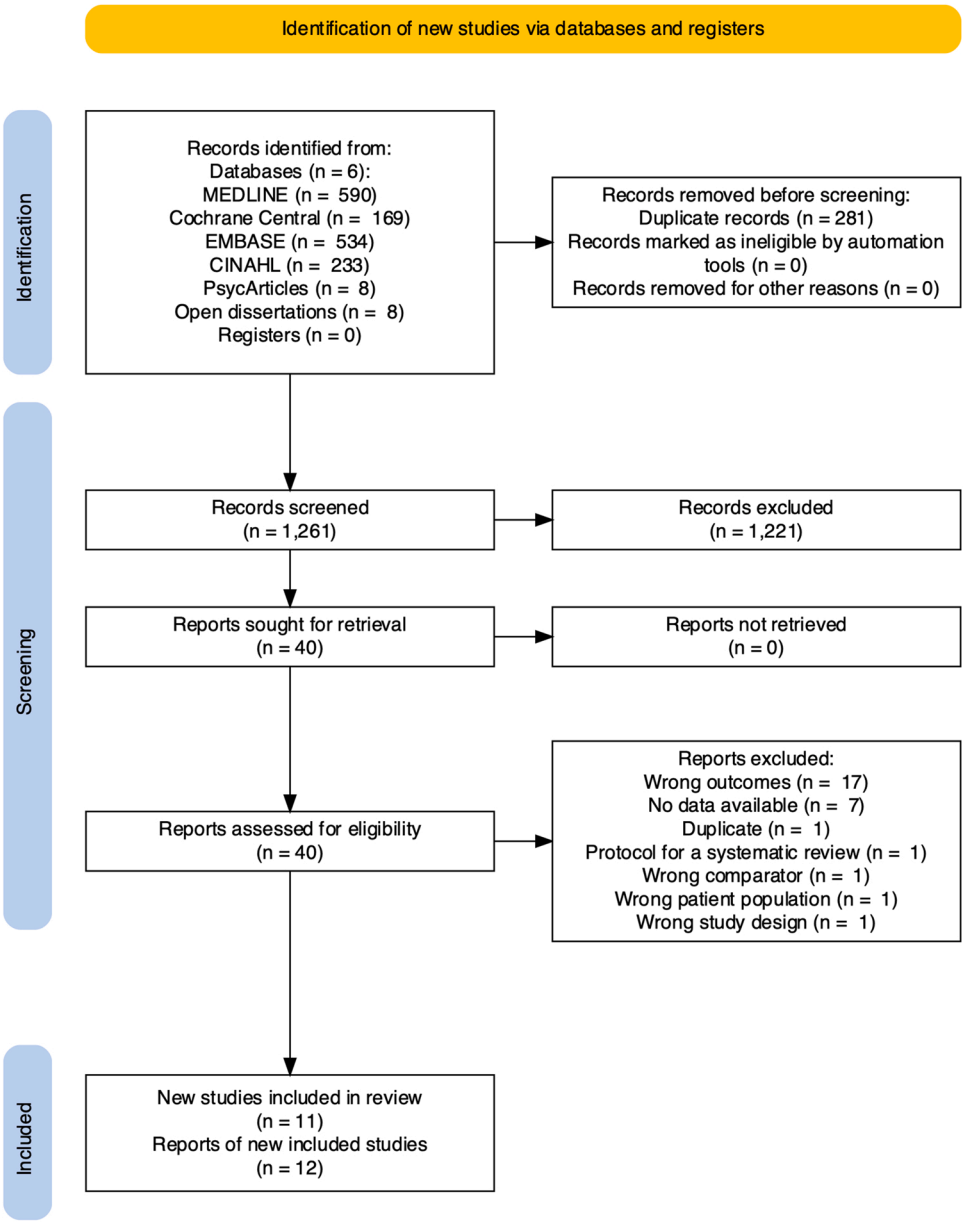

Fig. 1. Diagram of the study selection process for the Systematic Review, performed per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

management (Babineau, 2014). A total of eleven studies provided data relevant to our search aim and met inclusion criteria and were therefore included in the final review (Fig. 1). These studies totaled 5330 participants, of whom 64 % were male and 36 % were female. Among these studies, nine used observational designs, and two used experimental designs. The findings of each study are summarized in Table 1.

3.1. Observational studies

A total of nine observational studies met the inclusion criteria. Six studies reported findings from cross-sectional surveys, while three reported results from longitudinal designs. Opioid withdrawal was reported as a continuous measure in seven studies and a categorical measure in two studies. In addition, participants in observational studies reported consuming plant-based cannabis products, rather than isolated THC (Table 1).

Bergeria and colleagues conducted a cross-sectional online survey study including 200 individuals who had used opioids and cannabinoids within the preceding month, and who had experienced opioid withdrawal (Bergeria et al., 2020). Notably, Subjective Opioid Withdrawal Scale (SOWS) scores were significantly lower during cannabis use days than on abstinent days. Likewise, visual analog scale (VAS, range: 0–100) opioid withdrawal severity scores were significantly lower during cannabis use days than during abstinent days. "Anxiety" (76.2 %), "tremors" (54.1 %), and "trouble sleeping" (48.4 %) were the opioid withdrawal symptoms most frequently improved; while "yawning" (7.4 %), "tearing eyes" (6.6 %), and "running nose" (6.6 %) were the opioid withdrawal symptoms most frequently exacerbated by cannabis.

Epstein and colleagues conducted a clinical trial including 116 participants with OUD who were undergoing a 10-week outpatient methadone taper, among whom 46 participants used cannabis regularly (Epstein and Preston, 2015). Results indicated no difference in opioid withdrawal symptoms between participants who used cannabis and participants who did not use cannabis. In the subset of 46 persons who used cannabis regularly, a lagged analysis showed that periods of more severe opioid withdrawal were correlated with higher intensity of cannabis use. This finding, however, was not confirmed by a similar lagged analysis in the opposite temporal direction.

Hermann and colleagues conducted a cross-sectional study among 89 people with OUD who were engaged in an opioid treatment program (61 % receiving methadone and 39 % receiving buprenorphine) to estimate whether various drugs, including cannabis, alleviated opioid withdrawal (Hermann et al., 2005). To measure opioid withdrawal, the authors used a 5-point Likert scale. The results for cannabis were conflicting. Although half of the sample reported beneficial effects from cannabis, 37 % indicated that cannabis use was associated with worsening opioid withdrawal.

Scavone and colleagues used a retrospective cohort design to examine the association between patterns of cannabis use and treatment outcomes in a sample of 91 individuals who were receiving methadone treatment (Scavone et al., 2013b). In this study, the author reported participants' rates of cannabis use within the preceding 3 months. Additionally, a random sample of 35 persons who did not use cannabis but who received methadone treatment for OUD during the same period was included, as a control group. Results showed that cannabis use was higher during the induction onto methadone, decreasing significantly following the methadone dose stabilization. A contingency analysis showed that persons who used cannabis (n = 40) tended to experience lower severity of opioid withdrawal, indexed by the Clinical Opioid Withdrawal Scale (COWS) (Wesson and Ling, 2003) — such that there was an inverse association between frequency of cannabis use and opioid withdrawal severity.

In a cross-sectional study, Bagra and colleagues found that100 randomly selected persons with OUD who received buprenorphine for 3 months or longer, participants who were currently using cannabis received lower doses of buprenorphine (7.9 mg/day vs. 8.9 mg/day) (Bagra et al., 2018). There was no significant difference, however, in either acute (22.9 % vs. 13.8 %) or protracted opioid withdrawal (28.6 % vs. 27.7 %), measured by self-report and indexed as categorical outcomes. Notably, however, the duration or meaning of "protracted opioid withdrawal" was not defined by the authors. The most commonly reported withdrawal symptoms were body aches (22 %), followed by sleep disturbance (12 %) and irritability (9 %).

In another large cross-sectional study, approximately 35 % of participants reported substituting cannabis for opioids. (Lucas et al., 2019). Approximately 11.4 % of participants indicated fewer withdrawal symptoms, reported as a categorical outcome, as the main reason for substituting cannabis for opioids. Notably, 74.6 % of the 2032 participants surveyed reported daily cannabis use (1.5 g/day).

In a prospective study investigating the relationship between cannabis use, methadone-induced normalization of the hypothalamic-pituitary-adrenal (HPA) axis, and opioid withdrawal severity, the time course of the reduction in withdrawal symptoms reduced significantly ($p < .001$) among persons who used cannabis and persons who did not use cannabis (Nava et al., 2007). Still, there was no difference between the two groups, although between-group statistics were not provided.

A prospective observational study (Mayet et al., 2015) of 188 persons who received methadone for OUD cannabis use was monitored at baseline, 3, 6, and 12 months. Opioid withdrawal was measured with the Objective Opioid Withdrawal Scale (OOWS), an observer-rated 13-item instrument that assesses physical and affective withdrawal symptoms (range: 0–13) (Handelsman et al., 1987). The results, however, did not show an association between the number of withdrawal symptoms and either daily (OR = 1.03; 95 % CI 0.86, 1.21; $p = .67$) or non-daily (OR = 1.02; 95 % CI 0.88, 1.18; $p = .80$) cannabis use. No formal between-group statistics were reported, although there did not appear to be a significant effect in either group.

In a retrospective observational study (Rosic et al., 2021) including 2315 individuals who were receiving methadone or buprenorphine, approximately 70 % of those reporting cannabis use stated that they consumed cannabis daily, half of which reported cannabis-related adverse effects, including "slower thought process" (26 %) and "lack of motivation" (17 %). In addition, about 8.3 % of participants reported a perceived subjective improvement in withdrawal from opioids due to cannabis, but no formal withdrawal assessments were done.

In summary, four observational studies reported an association between cannabis exposure and the alleviation of opioid withdrawal (Bergeria et al., 2020; Lucas et al., 2019; Rosic et al., 2021; Scavone et al., 2013b); one study reported an association between cannabis exposure and worsening of opioid withdrawal (Hermann et al., 2005), and four studies reported that cannabis exposure was not associated with a change in opioid withdrawal severity (Bagra et al., 2018; Epstein and Preston, 2015; Mayet et al., 2015; Nava et al., 2007). Notably, two studies indicated that the frequency of cannabis use was inversely correlated with the severity of opioid withdrawal (Bergeria et al., 2020; Scavone et al., 2013b).

3.2. Experimental studies

A total of two experimental studies met the inclusion criteria. Altogether, these two experimental studies led to the inclusion of three experimental reports. Two manuscripts reported on findings from a human laboratory study, and one manuscript reported on findings from a treatment trial. These studies measured both subjective and observer-rated symptoms of opioid withdrawal in response to the administration of dronabinol, an oral synthetic form of THC (Table 1).

In a 5-week double-blind, placebo-controlled, within-subject study, 12 opioid-dependent persons were randomized to single doses of oxycodone (30 mg and 50 mg) and dronabinol (5 mg, 10 mg, 20 mg, and 30 mg) across 7 inpatient test sessions (Jicha et al., 2015). The primary outcomes of this initial report were heart rate, blood pressure, respiratory rate, and pupil diameter. At least 5 days before completing the first

Table 1
Study characteristics.

Study reference	Study design	Primary outcome (s)	Secondary outcome(s)	Study sample	Opioid condition	Cannabis or THC condition	Effect of cannabis or THC on opioid withdrawal	Other notes
Observational studies								
Bagra et al. (2018)	Cross-sectional	Dropout rate	Opioid withdrawal (Self-report, categorical) Buprenorphine dose Opioid use	100 adults receiving MOUD	Buprenorphine	Cannabis	No effect on dropout	Participants who used cannabis received lower doses of buprenorphine (7.9 mg/day vs. 8.9 mg/day, $p = .04$) Opioid use and withdrawal did not differ
Bergeria et al. (2020)	Cross-sectional	Opioid withdrawal (SOWS, VAS)	NA	200 adults reporting past-month opioid and cannabis use	Various	Various	Improvement in opioid withdrawal symptoms SOWS scores were lower during cannabis use days ($M = 16.2$, SEM = 1.4) than on abstinent days ($M = 27.8$, SEM = 1.3), ($t(121) = 9.4$, $p < .05$, $d = 0.84$) VAS opioid withdrawal severity scores were lower during cannabis use days ($M = 35.3$, SEM = 2.0), than during abstinent days ($M = 64.5$, SEM = 2.0), $t(121) = 11.2$ $p < .05$, $d = 0.88$)	"Tremors" (54.1 %) and "trouble sleeping" (48.4 %) were the opioid withdrawal symptoms most frequently improved
Epstein and Preston (2015)	Longitudinal (10 weeks)	Opioid withdrawal severity (24-item, 4-point Likert Scale, measured every 2 weeks)	NA	116 adults with OUD during a methadone taper in a clinical trial	Methadone	Cannabis	Opioid withdrawal did not differ between cannabis users and non-users	In a lagged analysis, weeks of greater severity of opioid withdrawal preceded weeks of cannabis use (effect-size $r = 0.20$, 95 % CI − 0.10,0.46, $p = .52$)
Hermann et al. (2005)	Cross-sectional	Opioid withdrawal (5-point Likert Scale)	NA	89 adults with OUD	Various 61 % methadone 39 % buprenorphine	Cannabis	50 % of participants reported beneficial effects from cannabis 15 % of participants reported no effect of cannabis on opioid withdrawal	37 % of participants reported that cannabis use was associated with worsening of opioid withdrawal
Lucas et al. (2019)	Cross-sectional	Opioid withdrawal (Self-report, categorical)	NA	2032 adults reporting cannabis use	Various	Various	11.4 % of participants reported fewer opioid withdrawal symptoms after cannabis use	35 % of participants reported that they substituted cannabis for opioids Participants who substituted cannabis for opioids tended to use more cannabis (1.71 g/day vs. 1.46 g/day); were more likely to use extracts/oral cannabis preparations as the primary method of consumption (21 % vs. 15 %, $p = .01$); and were more likely to use extracts daily (40 % vs. 26%, $p = .004$).
Mayet et al. (2015)	Longitudinal (12 months)	Opioid withdrawal (13-item OOWS)	NA	188 adults receiving MOUD	Various	Various	No association between the number of opioid withdrawal	Cannabis use did not affect the methadone-induced normalization of pre-

(*continued on next page*)

Table 1 (*continued*)

Study reference	Study design	Primary outcome (s)	Secondary outcome(s)	Study sample	Opioid condition	Cannabis or THC condition	Effect of cannabis or THC on opioid withdrawal	Other notes
							symptoms and either daily (OR = 1.03; 95 % CI 0.86, 1.21; $p = .67$) or non-daily (OR = 1.02; 95 % CI 0.88, 1.18; $p = .80$) cannabis use	treatment hypercortisolism
Nava et al. (2007)	Longitudinal (12 months)	Normalization of the HPA axis, indexed by ACTH and cortisol levels	Dropout rate Opioid craving Opioid withdrawal (Wang Scale)	121 adults receiving MOUD	Methadone	Cannabis	Cannabis use did not interfere with methadone-induced normalization of the HPA axis	Cannabis use did not affect opioid withdrawal, opioid craving, or dropout rate
Rosic et al. (2021)	Longitudinal (3 months)	Opioid use	Side-effects, self-reported impact on MOUD Opioid withdrawal (Self-report, categorical)	2315 adults receiving MOUD	Methadone and buprenorphine	Cannabis	8.3 % reported fewer opioid withdrawal symptoms with cannabis	Compared to occasional use, daily cannabis use was associated with lower odds of opioid use (OR = 0.61, 95 % CI 0.47, 0.79, $p < .001$)
Scavone et al. (2013a, 2013b)	Cross-sectional	Pattern of cannabis use Non-medical opioid use Methadone dose Dropout rate	Opioid Withdrawal (COWS)	91 adults receiving MOUD	Methadone	Cannabis	Cannabis use high during induction, reduced during stabilization No effect on methadone dose, opioid use, dropout rate	Objective ratings of opioid withdrawal decreased [$\chi^2_1 = 7.54$, $p = .006$] among cannabis-using patients during induction onto methadone Inverse association between frequency of cannabis use and opioid withdrawal severity [$\chi^2_2 = 6.71$, $p = .035$]
Experimental Studies								
Jicha et al. (2015) & Lofwall et al. (2016)	Double-blinded, placebo-controlled, within-subject, crossover design (7 laboratory sessions over 5 weeks)	Opioid withdrawal severity (SOWS, VAS)	Cognitive battery (continuous performance task)	12 opioid-dependent adults, switched to standard dose of oxycodone in the inpatient setting (30 mg orally four times per day)	Oxycodone 30, 60 mg Placebo	Dronabinol 5, 10, 20, 30 mg	Dronabinol 20 and 30 mg reduced opioid withdrawal severity ($p < .05$) The subjective (i.e., participant-rated) opioid withdrawal symptoms by dronabinol were up to 48 % higher than placebo — whereas for oxycodone, the magnitude of the effects was up to 70 % higher than placebo	Oxycodone was superior to dronabinol in reducing opioid withdrawal ($p < .05$) Dronabinol 30 mg produced higher VAS "good effects" than placebo (32.1 ± 7.2 vs. 5.5 ± 3.8) $p < .001$), but still smaller than oxycodone 30 mg (31.8 ± 7.9) and 60 mg (48.0 ± 6.0) Dronabinol 20 mg and 30 mg produced heart rate increases compared to placebo (107.6 ± 6.2 vs. 112 ± 3.4 vs. 84.4 ± 2.3 beats per minute, respectively) A higher dose of dronabinol, 40 mg, was discontinued following sustained tachycardia and anxiogenic effects
Bisaga et al. (2015)	Randomized controlled study (8 days in the patient setting, 7-week outpatient follow-up)	Success of receiving a second IM XR naltrexone injection 4 weeks later	Opioid withdrawal severity (SOWS)	Adults with OUD during induction onto IM XR naltrexone	Various	Dronabinol 30 mg (n = 40), placebo (n = 20) for during inpatient IM XR naltrexone induction and during 5 weeks in the outpatient setting	Reduction of severity of opioid withdrawal in dronabinol group	32% of regular cannabis users during the outpatient phase had significantly lower ratings of insomnia and anxiety and were more likely to complete the 8-week trial Trend for higher rates of induction onto XR

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Table 1 (*continued*)

Study reference	Study design	Primary outcome (s)	Secondary outcome(s)	Study sample	Opioid condition	Cannabis or THC condition	Effect of cannabis or THC on opioid withdrawal	Other notes
								IM naltrexone following the administration of dronabinol (66 %) compared to placebo (55 %) ($\chi^2_2 = 1.46$, $p = .23$)

Abbreviations: ATCH: Adrenocorticotropic hormone; IM XR: Intramuscular, Extended Release; HPA: Hypothalamic-Pituitary Adrenal.; MOUD: Medications for opioid use disorder; OUD: Opioid use disorder; SOWS: Subjective Opioid Withdrawal Scale. OOWS: Objective Opioid Withdrawal Scale; VAS: Visual Analog Scale. SEM: Standard Error of the Mean.

session, participants were stabilized on a total oral dose of oxycodone of 30 mg/day, divided into 7.5 mg doses administered four times per day. Then, approximately 21 h preceding each test session, a double-blind placebo was substituted for three oxycodone doses, to produce spontaneous opioid withdrawal. Results showed that dronabinol 20 mg and 30 mg, compared to placebo, produced increases in heart rate; conversely, dronabinol 5 mg and 10 mg did not differentiate from placebo. Notably, the study was originally designed to administer a higher dose of dronabinol, 40 mg, which was discontinued after participants experienced persistent tachycardia and anxiogenic effects.

Using the same dataset, Lofwall and colleagues reported on both subjective and objective (i.e., observer-rated) opioid withdrawal outcomes (Lofwall et al., 2016). Results showed that dronabinol 20 mg and 30 mg produced modest alleviation of subjective and objective opioid withdrawal symptoms approximately 3.5–4.5 h after dosing. Overall, the alleviation of subjective (i.e., participant-rated) opioid withdrawal symptoms by dronabinol was up to 48 % higher than by placebo. In contrast, for oxycodone, the magnitude of the effects was up to 70 % higher than placebo. Notably, the alleviation of opioid withdrawal produced by dronabinol was accompanied by increases in measures of abuse potential; sedation; attention deficits (indexed by lower percent correct responses on the Continuous Performance Test [CPT]); and tachycardia (Table 1). Notably, the participant-rated street values of dronabinol — a measure of abuse liability — were not statistically different from placebo, consistent with post-market surveillance data showing no evidence of dronabinol diversion, and with the change in dronabinol's Schedule from II to III (Calhoun et al., 1998).

Another randomized, placebo-controlled trial investigated the effects of dronabinol on opioid withdrawal among persons with OUD who were undergoing induction into extended-release (XR) intramuscular (IM) naltrexone (Bisaga et al., 2015). Using a between-subject design, before induction onto XR IM naltrexone, 40 persons with OUD received dronabinol 30 mg/day, and 20 received a placebo. The study medication was administered over 8 days in an inpatient setting, and participants were followed as outpatients for 5 weeks afterward. The SOWS indexed the severity of opioid withdrawal. In addition, the treatment retention at discharge from the inpatient setting and at 8 weeks was also assessed. Results showed that dronabinol alleviated opioid withdrawal during the inpatient phase upon acute induction onto IM XR naltrexone. Further, there was a trend for higher rates of induction onto XR IM naltrexone following the administration of dronabinol (66 %) compared to placebo (55 %) — this finding was not statistically significant. As acknowledged by the authors, participants who experienced precipitated withdrawal after induction onto XR IM naltrexone may also have received other ancillary medications (e.g., clonidine, clonazepam, and zolpidem). In addition, dronabinol's lack of withdrawal-alleviating effects during the outpatient phase was attributed to possible medication non-adherence. Finally, a post-hoc analysis indicated that 33 % of participants who used cannabis regularly during the outpatient phase experienced less severe anxiety and were more likely to complete the 8-week trial, but descriptive statistics were not provided.

In summary, one experimental study reported on the safety of dronabinol administration during opioid withdrawal, finding dose-dependent cardiovascular effects (tachycardia) (Jicha et al., 2015). The other two experimental reports indicated that dronabinol alleviated acute opioid withdrawal (Bisaga et al., 2015; Lofwall et al., 2016), indexed by both self-report and observer-rated measures.

3.3. *Quality rating of studies*

Most observational studies had a moderate risk of bias due to confounding. This was mainly due to a lack of adjustment for confounding, derived from the group assignment process — as participants were typically selected based on exposure to the intervention (i.e., cannabis) without considering the influence of clinical characteristics on the opioid withdrawal outcome. Bias due to the selection of participants was deemed low or moderate for most of the studies, except for one of the studies that selected participants based on past cannabis use. The classification of interventions was also considered as having a low or moderate risk of bias, as the groups were clearly defined at the start of the longitudinal studies. There was a lack of reporting on deviations from the intended intervention owing to a lack of description of the processes followed during the studies. No information was available for most of the studies concerning handling missing data. Lastly, the measurement of the outcome had a moderate to serious risk of bias, mainly because of the heterogeneity in measures of opioid withdrawal (Fig. 2).

The assessment of the risk of bias in the experimental studies showed low to moderate bias arising from the randomization process, deviation from the intended interventions, and the selection of the reported results. In addition, bias due to missing outcome data and measurement of the outcome was deemed low (Fig. 3). The certainty of the observational and experimental evidence was also assessed using the GRADE framework (Guyatt et al., 2011) (Table 2).

4. Discussion

In this systematic review, we examined the association between exposure to cannabis or its main psychoactive constituent, THC, and the alleviation of opioid withdrawal in humans. Data were extracted from eleven studies and twelve reports, providing observational and experimental evidence on the effects of cannabis and THC on several clinically relevant outcomes. First, observational studies reported conflicting findings. Four studies found an association between cannabis exposure and the alleviation of opioid withdrawal; one reported the opposite association; and four reported no relationship between these two variables. Second, the experimental studies reported mild-to-moderate withdrawal-alleviating effects of THC, administered as dronabinol. Notably, the opioid withdrawal-alleviating effects of dronabinol occurred acutely, approximately 3.5–4.5 h after dosing (Lofwall et al., 2016) or during a short inpatient induction onto XR IM naltrexone (Bisaga et al., 2015).

Likely explanations for the conflicting findings from observational

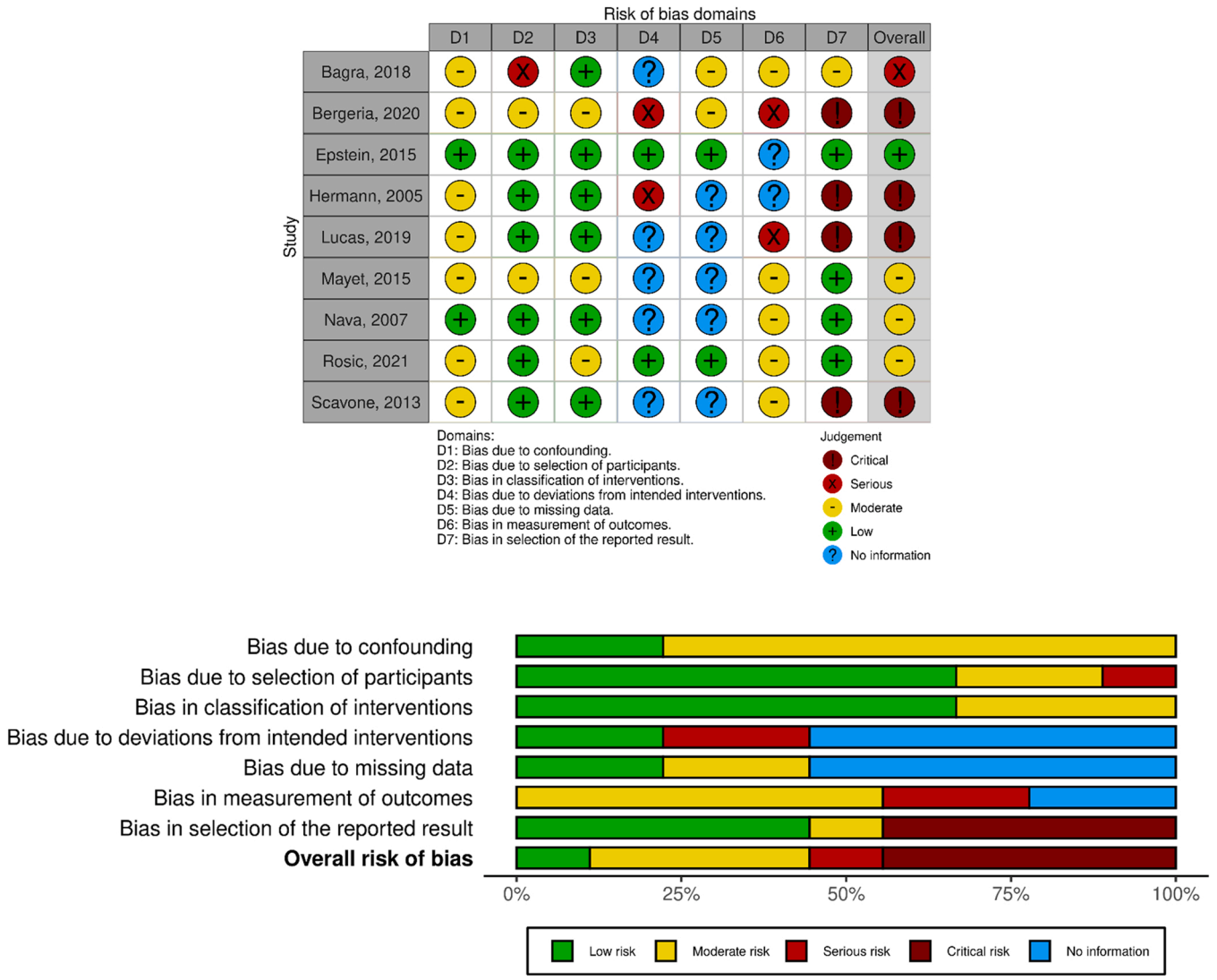

Fig. 2. Risk of Bias in Observational Studies assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).

studies included in this review are differences in participant characteristics and the dose of cannabis exposure. However, it is also possible that the type of opioid used (methadone vs. buprenorphine vs. illicit opioids [e.g., heroin]), the total daily opioid dose, and the duration of treatment may impact putative withdrawal-alleviating the effects of cannabis. Further, THC, the main psychoactive constituent of cannabis, is known to have biphasic effects, with lower doses relieving and higher doses promoting anxiety — in addition to inducing tachycardia and perceptual disturbance, which could, collectively, dose-dependently exacerbate the opioid withdrawal experience (De Aquino et al., 2018). Taken together, these factors may explain the mixed observational findings.

Unlike observational studies, the experimental studies included in this review afforded control over the opioid and cannabinoid dose and over the use of other drugs that may interfere with measures of opioid withdrawal. For example, THC, administered as dronabinol, alleviated opioid withdrawal acutely, although it is unclear whether a longer-term administration of dronabinol would improve opioid withdrawal outcomes.

Taken together, these human findings are dovetailed by a wealth of preclinical data showing opioid withdrawal-alleviating effects of cannabinoid agonizts and by a remarkable overlap between cannabinoid and opioid neural substrates of acute opioid withdrawal (Navarro et al., 2001; Scavone et al., 2013a). These findings also have implications for treating opioid withdrawal among persons who use cannabis-based products and for the methodologically sound development and mechanistic understanding of novel opioid withdrawal alleviation therapeutics.

4.1. *Clinical implications*

Findings from this systematic review have several clinical implications. First, the observational and experimental findings available thus far indicate that the proposed therapeutic window of cannabis or THC for opioid withdrawal may be limited by their cardiovascular (e.g., tachycardia) and psychiatric adverse effects (e.g., anxiety and exacerbation of the withdrawal experience) (De Aquino et al., 2018). Second, some observational data also indicated that opioid dose reductions (e.g., induction or taper) were associated with higher intensity of cannabis use (Scavone et al., 2013b). Thus, clinicians should carefully measure exposure to cannabis or THC during these critical periods, advising patients about the biphasic effects of cannabis and cannabinoid agonizts on anxiety and mood states, which are inextricably linked with the opioid withdrawal experience (Lutz and Kieffer, 2013). Third, given the unclear efficacy of cannabis and THC in alleviating opioid withdrawal, clinicians should continue to offer established interventions, including opioid agonist treatments (e.g., buprenorphine or methadone) and non-opioid ancillary medications (e.g., lofexidine), regardless of cannabis use status. Lastly, whether individuals with specific clinical

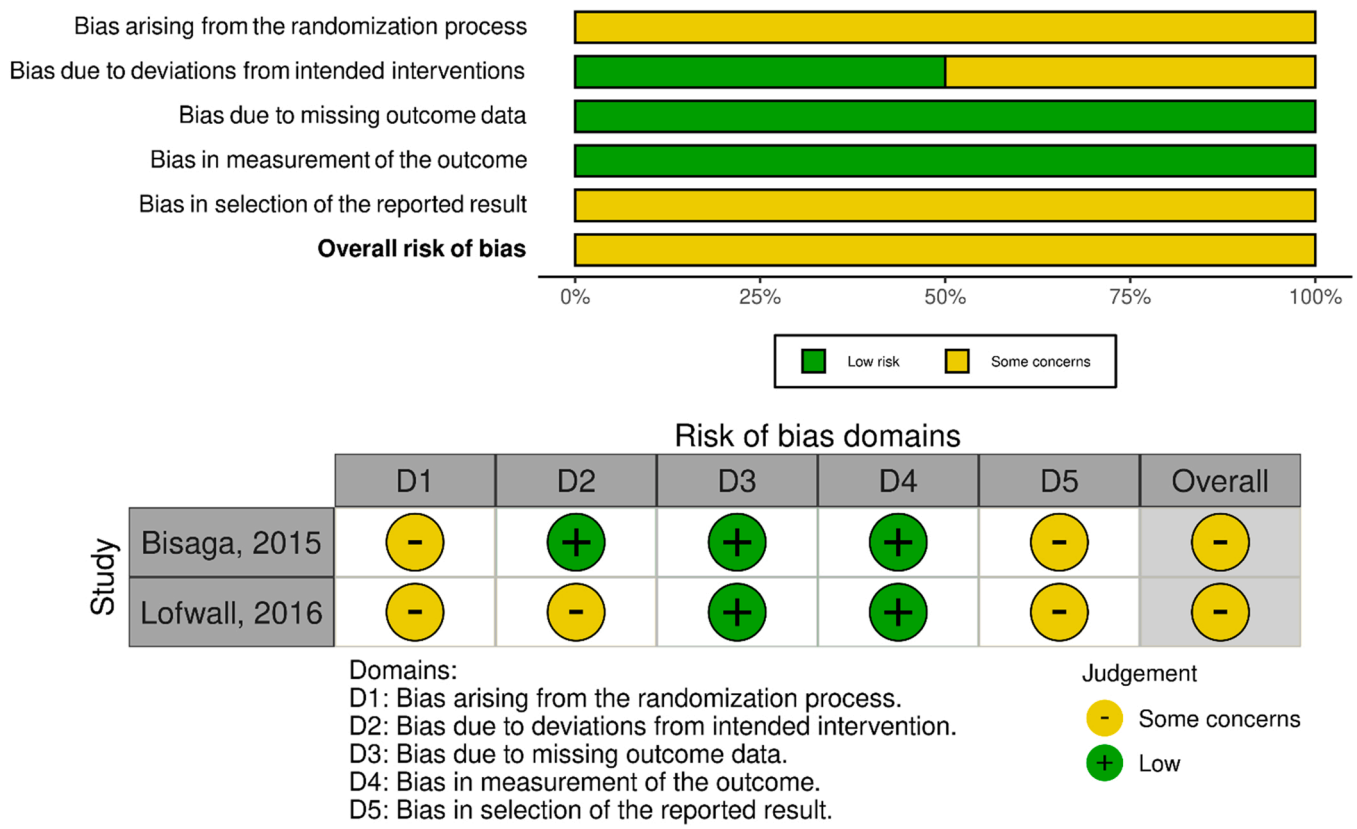

Fig. 3. Risk of Bias in Experimental Studies assessed using the Revised Cochrane Tool for Assessing Risk of Bias in Randomized Trials (RoB 2).

Table 2
GRADE assessment.

Certainty assessment							Impact	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Observational Studies									
9	Observational studies	Very serious[a]	Serious[b]	Serious[c]	serious[d]	None	Observational studies have shown mixed results for and against the use of cannabinoids for alleviating opioid withdrawal Most of the observational evidence comes from studies with a very serious risk of bias	⨁◯◯◯ Very low	Critical
Experimental Studies									
2	Randomized, placebo-controlled trials	Serious[e]	Serious[f]	Serious[c]	Serious[g]	Dose-response Therapeutic Window	RCT have shown some benefit of dronabinol for alleviating opioid withdrawal More research is needed before recommending for or against the use of cannabinoids for alleviating opioid withdrawal	⨁◯◯◯ Very low	Critical

Abbreviations: CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; NRCT: RCT: Randomized, Controlled Trials.

a. Most observational studies had a critical risk of bias, mostly due to confounding and selection of the reported results. b. Results were inconsistent across observational studies. c. Small sample sizes. d. Withdrawal was assessed with a range of different subjective and objective measures. e. Overall, the risk of bias for RCT was due to randomization process and the measurement of the outcome. f. Withdrawal symptoms were measured under different conditions. g. Tools used in the included RCTs use different approaches to measure withdrawal symptoms.

needs (e.g., chronic pain, anxiety, or insomnia) may particularly benefit from withdrawal alleviation effects of cannabinoids during induction onto (and taper from) pharmacotherapies for OUD remain to be determined in future clinical studies.

4.2. Methodological implications

We found that all experimental but not all observational studies reported opioid withdrawal-alleviating effects of cannabis or THC. This discrepancy likely stems from differences in the dose and type of opioid at baseline and the intensity/history of cannabis/THC exposure. Future

studies, therefore, should consider these factors, and conduct exploratory responder analyses, aiming to parse individuals who may derive withdrawal-alleviating effects from those who do not.

It is also worth noting that the duration of opioid withdrawal-alleviating effects of smoked and oral cannabinoids depends on their different pharmacokinetics (McGilveray, 2005). For example, dronabinol produces lower plasma levels than cannabis, influencing its clinical effects (Milman et al., 2014). In the experimental studies included, dronabinol was given once per day, despite its elimination half-life of 19–36 h — such that once per day dosing may not have been sufficient to provide consistent blood levels. Future studies should employ behavioral pharmacology and clinical trial methods to measure both acute and protracted effects of cannabinoids on opioid withdrawal, ideally employing Ecological Momentary Assessment (EMA) to capture more granular, dynamic changes in symptoms, increasing ecological validity (Kowalczyk et al., 2015). The impact of cannabis product chemotypes (e.g., THC-dominant vs. cannabidiol[CBD]-dominant), formulations (e.g., edibles, concentrates), and routes of administration (e.g., smoked, vaporized, oral) also warrants investigation in future studies (Spindle et al., 2019). A supervised consumption of products with known chemotypes and formulations would ensure adherence and an accurate estimation of dose-response relationships (DeWorsop et al., 2016).

Additionally, future studies should also consistently report both subjective and physical symptoms of opioid withdrawal since cannabinoid agonizts may influence primarily subjective symptoms (e.g., anxiety) (Bergeria et al., 2020; Meacham et al., 2022), which tend to arise before physical symptoms (Pergolizzi Jr et al., 2020; Swift and Stout, 1992). Finally, studies should also collect qualitative data on whether potentially anxiolytic and other therapeutic effects of cannabinoid products may compensate for dose-dependent adverse effects (De Aquino et al., 2019). These data may assist in optimizing the risk/benefit ratio of cannabis and its constituent cannabinoid persons seeking relief from opioid withdrawal.

4.3. Mechanistic implications

This systematic review also highlights the importance of understanding, at the mechanistic level, how cannabis and THC exert their proposed efficacy in alleviating opioid withdrawal against opioid-induced neuroadaptations. Cannabinoid and opioid receptors are G-protein coupled receptors with downstream effects of adenylyl cyclase activity, calcium channel activation, and downstream neurotransmitter release (Scavone et al., 2013a). Further, these receptors are densely co-localized in central nervous system regions that mediate the opioid withdrawal syndrome — especially the locus coeruleus (Pickel et al., 2004; Scavone et al., 2010). Future mechanistic studies should examine how opioids with different mechanisms of action (e.g., various levels of selectivity, intrinsic efficacy, affinity, and potency) at mu- and kappa-opioid and non-opioid receptors modulate the withdrawal-alleviating effects of cannabinoids. Likewise, to our knowledge, results from experimental human studies testing the withdrawal-alleviating effects of cannabinoids other than THC are not available. Thus, how cannabinoids with different mechanisms of action than THC (e.g., CBD, THC-CBD combinations, and fatty acid amide hydrolase [FAAH] inhibitors) may dose-dependently influence the availability of brain cannabinoid receptors in the locus coeruleus — thereby impacting the opioid withdrawal severity — remains to be explored (Ramesh et al., 2011). Finally, the sex-dependent effects of cannabinoids and sex-dependent phenotypes of opioid withdrawal warrant consideration in future mechanistic studies since emerging evidence shows that women may experience more adverse effects from cannabinoid agonizts (Cooper and Craft, 2018), as well as higher severity of opioid withdrawal than men (Dunn et al., 2020).

4.4. Limitations

To our knowledge, this is the first systematic review of the proposed efficacy of cannabis and THC in alleviating opioid withdrawal, and our review has several notable strengths. First, we used published and accepted guidelines to conduct and report systematic reviews (Moher et al., 2009). We also used a highly sensitive search strategy across several electronic databases, which yielded eleven studies that provided clinically relevant opioid withdrawal outcomes. Further, independent reviewers performed all stages of the review with good interrater reliability.

Still, despite its considerable strengths, most of the data summarized and appraised in this systematic review were derived from observational studies. Likewise, the experimental reports reviewed were deemed to generate low-certainty outcomes. To produce evidence that supports the wide generalizability of withdrawal-alleviating effects of cannabinoids, research must be conducted in the clinical setting during periods of higher severity of opioid withdrawal, such as induction into and taper of opioid agonizts. Further, since THC is a psychoactive compound, active blinding would increase confidence in withdrawal-alleviating findings (Casarett, 2018). As outlined above, another limitation is the lack of standardization of opioid withdrawal measures in the original studies. Opioid withdrawal is an intricate syndrome, composed of physical (e.g., from changes in pain sensitivity to cardiovascular symptoms); affective (e.g., from anxiety to anhedonia); and cognitive (e.g., from changes in attentional bias to opioid cues to opioid craving) domains — all of which can be modulated by cannabinoids. Future studies should, therefore, rigorously gather data on all these domains of the opioid withdrawal syndrome, using a combination of behavioral and psychophysical biomarkers, and recognizing that there might be subtle changes in these processes before an opioid withdrawal can be captured by symptom scales (Wang et al., 2010). Nonetheless, the results of this review may clarify the mixed findings reported in observational and experimental studies investigating opioid withdrawal alleviation by cannabis and THC — identifying gaps in knowledge and providing insights for future investigation.

5. Conclusion

Treating opioid withdrawal is challenging, often requiring adjunctive, non-opioid interventions — especially during vulnerable periods when the opioid dose is lower, such as during induction and taper. In this systematic review, we sought to synthesize and appraise the evidence for the opioid withdrawal-alleviating effects of cannabis and its main psychoactive constituent, THC. Despite the widespread legalization of cannabinoid products and their growing popularity in alleviating opioid withdrawal, only eleven mostly observational studies were deemed eligible for review. Results provide preliminary evidence that, although cannabis and THC may alleviate opioid withdrawal, these effects are likely to have a narrow therapeutic window. Further, withdrawal-alleviating effects of cannabinoids may depend on the type of opioid agonist, the baseline levels of opioid and cannabinoid exposure, individual factors, and the type of cannabis and constituent cannabinoid. More clinical and translational research is needed to ascertain whether the risk/benefit ratio of cannabinoids can be maximized during vulnerable periods of opioid pharmacotherapy, thereby improving quality of life and supporting recovery.

CRediT authorship contribution statement

JPD was responsible for the study concept and design. JPD, AB, and OG contributed to the acquisition of data. JPD, AB, and OG assisted with data analysis and interpretation of findings. JPD, AB, and OG drafted the manuscript. MS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version of the manuscript for publication.

Author Disclosures

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Conflict of Interest

No conflicts declared.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109702.

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