Clinical Psychology Review 82 (2020) 101939

Contents lists available at ScienceDirect

Clinical Psychology Review

journal homepage: www.elsevier.com/locate/clinpsychrev

Review

The relationship between cannabis use and patient outcomes in medication-based treatment of opioid use disorder: A systematic review

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A B S T R A C T

Despite high rates of cannabis use during medication-based treatment of opioid use disorder (MOUD), uncertainty remains around how cannabis influences treatment outcomes. We sought to investigate the relationship between cannabis use during MOUD and a number of patient outcomes. We searched seven databases for original peer-reviewed studies documenting the relationship between cannabis use and at least one primary outcome (opioid use, treatment adherence, or treatment retention) among patients enrolled in methadone-, buprenorphine-, or naltrexone-based therapy for OUD. In total, 41 articles (including 23 methadone, 7 buprenorphine, 6 naltrexone, and 5 mixed modalities) were included in this review. For each primary outcome area, there was a small number of studies that produced findings suggestive of a supportive or detrimental role of concurrent cannabis use, but the majority of studies reported that cannabis use was not statistically significantly associated with the outcome. No studies of naltrexone treatment demonstrated significantly worse outcomes for cannabis users. We identified methodological shortcomings and future research priorities, including exploring the potential role of adjunct cannabis use for improving opioid craving and withdrawal during MOUD. While monitoring for cannabis use may help guide clinicians towards an improved treatment plan, cannabis use is unlikely to independently threaten treatment outcomes.

1. Introduction

Opioid use disorder (OUD)[1] is a leading contributor to the global burden of disease from illicit drug use, which has grown by more than 50% since 2000 (Degenhardt et al., 2013). In jurisdictions across the United States and Canada, deaths from opioid-related overdose have skyrocketed as a result of the challenges associated with increased non-medical use of, and dependence on, prescription opioids (Paulozzi & Ryan, 2006) and the emergence of highly potent synthetic opioids (e.g., fentanyl) in the unregulated drug supply (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). Today, it is estimated that 353 in 100,000 people globally are living with an OUD, with high-income countries in North America experiencing a disproportionately high prevalence at 1168 per 100,000 (Degenhardt et al., 2018).

As OUD is a chronic disease with no cure, the current gold standard treatment for managing OUD is pharmacotherapy, usually in combination with psychosocial support such as counseling (Sofuoglu, DeVito, & Carroll, 2019). Three medication treatment modalities have been approved by the United States Food and Drug Administration (FDA): methadone (an opioid agonist), buprenorphine (a partial opioid agonist), and naltrexone (an opioid antagonist (Sofuoglu et al., 2019)). Under optimal treatment adherence and retention, medication-based treatment of OUD (MOUD) supports reductions in illicit opioid use (Mattick, Breen, Kimber, & Davoli, 2009), drug-related infectious disease (e.g., HIV, hepatitis C virus (Platt et al., 2017)), and overdose risk (Sordo et al., 2017), and supports retention in treatment for comorbidities (e.g., HIV (Lappalainen et al., 2015)) and improvements in health-related quality of life (Feelemyer, Des Jarlais, Arasteh, Phillips, & Hagan, 2014). However, patients tend to exhibit lower treatment retention when engaged in concurrent use of other substances including amphetamines, benzodiazepines, and cocaine (Hser et al., 2014). In some opioid treatment settings, testing positive for an illicit substance could result in termination of the treatment (McElrath, 2018).

The prevalence of cannabis use is high among patients seeking or receiving treatment for OUD (Bawor et al., 2015). Some studies have documented continued or intensifying cannabis use following MOUD initiation (Best et al., 2000; Nava, Manzato, & Lucchini, 2007; Schifano et al., 2012), and particularly in the interim period prior to dose stabilization (i.e., maintenance (Scavone, Sterling, Weinstein, & Van Bockstaele, 2013)). A number of early studies noted better clinical outcomes

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[1] Abbreviations: OUD = Opioid use disorder; MOUD = Medication-based treatment for opioid use disorder; THC = Tetrahydrocannabinol; CBD = Cannabidiol; PWUD = People who use drugs

https://doi.org/10.1016/j.cpr.2020.101939
Received 30 March 2020; Received in revised form 14 October 2020; Accepted 20 October 2020
Available online 24 October 2020

experienced by patients who engaged in cannabis use during methadone maintenance treatment (Best et al., 2000; Nirenberg, Liepman, Cellucci, Swift, & Sirota, 1996; Saxon, Wells, Fleming, Jackson, & Calsyn, 1996). These findings initially lent support to a hypothesis describing cannabis as a substitute for opioids during MOUD (Ellner, 1977), possibly as a strategy to self-manage symptoms of opioid withdrawal (e.g., pain, nausea)—an experimental practice documented as early as 1891 (Grinspoon, 1971). However, recent studies describing links between cannabis and worse (Fairbank, Dunteman, & Condelli, 1993) or unimproved (Epstein & Preston, 2003) methadone outcomes have since challenged this hypothesis. Further, although buprenorphine is now recommended as a first-line therapy in Canada (Bruneau et al., 2018) and interest in naltrexone as an alternative to methadone is growing (Ahamad et al., 2015), the potential impact of cannabis use on markers of success in these other OUD treatment modalities has not been well established.

In light of the quickly shifting legal landscape of medical and non-medical cannabis across North America and various European settings, along with the ongoing public health emergency of opioid-related overdose deaths, there is an urgent need to better understand how cannabis use might impact OUD treatment outcomes. This need comes at a time of polarized opinion within the medical community over the use of cannabis during MOUD. While some scientists are calling for increased exploration into cannabis-based interventions for OUD (Lucas, 2017; Rogeberg, Blomkvist, & Nutt, 2018), screening for cannabis remains a routine practice with potential consequences resulting from a positive test (e.g., denial of take-home doses) in some opioid treatment settings (Centre for Addiction and Mental Health, 2008; Substance Abuse and Mental Health Services Administration, 2015). We therefore sought to systematically search and review clinical and epidemiological literature to summarize the evidence on the impact of cannabis use on treatment outcomes for the three most common modalities of OUD pharmacotherapy—methadone, buprenorphine, and naltrexone.

2. Methods

We designed this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) group statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The protocol for this review has been registered in Prospero (CRD42019125097).

2.1. Search strategy

We searched the following scientific databases from inception to July 10, 2020: Medline, Embase, PsycInfo, Web of Science, CINAHL, and EBM Reviews. We combined search terms for cannabis and opioid substitution treatment (and their synonyms) using the appropriate Boolean operators. We included MeSH terms for cannabis and MOUD (e.g., "opioid substitution treatment", "methadone maintenance treatment") wherever possible. In addition, we searched Google Scholar with the terms "Cannabis" and "Opioids", retrieving all records with both terms in the title and the first 200 records with both terms as keywords. An example of our Medline search strategy is provided as a supplementary file (Table S1). Finally, we scanned reference lists of prominent articles and conference abstracts to manually add potentially relevant articles that had been missed in our database searches. We restricted our search to peer-reviewed articles published in the English language.

2.2. Eligibility criteria

Details pertaining to the population, interventions, comparison, outcomes and study designs (PICOS) of interest are provided in a supplemental table (Table S2). Briefly, studies that were considered relevant for this review were community-based epidemiological or clinic-based (observational or experimental) human research that assessed the association between cannabis use and clinical outcomes during methadone, buprenorphine, or naltrexone treatment for OUD using a quantitative measure of comparison (e.g., odds ratio, hazard ratio, proportional difference). We excluded qualitative research, case reports, case series, ecological studies, and descriptive studies. We only included studies that assessed the use of plant-based cannabis (as opposed to pharmaceutical cannabinoids such as dronabinol or nabilone) during treatment (i.e., at treatment outset or at least one time point throughout treatment) and did not restrict to any one method of detection (e.g., self-report, urine screen) or definition of cannabis use (e.g., any use, frequent use). However, we excluded studies if they only assessed lifetime exposure to cannabis or did not operationalize cannabis exposure at the patient-level (for example, living in a state with a medical cannabis law would not be considered an eligible exposure). The primary outcome areas of interest were: 1) opioid craving, opioid withdrawal, or non-prescribed opioid use; 2) treatment adherence; and 3) treatment stabilization and retention. We also considered the following secondary measures, wherever possible, from studies that reported at least one primary outcome: 1) health-related quality of life; and 2) other substance use during treatment.

2.3. Screening

All records were imported from their respective databases into Endnote (Version X7, Clarivate Analytics) and duplicates were removed. The primary author (SL) scanned all titles and eliminated records that clearly did not meet eligibility requirements (e.g., conference abstracts, articles published in a language other than English, commentaries). The remaining records were exported from Endnote into Covidence, a Cochrane-recommended online tool for streamlining the article screening and extraction process. In Covidence, both authors (SL and MSP) independently screened titles and abstracts for relevance. At this stage, articles were tagged as "Yes" (relevant), "No" (clearly not relevant") and "Maybe" (potentially relevant) based on information in the abstract. Only articles tagged with "Yes" or "Maybe" moved forward to the full-text screening stage. Any discordant coding by the reviewers resulting in conflict in the advancement of an article (i.e., "No/Maybe" or "No/Yes") was discussed until a consensus was reached. We adopted a conservative elimination approach at this stage whereby articles for which cannabis was possibly assessed but not mentioned in the abstract (e.g., studies examining predictors of treatment retention in which cannabis use was possibly measured but not reported in the abstract) were coded as "Maybe".

Full-text versions of all articles coded as "Yes/Yes", "Maybe/Yes", and "Maybe/Maybe" in the abstract screening stage were retrieved and independently assessed by the two reviewers. For each article eliminated at this stage, the main reason for exclusion was recorded. Any conflicts between reviewers were discussed until a consensus was reached.

2.4. Data extraction and quality assessment

For all articles meeting study eligibility, the primary author (SL) used a standardized form to capture detailed information on study methods, setting and population (including baseline group differences by cannabis use status if available), intervention/exposure, and outcomes. Data from each relevant study was abstracted in Covidence and assessed for completeness and accuracy by the secondary reviewer (MSP).

The National Institutes of Health's National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational and Cross-sectional studies was used to assess study quality (NIH NHLBI, n.d.). This tool uses 14 criteria to assess each study's potential for selection bias, information bias, measurement bias, and confounding. For each criteria item, the rater assigns an answer of "Yes" (indicating low potential for bias), "No" (indicating high potential for bias), "Not applicable", or "Cannot determine/Not recorded". As outlined by the NHLBI, these answers are not meant to translate into a final numeric score for overall

quality, but are useful in guiding the rater to a final assessment of the study's quality as "Poor", "Fair", or "Good". As some studies did not explicitly set out to quantify an independent association between cannabis use and a treatment outcome, but rather analyzed a cannabis use measurement post-hoc or as one of many patient characteristics, the quality rating assigned to each study may not necessarily reflect that study's propensity for reducing bias in addressing its primary research objective. The primary author (SL) rated all studies, and to ensure that ratings were fair and consistent, the secondary author (MSP) used the assessment tool to independently rate the quality of a random sample of 13 studies (32% of studies) and checked SL's scoring for the remaining studies. Any discrepancies in individual criteria assessments or overall quality ratings were discussed between reviewers until a consensus was reached. Although each study's quality rating was not directly based on numeric score, the proportion of eligible categories in which the raters marked "Yes" was calculated for each study after a quality rating was given. In general, this proportion was $> 75\%$ for studies rated as good quality, 50–75% for studies rated as fair quality, and $< 50\%$ for studies rated as poor quality.

2.5. Data synthesis and analysis

Owing to the substantial heterogeneity in cannabis exposure assessments, outcome measures, treatment modalities, and treatment times observed, we opted to not conduct a meta-analysis. We grouped studies by their assessed outcome and patient treatment modality (i.e., methadone, buprenorphine, naltrexone, mixed modalities) and conducted a qualitative assessment and narrative summary of findings. Study quality ratings were used to guide the narrative summary such that studies rated as good or fair quality were prioritized as example material to describe trends in findings. Wherever possible, we report adjusted estimates of the association between cannabis and an outcome. Bivariable estimates are reported in cases where cannabis was excluded from multivariable analyses or multivariable analyses were not performed.

3. Results

In total, 1686 (1143 unique) records were screened for eligibility. Title and abstract screening resulted in the exclusion of 1015 records. A full-text review of the remaining 128 articles resulted in a further 87 articles being excluded from consideration. A final 41 studies met the inclusion criteria. The PRISMA flowchart detailing the record screening and review process is shown in Fig. 1.

3.1. Summary of included studies

Among the 41 included studies, just over half ($n = 22$, 54%) were conducted in the United States, followed by Canada ($n = 5$), France and Israel ($n = 3$ each), Sweden and India ($n = 2$ each), and England, Scotland, Ireland and Italy ($n = 1$ each). One study used a comparative sample of patients from the United States and Israel. The median year of publication was 2014 (range: 1996–2019), and the median sample size was 176 (range: 36–7717). Methadone was the most commonly studied

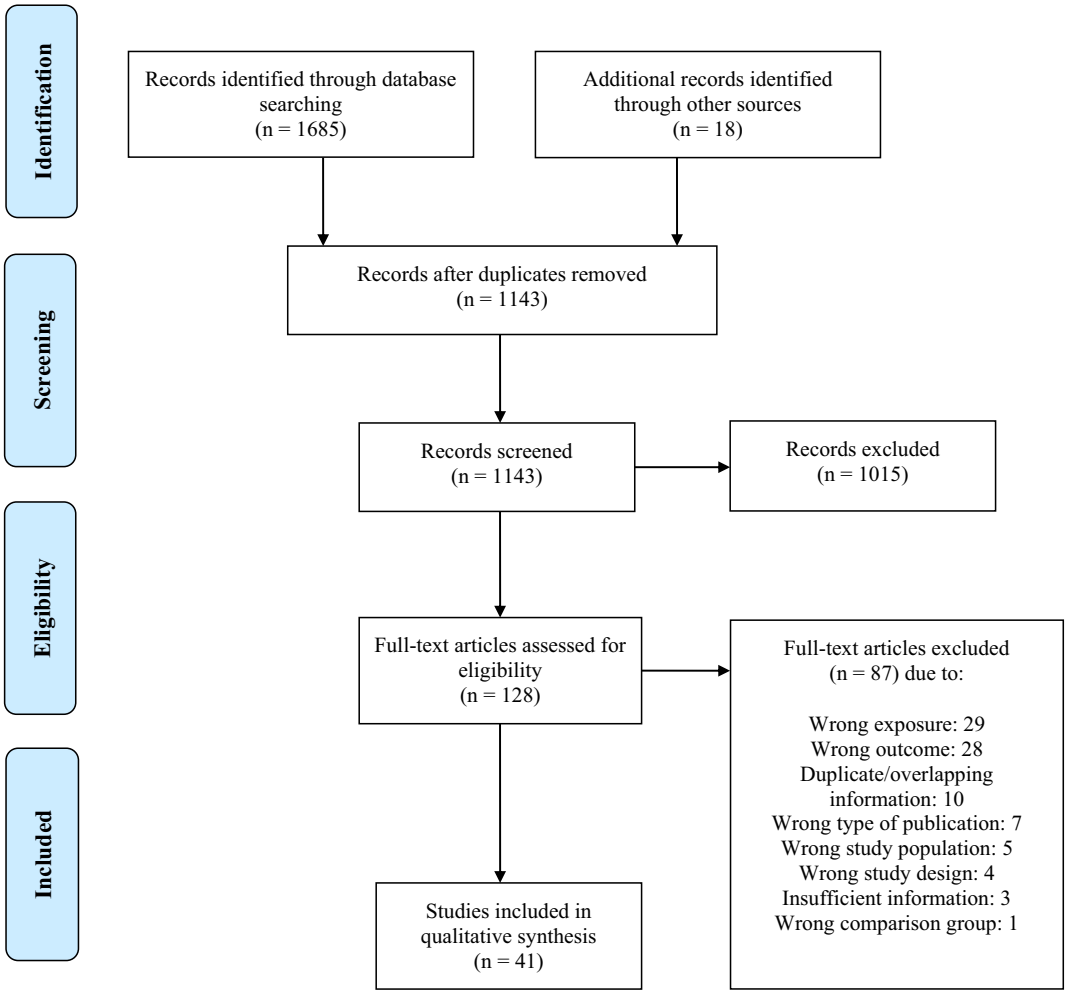

Fig. 1. PRISMA flow diagram illustrating the study selection process.

treatment modality ($n = 23$, 56%), followed by buprenorphine ($n = 7$, 17%) and naltrexone ($n = 6$, 15%). An additional five studies (12%) included patients on different modalities (e.g., methadone and buprenorphine patients). Several of the included studies examined multiple treatment outcomes, with retention being the most commonly studied primary clinical outcome across all treatment modalities ($n = 27$, 66%).

Study designs included clinic- or community-based prospective cohort studies ($n = 14$, 35%), secondary analyses of clinical trials ($n = 13$, 32%), retrospective patient chart reviews ($n = 9$, 23%), and cross-sectional studies ($n = 5$, 13%). No clinical trial with the primary objective of investigating plant-based cannabis as an adjunct treatment to OUD pharmacotherapy was identified. The majority of studies ($n = 24$, 59%), including 36% of prospective cohort, 62% of clinical trials, 89% of retrospective chart reviews, and 60% of cross-sectional studies, were rated as having fair methodological quality in assessing the relationship between cannabis use and a treatment outcome. Eight (20%) studies were considered good methodological quality, and nine (22%) were rated as poor. While all four study designs contributed to the poorly rated studies (including 36% of prospective cohort, 8% of clinical trials, 11% of retrospective chart reviews, and 40% of cross-sectional studies), only studies with prospective cohort (29%) and clinical trial designs (31%) were rated as having good quality. A detailed breakdown of the quality assessments for each study is provided in a supplementary file (Table S3).

3.2. Cannabis use measures

There was a high degree of heterogeneity across studies with regard to cannabis exposure assessment. Cannabis use was a primary focus in just over one-third ($n = 15$) of the included studies (Bagra, Krishnan, Rao, & Agrawal, 2018; Best et al., 1999; Budney, Bickel, & Amass, 1998; Epstein & Preston, 2003; Epstein & Preston, 2015; Franklyn, Eibl, Gauthier, & Marsh, 2017; Hill et al., 2013; Nava et al., 2007; Nirenberg et al., 1996; Raby et al., 2009; Scavone et al., 2013; Shams et al., 2019; Socías et al., 2018; Weizman, Gelkopf, Melamed, Adelson, & Bleich, 2004; Zielinski et al., 2017). These studies tended to record more detailed information about patterns of use (e.g., categorizing frequency of use, repeated measures throughout treatment) than studies in which cannabis was one of many potential predictors of a treatment outcome. Just over half of the studies ($n = 22$, 54%) used urine drug screens (UDS) to assess exposure to tetrahydrocannabinol (THC; the phytocannabinoid in cannabis responsible for its intoxicating effect). The remaining studies ($n = 19$, 45%) ascertained self-reported measurements of cannabis use with interviewer-administered questionnaires and scales. Less than half of studies ($n = 17$, 41%) produced an adjusted estimate of the association between cannabis use and a treatment outcome; however, potentially important confounding factors, including co-occurring substance use patterns and treatment dose, were rarely accounted for.

Most studies provided prevalence estimates for cannabis use at treatment baseline and/or throughout the study period. Using information from these studies, the median prevalence of cannabis use at treatment baseline was 23% (range: 12–67%), and the median prevalence of frequent (i.e., near-daily or daily) cannabis use was 18.5% (range: 16–33%). The median recorded cumulative prevalence of cannabis use throughout treatment (of varying lengths) was 58% (range: 28–79%).

3.3. Opioid craving, withdrawal, and non-prescribed use

Studies measuring non-medical opioid use (or influencing factors such as opioid craving and withdrawal) during MOUD are summarized in Table 1. We identified 23 studies (including 14 methadone (Best et al., 1999; Epstein & Preston, 2003; Levine et al., 2015; Nava et al., 2007; Nirenberg et al., 1996; Proctor et al., 2016; Scavone et al., 2013; Shams et al., 2019; Somers & O'Connor, 2012; Wasserman, Weinstein, Havassy, & Hall, 1998; Zielinski et al., 2017)), four buprenorphine (Abrahamsson et al., 2016; Bagra et al., 2018; Budney et al., 1998; Hill et al., 2013), two naltrexone (Church, Rothenberg, Sullivan, Bornstein, & Nunes, 2001; Raby et al., 2009), and three mixed modalities (Eastwood, Strang, & Marsden, 2019; Potter et al., 2013; Roux et al., 2011)) that examined associations between cannabis use and opioid use during treatment. The results of these studies produced mixed evidence resulting in no consistent pattern of a positive or negative impact of cannabis use at treatment outset or during treatment. The majority of studies ($n = 14$, 61%, including nine methadone (Epstein & Preston, 2003; Epstein & Preston, 2015; Levine et al., 2015; Lions et al. Lions et al., 2014; Nava et al., 2007; Nirenberg et al., 1996; Scavone et al., 2013; Somers & O'Connor, 2012; Weizman et al., 2004), all four buprenorphine (Abrahamsson et al., 2016; Bagra et al., 2018; Budney et al., 1998; Hill et al., 2013), and one naltrexone (Raby et al., 2009)) produced estimates that did not meet statistical significance. For example, Epstein and Preston (2003) analyzed secondary data from three methadone trials and did not find that individuals who used cannabis after achieving abstinence had a significantly higher risk of an opioid relapse (HR = 1.20, 95% CI: 0.69–2.09). Hill et al. (2013) conducted a secondary analysis of data from a trial comparing a 12-week buprenorphine-naloxone treatment to a two-week buprenorphine-naloxone detoxification among young opioid dependent patients and did not detect significantly different odds of opioid use for those who screened positive for cannabis use at baseline (OR = 0.99, 95% CI: 0.96–1.01) or throughout treatment (OR = 1.56, 95% CI: 0.86–2.80).

A small number of studies ($n = 4$, 17%, including three methadone (Proctor et al., 2016; Wasserman et al., 1998; Zielinski et al., 2017) and one mixed modalities (Roux et al., 2011)) noted possible negative impacts of cannabis use during treatment. For example, Wasserman et al. (1998) prospectively studied patients who had been stabilized on methadone for over three weeks and observed that self-reported cannabis use significantly increased the likelihood of subsequent relapse to heroin use ($X^2 = 7.62$, $p < 0.05$). By contrast, five studies (22%, including two methadone (Best et al., 1999; Shams et al., 2019), one naltrexone (Church et al., 2001), and two mixed modalities (Eastwood et al., 2019; Potter et al., 2013)) found evidence of significantly lower prevalence or frequency of opioid use among cannabis using patients. However, these studies were mixed in documenting a possible dose-response relationship between cannabis use and opioid use frequency. For example, in their cross-sectional study of patients on methadone, Shams et al. (2019) noted that any past 30-day cannabis use was significantly negatively associated with past 30-day heroin use (AOR = 0.45, 95% CI: 0.24–0.86), but no dose-response effect among cannabis users was observed. In a cross-sectional study of 200 methadone patients, Best et al. (1999) noted a statistically significant inverse relationship between cannabis and heroin use frequency, with cannabis non-users reporting the highest number of heroin use days in the previous month (5.8 days on average) and daily cannabis users reporting the fewest (0.8 heroin use days on average; $F = 11.07$, $p < 0.001$). However, a secondary analysis of a naltrexone trial recorded significantly fewer opioid-positive urine drug screens among moderate cannabis users (15.0%), but not frequent users (71.4%), relative to non-users (60.0%; $F = 9.381$, $p < 0.001$ (Church et al., 2001)).

Of the five studies (including three methadone (Epstein & Preston, 2015; Nava et al., 2007; Scavone et al., 2013), one buprenorphine (Bagra et al., 2018), and one naltrexone (Bisaga et al., 2015)) that measured opioid craving and/or withdrawal, three (60%, including two methadone (Epstein & Preston, 2015; Nava et al., 2007), and one buprenorphine (Bagra et al., 2018)) did not find a statistically significant relationship between cannabis use and opioid craving or withdrawal. The remaining two studies noted a significant reduction in at least one measurement of opioid withdrawal among cannabis users. For example, Scavone et al. (2013) conducted a retrospective chart review of 91 methadone outpatients and found a statistically significant inverse relationship between cannabis use frequency (categorized into none, occasional, frequent) and severity of opioid withdrawal during

Table 1
Summary of included studies: opioid craving, withdrawal, and non-prescribed use.

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Best et al. (1999); Scotland	Cross-sectional study	Fair	200 methadone patients on at a community drug clinic (mean age = 32 years, 30% women)	Past 30-day frequency (days) of cannabis use, self-reported at time of study, categorized as no use, occasional use, daily use	Past 30-day frequency (days) of heroin use, self-reported at time of study	The mean number of heroin use days was significantly higher for cannabis non-users (5.8) compared to occasional users (1.6) and daily users (0.8; $F = 11.07$; $p < 0.001$); the association remained significant in multivariable linear regression ($\beta = -0.248$, $p < 0.001$)
Epstein and Preston (2003); USA	Secondary analysis of pooled data from three clinical trials	Good	408 methadone outpatients from 3 clinical trials (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed by weekly UDS, categorized as 0%, 1–17%, 18–100%	(1) Frequency of opioid use, assessed with weekly UDS; (2) Relapse to opioid use after ≥3 weeks of abstinence, assessed with UDS	(1) Cannabis use frequency was not significantly associated with opioid use during stabilization or maintenance phases ($p > 0.05$); (2) Cannabis use during opioid abstinence was not a significant predictor of relapse to opioid use (HR = 1.20, 95% CI = 0.69–2.09; $p = 0.52$)
Epstein and Preston (2015); USA	Secondary analysis of a clinical trial	Fair	116 outpatients in a methadone taper phase of a clinical trial (mean age = 39 years, 47% women)	Any cannabis use, assessed with weekly UDS for 10 weeks	(1) Severity of opioid withdrawal, self-reported with 24-item symptom assessment questionnaire, assessed every 2 weeks; (2) Frequency of opioid use, assessed with weekly UDS	(1) Cannabis users had slightly higher withdrawal scores than non-users (least squares mean 28.29 vs. 26.06), but the difference was not significant ($F = 0.33$, $p = 0.57$); past-week cannabis use was not significantly associated with lower next-week withdrawal score ($F = 0.001$, $p = 0.98$); (2) Cannabis users and non-users had similar mean percentage of opioid-positive UDS (54% vs. 52%; p-value not reported)
Levine et al. (2015); USA	Retrospective chart review	Fair	290 methadone outpatients from one clinic (mean age = 50 years, 40% women)	Any cannabis use, assessed with UDS at treatment baseline	Frequency of opioid use over 1 year, assessed with UDS	Cannabis use in the first month of treatment was not significantly associated with opioid use among men or women in the study (statistics not reported)
Lions et al. (2014); France	Secondary analysis of a clinical trial	Fair	158 patients initiating methadone in either primary care or a specialized centre (median age = 33 years, 15% women)	Past-month daily cannabis use, assessed with OTI at treatment baseline and 12 months	Past-month opioid use, assessed with OTI at 12 months	Baseline cannabis use was not significantly associated with opioid use at 12 months (OR = 1.46, 95% CI = 0.61–3.53); daily cannabis use at 12 months was significantly associated with opioid use at 12 months in bivariable (OR = 2.81, 95% CI = 1.22–6.48) but not multivariable analysis (statistics not reported)
Nava et al. (2007); Italy	Prospective cohort study	Poor	121 community-recruited patients beginning methadone treatment (mean age = 29 years, 13% women)	Heavy cannabis use, defined as past 6 month use and current use ≥7 times per week, self-reported at treatment baseline	(1) Heroin craving, assessed with VAS at months 1, 3, 12; (2) Heroin withdrawal, assessed with Wang Scale at months 1, 3, 12; (3) Frequency of opioid use over 1 year, assessed with weekly UDS	(1) Significant reduction in opioid cravings among cannabis users ($Z = -5.24$, $p < 0.001$) and non-users ($Z = -5.02$, $p < 0.001$), but no significant between-group differences (statistics not reported); (2) Significant reduction in withdrawal symptoms among cannabis users ($Z = -7.58$, $p < 0.001$) and non-users ($Z = -7.30$, $p < 0.001$), but no significant between-group differences (statistics not reported); (3) Significant reduction in opioid use among cannabis users ($Z = -3.42$, $p < 0.001$) and non-users ($Z = -3.18$, $p <$

(continued on next page)

Table 1 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
						0.001), but no significant between-group differences (statistics not reported)
Nirenberg et al. (1996); USA	Prospective cohort study	Poor	70 methadone outpatients at an urban veterans medical site (mean age = 39 years, 1% women)	Frequency of cannabis, assessed with weekly UDS for 45 weeks, categorized as none (0%), intermittent (1–33%), moderate (34–67%), and consistent (68–100%)	Frequency of opioid use, assessed with weekly UDS for 45 weeks	No significant difference observed in the mean percent of opioid-positive UDS between cannabis non-users (10.8%), intermittent users (22.0%), moderate users (19.4%) or consistent users (8.8%; $F = 1.13$, $p = 0.34$)
Potter et al., 2013; USA	Secondary analysis of a clinical trial	Fair	731 participants who completed a 24-week methadone vs. buprenorphine-naloxone trial* *See Hser et al. for demographics of initial study sample	Past-year cannabis dependence diagnosis, assessed with WHO CIDI or DSM-IV checklist at treatment baseline	Any past 30-day opioid use, self-reported at the end of the 24-week trial	Patients with a baseline diagnosis of cannabis dependence were significantly less likely to report continued opioid use at the end of the trial (AOR = 0.48, 95% CI: 0.25–0.92)
Proctor et al. (2016); USA	Retrospective chart review	Fair	2410 methadone inpatients from 26 treatment sites across the USA (mean age = 35 years, 40% women)	Any cannabis use, assessed with UDS at intake (month 0) and months 3, 6, 9	Frequency of opioid use, assessed with UDS at months 3, 6, 9, and 12	Cannabis use at intake was not significantly associated with opioid use at any assessment (OR range = 0.23–1.17, all $p > 0.05$); Cannabis use in month 3 (AOR = 2.03, 95% CI = 1.03–3.98) and 9 (AOR = 5.19, 95% CI = 1.26–21.47) was associated with opioid use 3 months later; Cannabis use at month 6 was not associated with opioid use 3 months later (AOR = 0.31, 95% CI = 0.09–1.14)
Saxon et al. (1996); USA	Secondary analysis of a clinical trial	Fair	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Past 6-month frequency of cannabis use, self-reported using ASI at treatment intake, categorized on a scale from 0 (never) to 6 (≥4 times/day)	Frequency of opioid use, assessed with weekly UDS for up to 2 years	Baseline cannabis use frequency was not significantly associated with opioid use frequency during treatment (unadjusted β = 0.05, $p > 0.05$)
Scavone et al. (2013); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 40% women)	(1) Frequency of cannabis use, assessed with monthly UDS over 9 months, categorized as none, occasional (1–3 months), frequent (>3 months) or expressed as a percentage	(1) Opioid withdrawal severity, assessed with COWS during induction phase (subsample, $n = 40$); (2) Frequency of opioid use during induction and stabilization phases, assessed with monthly UDS	(1) Severity of opioid withdrawal decreased significantly with increasing cannabis use frequency category ($X^2 = 6.71$, $p = 0.035$); (2) Percentage of THC-positive UDS did not correlate significantly with opioid-positive UDS during induction ($r = 0.104$, $p = 0.332$) or stabilization ($r = 0.038$, $p = 0.734$)
Shams et al., 2019; Canada	Cross-sectional study	Fair	640 methadone patients recruited from 14 treatment sites across the province of Ontario (mean age = 38.8, 45.8% female)* *Study sample and timeframe overlaps with Zielinski et al., 2017; only outcomes that were not reported in Zielinski et al., 2017 are reported here.	(1) Any past 30-day cannabis use, self-reported using MAP at time of study (2) Past 30-day "heaviness" of cannabis use, self-reported using MAP at time of study (calculated as [n days used*typical dose in grams])	(1) Any past 30-day heroin use, self-reported using MAP at time of study (2) Any past 30-day illicit methadone use, self-reported using MAP at time of study	(1) Past 30-day cannabis use was significantly negatively associated with past 30-day heroin use (AOR = 0.45, 95% CI = 0.24–0.86); heaviness of cannabis use was not significantly associated; (2) Past 30-day cannabis use was not associated with past 30-day illicit methadone use (AOR = 1.73, 95% CI = 0.36–9.26); heaviness of cannabis use was not significantly associated
Somers and O'Connor (2012); Ireland	Retrospective chart review	Fair	117 patients starting methadone at one treatment site (mean age = 34 years, 36% women)	Any cannabis use, assessed with UDS, assessed at treatment baseline (month 0) and months 3, 9, 15	Opioid use, defined as ≥20% heroin-positive UDS during the 8-week period proceeding each exposure assessment	Cannabis use was not significantly associated with subsequent opioid use at any assessment point (OR range = 0.78–1.45, all $p < 0.05$)
Wasserman et al. (1998); USA	Prospective cohort study	Fair	74 patients stabilized on methadone treatment with ≥3 weeks of opioid abstinence (mean age = 43 years, 41% women)	Any cannabis use, self-reported and confirmed with UDS at baseline, 8 weeks, 6 months	Relapse to heroin use, assessed with UDS during weeks 2–8 and 6 months post-baseline	Baseline cannabis use was significantly associated with heroin relapse in weeks 2–8 (Cox $X^2 = 8.39$, $p < 0.004$) and 6 months later (Cox $X^2 = 7.90$,

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Table 1 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
						$p < 0.005$); cannabis use was significantly associated with relapse to heroin in the subsequent week (Cox $X^2 = 7.62$, $p < 0.006$)
Weizman et al. (2004); Israel	Prospective cohort study	Fair	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis abuse, assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	Heroin use, assessed with UDS at 12 months	Cannabis use was not significantly associated with heroin use 12 months after treatment initiation (statistics not reported)
Zielinski et al. (2017); Canada	Cross-sectional study	Fair	777 methadone patients recruited from 16 treatment sites across the province of Ontario (mean age = 38 years, 47% women)	(1) Any past 30-day cannabis use, self-reported using MAP at time of study; (2) Past 30-day "heaviness" of cannabis use, self-reported using MAP at time of study (calculated as [n days used*typical dose in grams])	Any past 3-month opioid use, assessed with regular (approx. weekly) UDS	(1) Cannabis use was not significantly associated with illicit opioid use overall (AOR = 1.16, 95% CI = 0.77–1.75); cannabis use was significantly associated with opioid use among women (AOR = 1.82, 95% CI = 1.18–2.82) but not men (AOR = 1.11, 95% CI = 0.73–1.69); (2) Heaviness of cannabis use was not significantly associated with opioid use among men (AOR = 1.01, 95% CI = 1.00–1.01) or women (AOR = 1.00, 95% CI = 0.99–1.01)
2. Buprenorphine						
Abrahamsson et al. (2016); Sweden	Prospective cohort study	Fair	44 outpatients initiating interim buprenorphine-naloxone treatment phase (mean age = 35 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported at treatment/study baseline	Any opioid use, assessed with UDS during interim treatment phase	Opioid-abstinent patients reported fewer mean days of cannabis use at baseline (5.9 vs. 8.6), but the difference was not significant ($p > 0.100$)
Bagra et al. (2018); India	Cross-sectional study	Poor	100 outpatients on buprenorphine-naloxone for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	(1) Any past 3-month opioid craving, self-reported at time of study; (2) Past 3-month opioid withdrawal, self-reported at time of study; (3) Past 3-month opioid use, self-reported using ASSIST at time of study	(1) Cannabis users had higher prevalence of opioid craving (22.9% vs. 16.9%), but the difference was not significant ($p = 0.650$); (2) Cannabis users had higher prevalence of acute (22.9% vs. 13.8%) and protracted (28.6% vs. 27.7%) opioid withdrawal symptoms, but the differences were not significant ($p = 0.748$, $p = 1.00$, respectively); (3) Cannabis users had higher prevalence of opioid use during treatment (17.1% vs. 13.8%), but the difference was not significant ($p = 0.660$)
Budney et al. (1998); USA	Secondary analysis of pooled data from three clinical trials	Fair	79 patients undergoing a 7–22 week buprenorphine taper and behavioural therapy, derived from a larger ($n = 107$) patient sample (mean age = 34 years, 37% women)	(1) Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS (2) Frequency of cannabis use, assessed with thrice-weekly UDS	Weeks of continuous opioid abstinence, assessed with thrice-weekly UDS	(1) Weeks of continuous opioid abstinence was not significantly different between cannabis users and non-users (8.4 vs. 8.5 weeks, $p > 0.05$); (2) Frequency of cannabis use did not correlate significantly with weeks of opioid abstinence ($r = -0.07$, p > 0.05)
Hill et al. (2013); USA	Secondary analysis of a clinical trial	Good	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	(1) Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1–19), frequent (≥20); (2) Cannabis use during treatment, assessed with UDS at weeks 4, 8, 12	Opioid use, assessed with UDS at weeks 4, 8, 12	(1) Baseline cannabis use frequency was not significantly associated with opioid use (OR = 0.99, 95% CI = 0.96–1.01); (2) Cannabis use during treatment was not significantly associated with opioid use (OR = 1.56, 95% CI = 0.86–2.80)
3. Naltrexone						
Bisaga et al. (2015); USA		Fair	60 patients initiating 8-week depot naltrexone trial with	Weekly cannabis use, self-reported (and confirmed	(1) Any opioid cravings, self-reported at baseline	(1) Weekly cannabis use during outpatient treatment

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Table 1 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
	Secondary analysis of a clinical trial		dronabinol (n = 40) or placebo (n = 20; mean age = 30 years, 17% women)	with UDS) at treatment baseline and weekly throughout trial	and weekly throughout 8-week trial; (2) Acute and protracted withdrawal symptoms, assessed with SOWS and HAM-D, respectively at baseline and weekly throughout trial	was not significantly associated with opioid craving (statistics not reported); (2) Weekly cannabis use at baseline was not significantly associated with acute withdrawal during inpatient phase ($F < 0.01$, $p = 0.96$); cannabis use during outpatient phase was not associated with acute withdrawal (statistics not reported), but was associated with lower severity of protracted withdrawal ($F = 4.43$, $p = 0.037$), driven by lower insomnia and anxiety scores
Church et al. (2001); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 24 weeks, categorized as none (0%), intermittent (1–50%), daily (51–100%)	Frequency of opioid use, assessed with weekly UDS over 24 weeks	Intermittent cannabis users had significantly fewer opioid-positive UDS (15.0%) compared to daily cannabis users (71.4%) and non-users (60.0%; $F = 9.381$, $p < 0.001$)
Raby et al. (2009); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1–79%), and consistent (≥80%)	Frequency of opioid use, assessed with twice-weekly UDS for 6 months	The mean proportion of treatment weeks with opioid-positive UDS did not differ significantly between cannabis non-users (0.37), intermittent users (0.25), and consistent users (0.39; $F = 0.80$, $p = 0.46$)
4. Mixed treatments						
Eastwood et al. (2019); England	Prospective cohort study	Good	7717 patients enrolled in methadone or buprenorphine treatment in England (mean age = 34 years, 27.9% women)	Cannabis use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months, categorized as Class 1 ("continued low-level"), Class 2 ("low and decreasing"), Class 3 ("high and increasing")	Heroin use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months	Members of the "decreasing" and "low-level" heroin use trajectories tended to belong to the "high and increasing" cannabis use group; e.g., relative to the "continued high-level" heroin group, "rapidly decreasing" heroin users were significantly more likely to be "high and increasing" cannabis users (RRR = 2.04, 95% CI = 1.62–2.56); please refer to the original study and its supplementary files for all findings
Roux et al. (2011); France	Prospective cohort study	Poor	235 community- recruited PWUD with HIV enrolled in methadone or buprenorphine treatment (median age = 34 years, 31% women)	Past 6-month daily cannabis use, self-reported every 6 months	Any non-medical use of opioids in the previous 6 months, self-reported every 6 months	Daily cannabis use was significantly associated with non-medical opioid use (AOR = 1.32, 95% CI = 1.08–1.60)

Note: 95% CI = 95% Confidence interval; (A)HR = (Adjusted) Hazard ratio; (A)OR = (Adjusted) Odds ratio; ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; CIDI = Composite International Diagnostic Interview; COWS = Clinical Opiate Withdrawal Scale; HAM-D = Hamilton Rating Scale for Depression; MAP = Maudsley Addiction Profile; PWUD = People who use drugs; RRR = Relative risk ratio; 95% CI = 95% Confidence interval; SCID-1 = Structural Clinical Interview for DSM-IV Axis 1 Disorders; SOWS = Subjective Opiate Withdrawal Scale; UDS = Urine drug screen; VAS = Visual Analogue Scale

treatment induction ($X^2 = 6.71$, $p = 0.035$); however, it should be noted that they did not observe a significant negative correlation between percentage of cannabis-positive and opioid-positive urine screens during this treatment stage ($r = 0.104$, $p = 0.332$). In a secondary analysis of a trial of dronabinol (a synthetic isomer of THC) as an adjunct treatment during a naltrexone induction, Bisaga et al. (2015) found that, although weekly cannabis use during the outpatient phase was not significantly associated with differences in opioid craving or acute withdrawal severity, weekly cannabis users exhibited significantly lower severity of protracted withdrawal symptoms ($F = 4.43$, $p = 0.037$)—a finding driven by lower insomnia and anxiety scores among weekly cannabis users.

3.4. Treatment adherence

A total of six studies (including two methadone (Roux et al., 2014; Scavone et al., 2013), two buprenorphine (Bagra et al., 2018; Fareed et al., 2014), and two naltrexone (Church et al., 2001; Raby et al., 2009)) measured cannabis use as a potential predictor of adherence to pharmacotherapy and are summarized in Table 2. Cannabis was not significantly associated with treatment adherence in the methadone studies (Roux et al., 2014; Scavone et al., 2013) and one of two buprenorphine studies (Bagra et al., 2018). The other buprenorphine study, which was rated as poor quality, found that patients who used cannabis were significantly less likely to adhere to their treatment, as denoted by a urine drug screen and pill count at a call-back interview ($\beta = 0.24$, one-sided $p = 0.02$ (Fareed et al., 2014)). The remaining two studies were

Table 2
Summary of included studies: treatment adherence.

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Roux et al. (2014); France	Secondary analysis of a clinical trial	Fair	145 patients on methadone treatment in a multi-site open-label clinical trial (median age = 32 years, 15% women)	Daily cannabis use in the previous month, self-reported with OTI at baseline (month 0) and months 3, 6, 12	Adherence to methadone, self-reported using a questionnaire at baseline (month 0) and months 3, 6, 12	Baseline cannabis use was not significantly associated with adherence at 12 months (OR = 1.19, 95% CI = 0.47–2.98; cannabis use at 12 months was not significantly associated with adherence at 12 months (OR = 1.92, 95% CI = 0.76–4.78)
Scavone et al. (2013); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 40% women)	(1) Past 30-day cannabis use, self-reported at treatment intake; (2) Any cannabis use, assessed with monthly UDS for 9 months	Total number of daily dispensation absences in the first 9 months of treatment	(1) Baseline cannabis use was not a significant predictor of treatment non-adherence ($t = 0.982$, $p = 0.330$); (2) Cannabis use in the methadone induction (pre-stabilization) phase was not associated with medication non-adherence ($t = 1.212$, $p = 0.230$)
2. Buprenorphine						
Bagra et al. (2018); India	Cross-sectional study	Poor	100 outpatients on buprenorphine for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	Mean number of days treatment was taken in the past 3 months at time of study	The mean number of compliant treatment days did not differ significantly between cannabis users and non-users (86.2 vs. 87.3, $p = 0.584$)
Fareed et al. (2014); USA	Cross-sectional study	Poor	69 buprenorphine-naloxone outpatients from a veteran affairs medical center (mean age = 52 years, 6% women)	Any cannabis use, assessed with UDS at call-back interview	Treatment adherence at time of call-back, determined by correct pill count and buprenorphine-positive UDS	Cannabis use was significantly associated with treatment non-compliance ($\beta = 0.24$, one-sided $p = 0.02$)
3. Naltrexone						
Church et al. (2001); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 24 weeks, categorized as none (0%), intermittent (1–50%), daily (51–100%)	Proportion of all naltrexone doses taken in 24-week period, reported by patient's significant other	Intermittent cannabis use was significantly associated with improved treatment compliance (81.2% of doses taken) compared to frequent cannabis use (34.6%) and non-use (32.8%; $F = 8.454$, $p < 0.001$)
Raby et al. (2009); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1–79%), and consistent (≥80%)	Treatment adherence, assessed with twice-weekly UDS over 6 months	Treatment adherence was significantly higher in intermittent cannabis users (0.86) than non-users (0.56) or consistent users (0.69; $F = 3.40$, $p = 0.03$)

Note: 95% CI = 95% Confidence interval; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; OR = Odds ratio; OTI = Opioid Treatment Index; UDS = Urine drug screen.

secondary analyses of naltrexone trials and both noted an inverted-U-shaped dose-response trend in which intermittent cannabis users exhibited significantly improved adherence relative to non-users or consistent users (Church et al., 2001; Raby et al., 2009).

3.5. Treatment retention

As shown in Table 3, we identified 27 studies (including 13 methadone (Epstein & Preston, 2003; Franklyn et al., 2017; Joe, 1998; Klimas et al., 2018; Nava et al., 2007; Peles, Linzy, Kreek, & Adelson, 2008; Peles, Schreiber, Sason, & Adelson, 2018; Scavone et al., 2013; Schiff, Levit, & Moreno, 2007; Weizman et al., 2004; White et al., 2014), five buprenorphine (Abrahamsson et al., 2016; Budney et al., 1998; Håkansson, Widinghoff, Abrahamsson, & Gedeon, 2016; Hill et al., 2013; Matson, Hobson, Abdel-Rasoul, & Bonny, 2014), six naltrexone (Bisaga et al., 2015; Chaudhry, Sultan, & Alam, 2012; Church et al., 2001; Dayal, Balhara, & Mishra, 2016; Jarvis et al., 2018; Raby et al., 2009) and three mixed modalities (Eastwood et al., 2019; Hser et al., 2014; Socías et al., 2018)) that examined a possible association between cannabis use and treatment retention or stabilization. Similar to the findings for opioid use, the majority of these studies ($n = 17$, 63%, including nine methadone (Epstein & Preston, 2003; Joe, 1998; Klimas et al., 2018; Nava et al., 2007; Peles et al., 2008; Peles et al., 2018; Saxon et al., 1996; Scavone et al., 2013; Weizman et al., 2004), four buprenorphine (Abrahamsson et al., 2016; Budney et al., 1998; Håkansson et al., 2016; Hill et al., 2013), and four naltrexone (Chaudhry et al., 2012; Church et al., 2001; Dayal et al., 2016; Jarvis et al., 2018)) did not find that cannabis use was significantly associated with a patient's length of time in, or ability to stabilize on, treatment. For example, Peles et al. (2008) analyzed data from two prospective cohorts of methadone patients in Las Vegas, USA and Tel Aviv, Israel and found similar retention times between patients who did and did not use cannabis after one year of treatment in Tel Aviv (3.4 vs. 3.7 years, respectively; $X^2 = 1.8$, $p = 0.20$) and Las Vegas (2.1 vs. 2.5 years, respectively; $X^2 = 0.8$, $p = 0.40$); although retention time was significantly shorter for patients who used cannabis at treatment baseline in Las Vegas (1.6 vs. 2.2 years, respectively, $X^2 = 4.2$, $p = 0.04$), the authors noted that the association lost significance after adjusting for several treatment covariates. Five studies (19%; including three methadone (Franklyn et al., 2017; Levine et al., 2015; White et al., 2014), one buprenorphine (Matson et al., 2014), and one mixed modalities (Hser et al., 2014)) suggested a possible negative impact of cannabis on treatment retention. For example, in their chart review of young opioid-dependent outpatients treated with buprenorphine-naloxone, Matson et al. (2014) noted that

Table 3
Summary of included studies: treatment stabilization and retention.

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
1. Methadone						
Epstein and Preston (2003); USA	Secondary analyses of pooled data from three clinical trials	Good	408 outpatients in clinical methadone treatment studies (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed with weekly UDS, categorized as 0%, 1–17%, 18–100%	Time to treatment discontinuation, up to 25 weeks (2 studies) or 29 weeks (1 study)	Frequency of cannabis use during treatment was not significantly associated with drop-out (range of *p*-values from survival analysis in 3 studies = 0.62–0.79)
Franklyn et al. (2017); Canada	Retrospective chart review	Fair	644 patients initiating methadone at 58 treatment sites in Ontario (median age = 33 years, 44% women)	(1) Any cannabis use at baseline, assessed with UDS; (2) Heavy cannabis use during treatment, assessed with UDS for 18 months, categorized as ≥75% vs. <75%	Time to treatment discontinuation, up to approx. 18 months	(1) Baseline cannabis use was significantly associated with drop-out (AHR = 1.39, 95% CI = 1.06–1.83); in sex-stratified analyses, baseline cannabis use was significantly associated with drop-out in women but not men (2) Heavy cannabis use was significantly associated with drop-out (AHR = 1.48, 95% CI = 1.13–1.93); in sex-stratified analyses, heavy use was associated with drop-out among men but not women
Joe (1998); USA	Prospective cohort study	Fair	981 outpatients on methadone treatment at 11 sites (mean age = 37 years, 39% women)	Weekly cannabis use, self-reported at treatment/ study intake	Retained in treatment for at least 360 days	Baseline weekly cannabis use was not significantly associated with treatment discontinuation (AOR = 1.14, $p > 0.05$)
Klimas et al. (2018); Canada	Prospective cohort study	Poor	823 community-recruited PWUD on methadone treatment and report alcohol use (median age = 42 years, 40% women)	Past 6-month daily cannabis use, self-reported every 6 months	Time to treatment discontinuation, estimated as the mid-point between last interview report of MMT to first interview report of no MMT	Daily cannabis use was not significantly associated with treatment discontinuation (HR = 0.84, 95% CI = 0.65–1.11)
Levine et al. (2015); USA	Retrospective chart review	Fair	290 methadone outpatients from one clinic (mean age = 50 years, 40% women)	Any cannabis use, assessed with UDS in the first month of treatment	Retained in treatment for at least 1 year	Cannabis abstinence in the first month of treatment was significantly associated with being retained on treatment 1 year later among men (AOR = 5.00, 95% CI = 1.61–14.29) and women (AOR = 9.09, 95% CI = 2.33–33.33)
Nava et al. (2007); Italy	Prospective cohort study	Poor	121 community-recruited patients beginning methadone treatment (mean age = 29 years, 13% women)	Heavy cannabis use, defined as past 6-month use and current use ≥7 times per week, self-reported at treatment baseline	Treatment discontinuation, assessed at 2 weeks, 3 months, 12 months post-intake	Cannabis users had slightly higher treatment retention, but the difference was not significant (statistics not reported)
Peles et al. (2008); USA & Israel	Prospective cohort study	Good	794 methadone outpatients from treatment clinics in Tel-Aviv (n = 492, mean age = 36.7, 27.2% female) and Las Vegas (n = 302, mean age = 43.4, 37.1% female)	Any cannabis use, assessed with UDS at treatment baseline (month 1) and after one year (month 13)	Time to treatment discontinuation, up to 5.8 years	Baseline cannabis use was associated with shorter treatment retention in Las Vegas (1.6 vs. 2.2 years; X^2 = 4.2, p = 0.04) but not Tel-Aviv (3.4 vs. 3.3 years; X^2 = 0.2, p = 0.80); in multivariable analysis, the association between cannabis use and treatment retention in the Las Vegas sample was no longer statistically significant (statistics not reported); (2) Cannabis use at 13 months was not associated with retention in Las Vegas (2.1 vs. 2.5 years; X^2 = 0.8, p = 0.40) or Tel-Aviv (3.4 vs. 3.7 years; X^2 = 1.8, p = 0.20)
Peles et al. (2018); Israel	Prospective cohort study	Poor	890 patients admitted to methadone treatment program at a medical centre (25% female)* *Study sample includes those from Tel-Aviv in Peles et al., 2008, but the follow-	Cannabis use, assessed at treatment admission (month 1) with UDS	Time to treatment discontinuation, up to 24 years	Cannabis use at treatment admission was not significantly associated with treatment retention (p = 0.8)

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Table 3 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
			up period and sample size are increased.			
Saxon et al. (1996); USA	Secondary analysis of a clinical trial	Fair	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Frequency of cannabis use in the previous 6 months, self-reported using ASI at treatment baseline	Retained in treatment up to 18 months	Baseline cannabis use frequency was not significantly associated with 18-month treatment retention (AHR = 1.08, 95% CI = 0.97–1.20)
Scavone et al. (2013); USA	Retrospective chart review	Fair	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 39% women)	Any cannabis use during treatment induction, assessed with UDS	Retained in treatment up to 9 months	Cannabis use during induction phase was not significantly associated with early treatment drop-out (X^2 = 3.01, p = 0.222)
Schiff et al. (2007); Israel	Retrospective chart review	Poor	2683 methadone patients from 8 treatment sites (mean age = 43 years, 12% women)	Any cannabis use, assessed with UDS for 13 months	Percentage of days in treatment (1–13 month period), categorized as 100% vs. 0%	Cannabis use during treatment was significantly associated with treatment retention retention (AOR = 1.43, 95% CI = 1.15–1.78)
Weizman et al. (2004); Israel	Prospective cohort study	Fair	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis abuse, assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	Number of days in treatment, up to 12 months	Cannabis use was not significantly associated with treatment retention in bivariable analysis (HR = 0.84, 95% CI = 0.65–1.09), or after adjusting for co-occurring substance use (statistics not reported)
White et al. (2014); USA	Retrospective chart review	Fair	604 methadone patients at a private, non-profit treatment centre (mean age = 53 years, 49% women)	Any cannabis use, assessed with UDS during the 3-month study baseline period	Retained in treatment at the re-assessment period (14–16 months after study baseline)	Baseline cannabis use was significantly associated with treatment discontinuation (OR = 3.3, 95% CI = 1.6–6.8), but cannabis-only use was not significantly associated with early discontinuation (OR = 0.5, 95% CI = 0.7–9.8)
2. Buprenorphine						
Abrahamsson et al. (2016); Sweden	Prospective cohort study	Fair	44 outpatients initiating interim buprenorphine-naloxone treatment phase (mean age = 35 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported at treatment/ study baseline	Successful transfer from intermediate to full-scale treatment	Patients who were successfully transferred to full-scale treatment had significantly fewer mean days of cannabis use at baseline (5.2 vs. 10.4, p = 0.059); in a multivariable model, cannabis use was no longer significantly associated with successful transfer (p = 0.270)
Budney et al. (1998); USA	Secondary analysis of pooled data from three clinical trials	Fair	79 patients undergoing a 7–22 week buprenorphine taper and behavioural therapy, derived from a larger (n = 107) patient sample (mean age = 34 years, 37% women)	(1) Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS (2) Frequency of cannabis use, assessed with thrice-weekly UDS	Percentage of treatment weeks completed	(1) The percentage of weeks retained on treatment did not differ significantly between cannabis users and non-users (65% vs. 60%, $p > 0.05$); (2) Frequency of cannabis use did not correlate significantly with weeks of treatment retention ($r = -0.21$, $p > 0.05$)
Håkansson et al. (2016); Sweden	Prospective cohort study	Good	36 patients entering full-scale buprenorphine-naloxone treatment following interim treatment (median age = 33 years, 11% women)	Past 30-day frequency (days) of cannabis use, self-reported using ASI at baseline and assessed with weekly UDS throughout interim and full-scale treatment	Retained in treatment 9 months after intake	Retention in treatment was not significantly associated with frequency of cannabis use at baseline (p = 0.689) or during either interim (p = 0.297) or full-scale treatment phase (p = 0.965)
Hill et al. (2013); USA	Secondary analysis of clinical trial	Good	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1–19), frequent (≥20)	Retained in treatment 12 weeks after intake	The proportion of patients retained on treatment did not differ significantly by frequency of baseline cannabis use (non-use: 52%, occasional use: 39%, frequent use: 44%; p = 0.38)
Matson et al. (2014); USA	Retrospective chart review	Fair	103 youth buprenorphine-naloxone outpatients from one clinic (mean age = 19 years, 50% women)	Any cannabis use, assessed with UDS at treatment intake and periodically over 1 year	Treatment discontinuation, defined as not returning for a scheduled treatment visit	Cannabis use at the previous treatment visit was significantly associated with treatment discontinuation at

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Table 3 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
						the next visit (HR = 1.73, 95% CI = 1.14–2.63)
3. Naltrexone						
Bisaga et al. (2015); USA	Secondary analysis of a clinical trial	Fair	60 patients initiating 8-week depot naltrexone trial with dronabinol ($n = 40$) or placebo ($n = 20$; mean age = 30 years, 17% women)	Weekly cannabis smoking, self-reported (and confirmed with UDS) at treatment baseline and weekly throughout trial	(1) Inpatient phase: Successful transfer to injectable naltrexone; (2) Outpatient phase: time to treatment/study drop-out	(1) No association between weekly cannabis use at baseline and successful transfer to outpatient phase ($X^2 = 1.45$; $p = 0.230$); (2) Weekly cannabis use during treatment was associated with longer treatment retention (HR = 4.83, 95% CI = 1.09–21.36)
Chaudhry et al. (2012); USA	Retrospective chart review	Fair	142 patients on naltrexone at one treatment site (mean age = 26 years, 6% women)	Past-week frequency (days) of cannabis use, self-reported at outpatient assessment, categorized as none (0), occasional (1–5), and frequent (6–7)	Successful progression to treatment phase 3 (≥17 weeks of treatment)	Odds of treatment retention were significantly lower for frequent (OR = 0.46, 95% CI = 0.19–1.11) and occasional cannabis users (OR = 0.32, 95% CI = 0.12–0.71), relative to non-users (any vs. none, $p = 0.04$); cannabis use was not significantly associated with retention in a multivariable model (statistics not reported)
Church et al. (2001); USA	Secondary analysis of a clinical trial	Fair	47 community-recruited patients initiating naltrexone (mean age = 34 years, 23% women)	Frequency of cannabis use, assessed with twice-weekly UDS, categorized as none (0%), intermittent (1–50%), daily (51–100%)	Retained in treatment up to 24 weeks	Intermittent cannabis users were retained in treatment for more days (92.7) than frequent users (51.6) or non-users (48.0), but the association was not statistically significant ($F = 1.932$, $p = 0.159$)
Dayal et al. (2016); India	Prospective cohort study	Fair	140 opioid-dependent outpatients on naltrexone treatment at a tertiary care site (mean age = 32 years, 1% women)	Any cannabis use, self-reported at treatment baseline	Retained in treatment at 90 days, 180 days	Baseline cannabis users had significantly higher treatment retention at 90 days ($X^2 = 6.86$, $p = 0.009$) but not at 180 days ($X^2 = 2.69$, $p = 0.100$); in multivariable analysis, baseline cannabis use was not significantly associated with treatment discontinuation (90 days: AOR = 0.46, 95% CI = 0.19–2.21; 180 days: AOR = 0.10, 95% CI = 0.17–3.46)
Jarvis et al. (2018); USA	Secondary analysis of a clinical trial	Poor	144 patients beginning a clinical trial for oral naltrexone (mean age = 43 years, 29% women)	Past 30-day frequency (days) of cannabis use, self-reported at study intake	Successful completion of outpatient oral naltrexone induction phase	Mean baseline cannabis use days did not differ significantly between those who successfully completed induction (4.6 days) and those who dropped out (3.6 days, $p = 0.485$)
Raby et al. (2009); USA	Secondary analysis of a clinical trial	Good	63 patients in a controlled trial of behavioural naltrexone therapy at one site, (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1–79%), and consistent (≥80%)	Time (days) to treatment discontinuation, up to 182 days	Intermittent cannabis use was significantly associated with longer treatment retention relative to non-use (AHR = 0.23, 95% CI: 0.09–0.57); consistent cannabis use was not significantly associated with longer retention (AHR = 1.42, 95% CI = 0.49–4.1)
4. Mixed treatments						
Eastwood et al. (2019); England	Prospective cohort study	Good	7717 patients enrolled in methadone or buprenorphine treatment in England (mean age = 34 years, 28% women)	Cannabis use trajectory over 5 years, determined with latent trajectory analysis from self-reported measures obtained every 6 months, categorized as Class 1 ("continued low-level"), Class 2 ("low and decreasing"), Class 3 ("high and increasing")	Successful completion and no presentation for further treatment within 6 months (summative measure based on opioid/cocaine abstinence, treatment completion, remission from OUD, etc.), assessed in year 6 and 7	Within the "decreasing then increasing" heroin use trajectory, cannabis trajectory 2 was significantly negatively associated with treatment success (relative to group 1; AOR = 0.50, 95% CI = 0.28–0.92); within the "rapid decreasing heroin use" trajectory, cannabis trajectory 2 was positively associated with treatment

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Table 3 (*continued*)

Study	Study design	Quality	Study sample	Exposure	Outcome	Findings
						success (relative to group 1; AOR = 2.39, 95% CI = 1.29–4.40); please refer to the original study and its supplementary files for all findings
Hser et al. (2014); USA	Secondary analysis of a clinical trial	Good	1267 patients from 9 opioid treatment programs across the country (mean age = 37 years, 32% women)	Any cannabis use, assessed with weekly UDS over 24 weeks	Time to treatment discontinuation, up to 24 weeks	Cannabis use was significantly associated with treatment discontinuation in buprenorphine (HR = 1.78, 95% CI = 1.32–2.40) and methadone (HR = 3.43, 95% CI = 2.01–5.88) groups.
Socías et al. (2018); Canada	Prospective cohort study	Good	820 community-recruited people initiating methadone or buprenorphine-naloxone treatment (median age = 38, 42% women)	Frequency of past 6-month cannabis use, self-reported every 6 months, categorized as ≥daily, <daily, and none	Retained in treatment for an approximate 6-month period, defined as self-reported methadone or buprenorphine treatment in the current and immediately previous 6-month period	Daily cannabis use was significantly associated with improved treatment retention relative to no use (AOR = 1.20, 95% CI = 1.02–1.43); occasional use was not significantly associated with treatment retention (AOR = 1.00, 95% CI = 0.87–1.14)

Note: 95% CI = 95% Confidence interval; (A)HR = (Adjusted) Hazard ratio; (A)OR = (Adjusted) Odds ratio; ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; OUD = Opioid use disorder; SCID-1 = Structural Clinical Interview for DSM-IV Axis 1 Disorders; UDS = Urine drug screen

any cannabis use at a study visit significantly increased the likelihood of not returning for a subsequent treatment visit (HR = 1.73, 95% CI: 1.14–2.63). Similar to the distribution of findings for opioid use, a handful of studies (n = 5, 19%; including one methadone (Schiff et al., 2007), two naltrexone (Bisaga et al., 2015; Raby et al., 2009), and two mixed modalities (Eastwood et al., 2019; Socías et al., 2018)) also noted significantly higher retention among cannabis users, yet there was again inconsistency between studies in the apparent dose-response effect. For example, in the study by Socías et al. (2018) of community-recruited people who use drugs initiating opioid agonist (methadone or buprenorphine) treatment, the odds of remaining in retention six months later were significantly increased for daily cannabis users (AOR = 1.20, 95% CI: 1.02–1.43), but not occasional users (AOR = 1.00, 95% CI: 0.87–1.14), relative to non-users; whereas, Raby et al. (2009) noted that cannabis use on an intermittent (AHR = 0.23, 95% CI: 0.09–0.57), but not consistent (AHR = 1.42, 95% CI: 0.49–4.10), basis was significantly associated with longer time retained in naltrexone treatment. A similar trend was also noted in the study by Church et al. (2001), in which intermittent cannabis users were retained for longer (92.7 days) than frequent (51.6 days) or non-users (48.0 days), but the association did not meet statistical significance (p = 0.159).

3.6. Secondary outcomes

We reviewed each of the above studies for their reporting of one or more secondary outcomes of interest including other substance use and measures of physical or psychological health. These findings are summarized in Table 4.

Eleven studies (including seven methadone (Best et al., 1999; Epstein & Preston, 2003; Nirenberg et al., 1996; Saxon et al., 1996; Scavone et al., 2013; Shams et al., 2019; Weizman et al., 2004), three buprenorphine (Bagra et al., 2018;Budney et al., 1998 ; Hill et al., 2013), and one naltrexone (Raby et al., 2009)) examined the relationship between cannabis use and other substance use during treatment. Three studies (two methadone (Best et al., 1999; Shams et al., 2019) and one naltrexone (Bagra et al., 2018)) noted significantly increased alcohol use among cannabis-using patients. Eight studies (including six methadone (Best et al., 1999; Epstein & Preston, 2003; Nirenberg et al., 1996; Saxon et al., 1996; Shams et al., 2019; Weizman et al., 2004), two buprenorphine (Budney et al., 1998; Hill et al., 2013), and one naltrexone (Raby et al., 2009)) looked for differences in cocaine (or crack) use between cannabis using and non-using patients, and produced mixed findings. Two of these studies (including one methadone (Weizman et al., 2004) and one naltrexone (Raby et al., 2009)) detected significantly increased cocaine use among cannabis-using patients, while Saxon et al. (1996) and Best et al. (1999) recorded significant prospective and cross-sectional inverse associations, respectively, between frequency of cannabis and frequency of crack/cocaine use among methadone patients. The remaining five studies did not find that frequency of cannabis use correlated signfiicantly with cocaine use during MOUD. Another seven studies (including five methadone (Best et al., 1999; Nirenberg et al., 1996; Scavone et al., 2013; Shams et al., 2019; Weizman et al., 2004), one buprenorphine (Budney et al., 1998), and one naltrexone (Raby et al., 2009)) examined benzodiazepine use during treatment. Similarly, these studies were inconsistent in their findings, with three methadone studies finding benzodiazepine use to increase significantly with cannabis use frequency (Best et al., 1999; Scavone et al., 2013; Weizman et al., 2004), and the remaining four studies not detecting significant differences in benzodiazepine use according to cannabis use status.

Six studies (including four methadone (Best et al., 1999; Epstein & Preston, 2003; Shams et al., 2019; Zielinski et al., 2017), and two buprenorphine (Bagra et al., 2018; Budney et al., 1998)) employed some measurement of physical, psychological, and/or general health in relation to cannabis use. Two cross-sectional methadone studies observed significantly poorer health indicators among cannabis-using patients: Best et al. (1999) found that frequent cannabis users had significantly lower general health, which was driven by poorer appetite among frequent users, and Zielinski et al. (2017) noted significantly poorer psychological functioning among cannabis users. Otherwise, cannabis use status was not significantly related to measures of psychological health (Bagra et al., 2018; Budney et al., 1998; Epstein & Preston, 2003), pain interference (Shams et al., 2019), or other indicators of physical health and functioning (Bagra et al., 2018; Zielinski et al., 2017).

4. Discussion

We systematically searched the peer-reviewed scientific literature and synthesized findings of 41 observational and experimental studies documenting the relationship between cannabis use and treatment

Table 4
Summary of included studies: secondary outcomes (quality of life and other substance use).

Study	Study design	Study sample	Exposure	Outcome	Findings
1. Methadone					
Best et al. (1999); Scotland	Cross-sectional study	200 methadone patients on at a community drug clinic (mean age = 32 years, 30% women)	Past 30-day frequency (days) of cannabis use, self-reported at time of study, categorized as no use, occasional use, daily use	(1) Frequency of past 30-day alcohol use, self-reported using MAP at time of study; (2) Frequency of past 30-day crack cocaine use, self-reported using MAP at time of study; (3) Frequency of past 30-day illicit benzodiazepine use, self-reported using MAP at time of study; (4) Psychiatric wellbeing score, assessed with BSI at time of study; (5) General health score, assessed with MAP at time of study	(1) Cannabis non-users reported significantly more alcohol use days (9.6) than daily users (4.3), $F = 5.24$, $p < 0.01$; the association remained significant in a multivariable model ($\beta = -0.148$, $p = 0.029$); (2) Cannabis non-users reported significantly more crack use days (1.7) than daily users (0.1; $p < 0.05$, $F = 4.67$, $p < 0.05$); not tested in multivariable model; (3) Daily cannabis users reported significantly more benzodiazepine use days (8.2) than occasional (5.2) and non-users (4.0; $F = 2.95$, $p = 0.05$); not tested in multivariable model; (4) Daily cannabis users scored significantly higher (19.0) than non-users (14.3) and occasional users (14.3) for severity of psychiatric problems (anxiety and depression; $F = 6.44$, $p < 0.01$); in a multivariable model, anxiety and depression scores were not significantly associated with frequency of cannabis use ($\beta = 0.099$, $p = 0.224$ and $\beta = 0.080$, $p = 0.331$, respectively); (5) Daily users exhibited poorer general health (score = 50.8) than occasional (44.4) or non-users (47.7, $p < 0.0.5$); in a multivariable model, total health score was not significantly associated with frequency of cannabis use ($\beta = -0.102$, $p = 0.267$)
Epstein and Preston (2003); USA	Secondary analysis of pooled data from three clinical trials	408 methadone outpatients from 3 clinical trials (mean age = 39 years, 60% women)	Frequency of cannabis use, assessed by weekly UDS, categorized as 0%, 1–17%, 18–100%	(1) Use of primary illicit drug (cocaine in 2 studies; opioids in 1 study) during intervention (contingency management) phase, assessed with weekly UDS; (2) Resume use of primary drug after intervention phase, assessed with weekly UDS; (3) Psychosocial functioning, assessed with ASI at post-treatment follow-ups (3, 6, 12 months)	(1) Cannabis use frequency was not significantly associated with continued primary drug use during stabilization (statistics not reported); (2) Cannabis use frequency was not significantly associated with primary drug use during the maintenance phase (statistics not reported); (3) Cannabis use frequency was not significantly associated with differences in psychosocial functioning (statistics not reported)
Hill et al. (2013); USA	Secondary analysis of clinical trial	152 young people initiating a 12-week treatment or 2-week detoxification with buprenorphine-naloxone (mean age = 19 years, 41% women)	Past 30-day frequency (days) of cannabis use, self-reported at baseline, categorized as none (0), occasional (1–19), frequent (≥20)	Cocaine use, assessed with UDS at 4, 8, and 12 weeks	Cannabis use was significantly positively associated with baseline cocaine use ($p < 0.04$), but not significantly associated with cocaine use during treatment (statistics not reported)
Nirenberg et al. (1996); USA	Prospective cohort study	70 methadone outpatients at an urban veterans medical site (mean age = 39 years, 1% women)	Frequency of cannabis use over 45 weeks, assessed with weekly UDS, categorized as none (0%), intermittent (1–33%), moderate (34–67%), and consistent (68–100%)	(1) Frequency of cocaine use over 45 weeks, assessed with weekly UDS; (2) Frequency of benzodiazepine use over 45 weeks, assessed with weekly UDS	(1) Frequency of cocaine did not differ significantly by cannabis use frequency ($F = 1.17$, $p = 0.33$); (2) Frequency of benzodiazepine use did not differ significantly by cannabis use frequency ($F = 2.10$, $p = 0.11$)
Saxon et al. (1996); USA	Secondary analysis of a randomized controlled trial	337 patients beginning methadone at an urban treatment site (mean age = 38 years, 38% women)	Past 6-month frequency of cannabis use, self-reported using ASI at treatment intake, categorized on a scale from 0 (never) to 6 (≥4 times/day)	(1) Frequency of any illicit drug use, assessed with weekly UDS for up to 2 years; (2) Frequency of cocaine use, assessed with weekly UDS for up to 2 years	(1) Frequency of cannabis use was not significantly associated with frequency of any illicit drug use (unadjusted $\beta = 0.06$, $p > 0.05$); (2) Baseline cannabis use frequency was significantly and

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Table 4 (*continued*)

Study	Study design	Study sample	Exposure	Outcome	Findings
					negatively associated with frequency of cocaine use (adjusted $\beta = -0.11$, $p < 0.05$)
Scavone et al. (2013); USA	Retrospective chart review	91 methadone outpatients enrolled at one treatment site (mean age = 39 years, 39% women)	Frequency of cannabis use over 9 months, assessed with monthly UDS	Frequency of illicit benzodiazepine use over 9 months, assessed with monthly UDS	Frequency of cannabis use was significantly positively correlated with frequency of illicit benzodiazepine use during treatment ($r = 0.374$, $p < 0.01$)
Shams et al. (2019); Canada	Cross-sectional study	640 methadone patients recruited from 14 treatment sites across the province of Ontario (mean age = 38.8, 45.8% female)	(1) Any past 30-day cannabis use, self-reported using MAP at time of study (2) Past 30-day "heaviness" of cannabis use, self-reported using MAP at time of study (calculated as [n days used*typical dose in grams])	(1) Any past 30-day alcohol use, self-reported using MAP at time of study (2) Any past 30-day illicit benzodiazepine use, self-reported using MAP at time of study (3) Any past 30-day powder cocaine or crack cocaine use, self-reported using MAP at time of study; (4) Any past 30-day amphetamine use, self-reported using MAP at time of study; (5) Level of pain interference, assessed with BPI at time of study	(1) Past 30-day cannabis use was significantly positively associated with past 30-day alcohol use (AOR = 1.46, 95% CI = 1.04–2.06); heaviness of cannabis use was not associated; (2) Cannabis use was not significantly associated with benzodiazepine use (AOR = 1.49, 95% CI = 0.77–2.89); heaviness of cannabis use was not associated; (3) Cannabis use was not significantly associated with powder cocaine or crack cocaine use (AOR = 1.42, 95% CI = 0.88–2.88; AOR = 1.06, 95% CI = 0.54–2.10, respectively); heaviness of cannabis use was not associated with either measure of cocaine use; (4) Cannabis use was not significantly associated with amphetamine use (AOR = 0.87, 95% CI = 0.31–2.40); (5) Cannabis use was not significantly associated with pain interference (AOR = 0.98, 95% CI = 0.94–1.03); heaviness of cannabis use was not associated
Weizman et al. (2004); Israel	Prospective cohort study	176 patients starting methadone treatment at one clinic (mean age = 38 years)	Cannabis abuse, assessed with SCID-1 on patients who screened positive for possible cannabis abuse (≥3 consecutive cannabis UDS over 12 months)	(1) Benzodiazepine use, assessed with UDS at 12 months; (2) Amphetamine use, assessed with UDS at 12 months; (3) Cocaine use, assessed with UDS at 12 months; (4) Total number of illicit drugs used, assessed with UDS at 12 months	(1) Benzodiazepine use was significantly more frequent among patients who abused cannabis ($F = 18.48$, $p < 0.001$); (2) Amphetamine use was significantly more frequent among patients who abused cannabis ($F = 9.29$, $p = 0.003$); (3) Cocaine use was significantly more frequent among patients who abused cannabis ($F = 4.06$, $p = 0.045$); (4) The mean number of distinct classes of drugs used at month 3 was significantly higher among patients who abused cannabis (1.6 vs. 0.79; $t = 5.63$, $p < 0.001$)
Zielinski et al. (2017); Canada	Cross-sectional study	777 patients on methadone at treatment sites across the province (mean age = 38, 47% women)	Past 30-day cannabis use, self-reported using MAP at time of study	(1) Psychological functioning, assessed with MAP (0–40 points) at time of study; (2) Physical functioning, assessed with MAP (0–40 points) at time of study	(1) Cannabis users had significantly poorer psychological functioning (MAP score: 14.27 vs. 12.90, $p = 0.040$); (2) Cannabis users had slightly worse physical functioning, but the difference was not significant (16.02 vs. 15.06, $p = 0.085$)
2. Buprenorphine					
Bagra et al. (2018); India	Cross-sectional study	100 outpatients on buprenorphine for ≥3 months at a community drug treatment clinic (mean age = 44 years, 0% women)	Past 3-month cannabis use, self-reported using ASSIST at time of study	(1) Past 3-month alcohol use, self-reported using ASSIST at time of study; (2) Quality of life, assessed with WHOQOL-Bref at time of study	(1) Cannabis users had a significantly higher prevalence of alcohol use (57.1% vs. 24.6%, $p = 0.001$); (2) Mean scores for physical, psychological, social, and environmental quality of life did not differ significantly between cannabis users and non-users (all $p < 0.05$)

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Table 4 (*continued*)

Study	Study design	Study sample	Exposure	Outcome	Findings
Budney et al. (1998); USA	Secondary analysis of pooled data from three clinical trials	79 patients undergoing a 7–22 week buprenorphine taper and behavioural therapy, derived from a larger ($n = 107$) patient sample (mean age = 34 years, 37% women)	Any cannabis use, self-reported (past 30-days) at treatment baseline, and assessed with thrice-weekly UDS	(1) Frequency of cocaine use, assessed with thrice-weekly UDS; (2) Frequency of benzodiazepine use, assessed with thrice-weekly UDS; (3) Psychosocial functioning, self-reported (ASI) at treatment baseline and 12-month follow-up	(1) The percentage of cocaine-positive UDS did not differ significantly between cannabis users and non-users (13% vs. 14%, $p > 0.05$); (2) The percentage of benzodiazepine-positive UDS did not differ significantly between cannabis users and non-users (32% vs. 40%, $p < 0.05$); (3) No significant pre-post changes between cannabis users and non-users in any ASI subscales (e.g., mean psychiatric score change = −0.01 for cannabis users and 0.04 for non-users, $p < 0.05$)
3. Naltrexone					
Raby et al. (2009); USA	Secondary analysis of a clinical trial	63 patients in a controlled trial of behavioural naltrexone therapy at one site (mean age = 36 years, 17% women)	Frequency of cannabis use, assessed with twice-weekly UDS for 6 months, categorized as none (0%), intermittent (1–79%), and consistent (≥80%)	(1) Frequency of cocaine use over 6 months, assessed with twice-weekly UDS; (2) Frequency of benzodiazepine use over 6 months, assessed with twice-weekly UDS	(1) Proportion of cocaine-positive UDS increased significantly with cannabis use frequency (non-users = 0.07, intermittent users = 0.25, consistent users = 0.39, $p < 0.009$); (2) Proportion of benzodiazepine-positive UDS did not differ significantly between cannabis non-users (0.37), intermittent users (0.25), or consistent users (0.39, $p > 0.05$)

Note: ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Tool; BPI = Brief Pain Inventory; BSI = Brief Symptom Inventory; HAM-D = Hamilton Rating Scale for Depression; MAP = Maudsley Addiction Profile; SOWS = Subjective Opioid Withdrawal Scale; WHOQOL-Bref = World Health Organization - Quality of Life - Brief version.

outcomes among patients undergoing methadone-, buprenorphine-, or naltrexone-based treatment of OUD. Our work builds on a review by McBrien et al. (2019) on cannabis use during methadone maintenance treatment by widening the scope of research to all three FDA-approved medications for the management of OUD and exploring additional outcomes potentially impacted by the use of cannabis including opioid craving, withdrawal, medication adherence, and quality of life. We observed some notable differences between treatment modalities. Similar to McBrien et al. (2019), we describe mixed findings across methadone studies: the majority of studies did not document a significant (positive or negative) impact of cannabis on a treatment outcome, while some studies produced contradictory findings of positive (e.g., Best et al., 1999; Schiff et al., 2007) or negative (e.g., Levine et al., 2015; Wasserman et al., 1998) associations. Among studies restricted to buprenorphine patients only, we did not find any evidence to suggest a beneficial effect of cannabis, and we identified a small number of studies that were indicative of significantly lower buprenorphine adherence and retention among cannabis users (Fareed et al., 2014; Hser et al., 2014; Matson et al., 2014). By contrast, we did not find any evidence to suggest that cannabis use is associated with significantly more opioid use, reduced treatment adherence, or shorter treatment retention among patients taking naltrexone, and we found some studies suggestive of improved outcomes in all three primary outcome areas (Bisaga et al., 2015; Raby et al., 2009).

There is an emerging pharmacological rationale for the use of cannabis to address opioid craving and withdrawal (Scavone et al., 2013). For example, preclinical experiments have demonstrated that exogenous agonists of the endogenous cannabinoid receptors (e.g., the phytocannabinoid THC) lowers the severity of protracted withdrawal symptoms (Vela, Ruiz-gayo, & Fuentes, 1995; Yamaguchi et al., 2001). Recent experimental research demonstrates that repeated administration of the phytocannabinoid cannabidiol (CBD) reduces cue-induced anxiety and craving and exerts protracted effects one week later among opioid-dependent patients with short-term abstinence (Hurd et al., 2019). Notably, we did not find any evidence across treatment modalities to suggest that cannabis use increases cravings for opioids or worsens the severity of withdrawal symptoms, and we noted some evidence of improvements in these outcomes for cannabis-using patients transitioning onto naltrexone (Bisaga et al., 2015) and methadone treatment (Scavone et al., 2013). The remaining three methadone studies that measured opioid withdrawal did not observe an association between cannabis and withdrawal severity. One possibility, as noted by Hill et al. (2013), is that cannabis helps to mitigate post-acute withdrawal symptoms arising from treatment with an opioid antagonist, rather than an agonist, which would explain the generally more positive results seen for naltrexone adherence and retention among cannabis-using patients. This interpretation would leave open the possibility that patients treated with an agonist could also experience symptom mitigation from cannabis if their treatment is not effectively suppressing withdrawal. Although additional research is needed, Epstein and Preston (2015) began to probe this withdrawal management hypothesis by taking repeated measures of cannabis use and withdrawal symptoms during a methadone dose taper. They noted that, although cannabis use increased slightly (and not significantly) in the week following higher withdrawal, cannabis use did not precede significant reductions in withdrawal scores in the subsequent week, suggesting that cannabis was not effective in curbing withdrawal.

Treatment dose is one of the strongest predictors of longer-term patient success on MOUD (Hser et al., 2014; Peles, Schreiber, & Adelson, 2006; Saxon et al., 1996; Villafranca, McKellar, Trafton, & Humphreys, 2006). It is plausible that patients receiving sub-optimal treatment doses are more likely to self-medicate with cannabis. Studies that do not measure or account for dose adequacy may mask a potential positive influence of cannabis on treatment outcomes. A small number of included studies ($n = 7$) compared treatment dose between cannabis using and non-using patients, and three (43%) noted significantly lower medication doses among patients who were using cannabis during treatment (Bagra et al., 2018; Franklyn et al., 2017; Zielinski et al.,

2017), while four (57%) did not find group differences (Best et al., 1999; Nava et al., 2007; Scavone et al., 2013; Weizman et al., 2004). Future research should examine these patient outcomes across strata of treatment dose and cannabis use to test whether cannabis acts as an effect modifier in this relationship.

Some studies measured varying levels of exposure to cannabis (e.g., frequency or amount used), but a clear dose-response pattern could not be discerned, owing to discrepant findings across these studies. It is possible that differences between patient samples explain these discrepant findings. One possibility is that high frequency cannabis use corresponds to intentional therapeutic applications in certain patient populations (e.g., community-based samples) while corresponding to higher-risk drug use and dependence or structural marginalization such as homelessness, poverty, and criminalization in others (e.g., clinic-based samples). For example, Socías et al. (2018) observed higher six-month retention among daily cannabis users in their community-recruited study of highly marginalized people initiating methadone or buprenorphine-naloxone in Vancouver, Canada, a setting with liberal access to cannabis. In an analysis drawing on data from people who use drugs (PWUD) living with pain in the same setting, Lake et al. (2019) found that those engaging in daily cannabis use were more likely than occasional users to report intentional therapeutic reasons for use, and a further characterization of cannabis-using PWUD from this setting indicates that occasional users constitute a more socially and structurally marginalized group of higher-risk drug users (Lake et al., 2020). In contrast, high-frequency use of cannabis may correlate more readily to poorer patient outcomes (particularly treatment adherence and retention) considering practices in certain clinical settings (particularly across the United States) that respond to evidence of ongoing illicit substance use, including cannabis use, with punitive policies such as denial of take-home doses and even involuntary patient discharge (ASAM, 2013). In turn, such policies could have a disproportionately negative impact on adherence or retention for cannabis users. Indeed, at least eight of the reviewed studies (including five from the United States (Budney et al., 1998; Levine et al., 2015; Matson et al., 2014; Saxon et al., 1996; White et al., 2014), two from Sweden (Abrahamsson et al., 2016; Håkansson et al., 2016), and one from Israel (Weizman et al., 2004)) explicitly stated that some patient privileges (e.g., take-home doses, dose increases, remaining in the program) were contingent on drug-free urine screens. The current review demonstrates that the implications for cannabis use concurrent with MOUD are likely to vary across individuals; as such, cannabis use during MOUD should be considered on an individual-basis. Clinicians working with individuals on MOUD who are interested in cannabis as an adjunctive therapy may benefit from taking a patient-centered approach and clarifying why and how the patient feels cannabis use may assist in their treatment progress. This is a departure from the long-held approach of abstinence-only recovery programs. Future research should consider individual differences such as cannabis use history, motivations for use, personality factors, and mood to determine for who and when cannabis use is indicated or contraindicated in the treatment of OUD.

While this review fulfills a critical need to collect, synthesize, and compare findings pertaining to cannabis use during MOUD, it was met with a number of limitations. We restricted our search to peer-reviewed articles published in English, and it is possible that we missed potentially important clinical findings published in another language. We opted not to conduct a meta-analysis, concluding that any numerical result would be rendered clinically meaningless due to the heterogeneity across studies in variable measurement, treatment times, and modalities. For example, within each outcome area of interest, there was a lack of consistency in outcome measurement (e.g., past 30-day self-reported frequency of heroin use vs. current detection of various opioids in urine), which may have also played a role in discrepant findings across studies. This shortcoming is well illustrated by the fact that Shams et al. (2019) noted significantly lower odds of self-reported heroin use by cannabis users on methadone treatment, whereas Zielinski et al. (2017) analyzed data from an overlapping study sample over the same time period and did not find evidence of significantly lower odds of opioid use detected via urine drug screen for cannabis users. Our review did not report on the efficacy of pharmaceutically manufactured cannabinoid medications (e.g. dronabinol) as adjunctive medication in MOUD. To our knowledge, findings from only one study were excluded on this basis: Bisaga et al. (2015) randomized patients undergoing a naltrexone induction to receive dronabinol or a placebo and observed significantly lower severity of withdrawal among patients randomized to dronabinol. However, a secondary finding of this study pertaining to cannabis use during the trial was retained in the review.

This review is also limited by certain methodological shortcomings of the included research. Many studies were limited by small sample sizes, short observation periods, and over-representation of certain patients (particularly white males). As noted, the included studies exhibited a high degree of heterogeneity with respect to the measurement of cannabis use, with some studies measuring cannabis use in much greater detail (e.g., repeated frequency measures throughout treatment) than others (e.g., any use at treatment baseline). There are several factors contributing to this lack of consistency. First, a universally accepted and scientifically supported standardized unit to measure cannabis (or cannabinoid content, e.g., THC) exposure has yet to be established and implemented across studies (although some have been proposed, e.g., (Freeman & Lorenzetti, 2020)). Second, the majority of studies were not explicitly focused on the influence of cannabis use on treatment outcomes; as a result, crude measurements of any cannabis use (either self-reported or positive urine screens) at treatment baseline or over the treatment period were often used. These measures may fail to capture a biological effect if one does exist, as the time between the actual exposure and the outcome is likely to vary widely between patients in a given study. In addition, studies lacking an explicit cannabis-related objective rarely accounted for potentially important confounding or mediating factors (e.g., social and economic adversities, medication dose, treatment satisfaction, co-occurring substance use patterns, opioid withdrawal and craving). However, given the generally non-significant cannabis-related findings of these broader studies, coupled with the mixed results of the 15 studies with cannabis as a primary focus, the overall consensus of this review is unlikely to be biased by selective reporting or unpublished null data. While several of the review's findings emerged from randomized controlled trials, cannabis was not the randomized intervention in any of these studies. Given high rates of cannabis use during MOUD, clinical trials involving plant-based cannabinoids (vs. placebo) are a critical next step towards understanding the therapeutic applications of cannabis in real-world OUD treatment settings. Finally, no studies collected detailed data on the type of cannabis used or method used to consume it. Biochemical and pharmacological exploration of cannabis' interaction with the endogenous cannabinoid system has given rise to a theory known as the "entourage effect" (Ben-Shabat et al., 1998; Russo, 2011), which suggests that whole cannabis might serve as a more suitable treatment candidate than any cannabinoid alone (e.g., CBD, THC or pharmaceutical formulations of THC such as dronabinol); however, pilot trials will be needed to determine optimal cannabis chemovars (colloquially referred to as "strains" (Russo, 2018)), as each is likely to produce different effects based on its own unique composition of cannabinoids (most notably THC and CBD) and terpenoids (components that are responsible for the aroma and flavour of the plant and have a synergistic relationship with cannabinoids (Russo & Marcu, 2017)). Considering the newly legal status of non-medical cannabis in Canada, collecting patient data on desired and perceived effects of different cannabis products and modes of consumption would be a feasible and useful preliminary step.

5. Conclusions

In this review summarizing the relationship between cannabis use and a number of treatment outcomes among patients engaged in MOUD,

we did not find consistent or compelling evidence to support either of the opposing claims that co-use of cannabis is detrimental or beneficial to treatment success, as the majority of studies did not record a statistically significantly association between cannabis use and treatment outcomes. For each outcome of interest, a small number of studies produced evidence to suggest a beneficial or impeding role of concurrent cannabis use. The exception was withdrawal, for which we did not find any evidence to suggest a worse outcome for cannabis users. Many of the reviewed studies were not designed to measure an independent effect of cannabis and are thus subject to bias. Given prevalent co-use of cannabis by people in MOUD, there is a clear need for rigorous experimental research to establish the feasibility and effectiveness of adjunctive cannabis for OUD pharmacotherapy—particularly in the early stages of treatment when withdrawal may be more severe. The current state of evidence would also be strengthened by more observational studies designed with cannabis use as a primary exposure of interest. The majority of studies did not find treatment outcomes to differ by cannabis use. Given high rates of cannabis use documented among patients, medication-based treatment programs should reconsider punitive policies that treat ongoing cannabis use as a "non-compliant" patient behaviour, as the evidence reviewed here would suggest that such policies may pose a higher threat to treatment success than cannabis use itself. Clinicians who work with individuals using cannabis concurrently during MOUD should take a patient-centered approach to ensure that cannabis use plays a supportive, rather than interruptive, role in their treatment progress.

Role of funding sources

This work was supported through doctoral scholarships (recipient: Stephanie Lake) from the Canadian Institutes of Health Research and the Pierre Elliott Trudeau Foundation. The funders had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Contributors

SL designed the study, wrote the protocol, and conducted the literature searches. SL and MSP screened the articles for inclusion. SL extracted study data from full-text records, and MSP checked the extracted data for accuracy. SL and MSP conducted the quality assessments. SL wrote the first draft of the manuscript, MSP contributed to subsequent drafts. Both authors approved the final version of the manuscript.

Declaration of Competing Interest

None.

Acknowledgments

SL is supported through doctoral awards from the Canadian Institutes of Health Research (CIHR) and the Pierre Elliott Trudeau Foundation. MSP is supported through a CIHR Vanier Doctoral Award. The authors would like to thank Mohammad Karamouzian and Jan Klimas for their support in developing the search and quality assessment protocols for this review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpr.2020.101939.

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