Title: Cannabis is Not an Exit Drug for Patients with Opioid Use Disorder: A Systematic Review and Meta-Analysis

Heather McBrien HBSc.[1], Candice Luo BHSc.[2], Nitika Sanger HBSc. [3], Laura Zielinsk MSc i[4], Meha Bhatt MSc [5], Xi Ming Zhu BSc.[6], David Marsh MD[7], Lehana Thabane PhD, MSc [8,9], Zainab Samaan MBChB, MSc, DMMD, PhD, MRCPsych,[9,10]*

[1]Statistical Sciences Program, University of Toronto, Toronto, Canada.
[2]Michael G. DeGroote School of Medicine, Hamilton, Ontario, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada
[3]Medical Science Graduate Program, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada.
[4]MiNDS Neuroscience Graduate Program, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada.
[5]Health Research Methodology Graduate Program, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada.
[6]St. George's Hospital Medical School, University of London, London, United Kingdom.
[7]Northern Ontario School of Medicine, Ramsay Lake Road, Sudbury, Ontario P3E 6H6, Canada.
[8]Biostatistics Unit, Research Institute at St Joes, St. Joseph's Healthcare Hamilton, 50 Charlton Avenue E., Hamilton, ON L8N 4A6, Canada.
[9]Department of Health Research Methods, Evaluation, and Impact, McMaster University, Hamilton, Canada
[10]Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada.

***Corresponding author:**
Dr. Zainab Samaan, MBChB, DMMD, MSc, MRCPsych, PhD
Mood Disorders Program, St. Joseph's Healthcare Hamilton
100 West 5th St., Hamilton, ON, L8N 3K7
Telephone: 905 522 1155 ext. 36372, Fax: 905 575 6029

Funding
This work was funded by the Canadian Institute for Health Research catalyst grant investigating cannabis use on opioid addiction, Grant #155404

Declaration of Interest
The authors declare that they have no competing interests.

Abstract:

Introduction: Opioid use disorder (OUD) is a fundamental component of the ongoing opioid epidemic. Although methadone maintenance therapy (MMT) is the most common treatment used for OUD, its effectiveness is inconsistent. Rates of cannabis use among patients on MMT are high, and cannabis may be associated with MMT outcomes. This review examined the effect of cannabis on continued opioid use of patients on MMT to test the hypothesis that cannabis use is associated with reduction in opioid use.

Methods: We searched Medline/PubMed, EMBASE, PsycINFO, and CINAHL from inception to July 2018. We summarized the effects of cannabis use on illicit opioid use during MMT and treatment retention and poly-substance use. We conducted meta-analyses of those primary outcomes using a random effects model.

Results: We included 23 studies in our review. Six studies with a total number of participants of 3676 were meta-analyzed examining cannabis and illicit opioid use during MMT. The results showed that cannabis use did not reduce opioid use during MMT (OR 0.39, 95% CI 0.09, 1.79, p=0.23). Cannabis use did not affect retention. The overall quality of evidence was very low, with a high risk of bias, due to the nature of observational studies.

Interpretation: There is no evidence to suggest that cannabis helps patients with OUD stop using opioids. Despite the included studies methodological limitations, this evidence is generated using a large sample and rigorous systematic review methods providing the best and most up-to-date data on the association between cannabis and opioid use.

PROSPERO Registration: CRD42015029372

Introduction:

The current epidemic of opioid use and overdose deaths, with roots in the 1990s and 2000s, when the use of prescription opioids for chronic pain began to increase (1–4), has since escalated so far that the number of yearly opioid-related deaths in Ontario has tripled since 2000 (5). There were 3987 opioid related deaths in Canada in 2017, and fentanyl and its analogues were involved in 72% those deaths (5).

Opioid use disorder (OUD) is a fundamental component of this crisis (6,7). Despite its stark morbidity and mortality, the high rates of HIV and Hepatitis C infection among patients with OUD, high unemployment rates, and death rates – treatment options are limited in scope and effectiveness (8,9). Methadone maintenance therapy (MMT) is commonly used for OUD (10,11), whereas other opioid substitutions treatments have gained ground more recently (12). Despite its reported benefits in managing OUD, the number of patients on MMT who continue to use illicit opioids is relatively high at 52% (13). It has been suggested that cannabis use may reduce opioid use in other settings such as pain management, however there is no evidence to support cannabis use in OUD treatment.

The rates of cannabis use among patients on MMT are far higher than those in the general population: about a third of Canadians have used cannabis once in their lifetime (14), but 59.7 of males and 43.5% of females reported using cannabis while receiving MMT (15–17).

Recent studies have found that in states in the USA with dispensary-based medical cannabis laws, fewer prescription opioids are dispensed (18), and that these states have lower opioid overdose death rates (19).

In the wake of these studies, some high-profile organizations have suggested that cannabis should be legalized not only as a mechanism to lower prescription use, but as a method for coping with opioid withdrawal symptoms (20). These changes made news headlines labeling cannabis as an "exit drug"(20).

However, the 'exit hypothesis' has not been examined scientifically. With the rapid expansion of medical cannabis dispensaries around Canada and the impending legalization of cannabis, this question has never been more relevant.

We examine the relationship between cannabis and opioid use during MMT. We ask, 1) does the exit hypothesis hold in patients with opioid use disorder? 2) does cannabis use improve treatment retention in OUD? and 3) does cannabis use in this population reduce the risk of other drugs use?

Methods:

This review is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21), and it has been registered with PROSPERO (No. CRD42015029372). The detailed methods have been published in a protocol in *Systematic Reviews* (16).

We searched MEDLINE/PubMed, EMBASE, PsychINFO, and CINAHL from inception to July 2018 for relevant studies, and we also searched grey literature using the ProQuest Theses and Dissertations Global database. We applied no language or demographic restrictions.

We included studies that looked at the association between cannabis and outcomes of methadone maintenance therapy. To meet our inclusion criteria, a study had to measure outcomes of MMT by measuring participants' illicit opioid use during the treatment, or by

treatment retention rates by cannabis use. We excluded studies where the sample included patients on other opioid substitution therapies such as buprenorphine and the study did not perform separate analyses on methadone receiving patients only. We included only methadone treatment because it was the most commonly used treatment and to avoid heterogeneity by including different treatment interventions. There were no other exclusion criteria.

We screened all articles in duplicate at all stages and performed data extraction in duplicate. We measured inter-rater agreement with the kappa statistic calculation, and we assessed risk of bias for each included study in duplicate using the modified Newcastle-Ottawa Scale (NOS) (22). We measured the overall quality of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (23).

We performed meta-analyses, using random effects models. The first analysis included studies that measured outcomes of MMT by measuring the association between cannabis use and illicit opioid by patients on methadone therapy. The other meta analyses included studies that assessed the association between cannabis use and methadone treatment retention and subgroup analyses to explain heterogeneity. A study was considered for inclusion in the meta analyses if it produced, or included enough information to generate an odds ratio, which was then calculated using RevMan version 5.3 software (22). If a study included multiple points of measurement for cannabis use, we used the baseline measurement. Some studies measured cannabis use both prior to treatment and during treatment, and we chose to use the in-treatment cannabis measurement. In studies that included multiple follow-up points for the outcome measurement, we included the latest follow-up time point in the meta-analysis.

We performed a sensitivity analysis by excluding all studies with NOS scores of 0 and 1 and redoing both meta-analyses. We also performed subgroup analyses, but we were unable to do all of those planned in the published protocol because some of the studies didn't contain the necessary information.

Results:

Of the 2,467 unique citations screened, 23 studies were included. Inter-rater agreement was acceptable for both title/abstract, κ=0.63 (95% CI: 0.57-0.69) and full text screening, κ =0.60 (95% CI: 0.45-0.74). Although we did not apply any age restrictions, all studies were of an adult population. In studies that reported the proportion of participants with any recent or current (i.e. not lifetime measurements) cannabis use, the prevalence varied from 11.2% to 78.6%. All of the studies we included has a moderate or high risk of bias on at least one NOS criterion. Detailed study characteristics are summarized in Table 1, along with NOS ratings in Table 2.

Illicit Opioid Use as an Outcome:

Twelve studies examined the relationship between cannabis use and illicit opioid use or opioid relapse (15,24–34). Of those, the vast majority showed no significant association (see Table 1A).

The meta-analysis of the effect of cannabis use on illicit opioid use included six studies and did not show a significant effect (OR=0.39, 95% CI=0.09-1.79, p = 0.23), and there was significant heterogeneity in the studies included with an I^2 of 96%, [$\chi^2(6)$=141.54, p<0.00001]. These results didn't change when we excluded studies with a high risk of bias. We conducted subgroup analyses by country and method of cannabis use measure (i.e. objective vs. patient

reported or subjective), and all the results showed no effect of cannabis on opioid use (Figure 2 B and C).

The overall quality of evidence (as assessed using GRADE) was very low, with critical issues of inconsistence and imprecision, in addition to having a moderate risk of bias. Due to the nature of the observational study designs, GRADE ratings of quality start from low and any additional concern in quality assessment will make the quality very low. There was no evidence of publication bias.

Treatment Retention as an Outcome:

Eleven studies investigated the influence of cannabis use on methadone maintenance treatment retention (27,28,30,33–40). The majority (eight) of the studies found no significant association between cannabis use and treatment retention (Table 1B).
The pooled analysis showed no significant effect of cannabis use on treatment retention (OR=0.48, 95% CI=0.18,1.28, $p = 0.14$). The analysis had significant heterogeneity, with an I^2 of 90%, [$\chi^2(4)=41.62$, $p<.0001$]. The sensitivity analysis conducted by excluding studies with high risk of bias did not change the result. In the subgroup analysis results by country, we found studies conducted in USA showed cannabis use to be significantly associated with decreased retention rates, OR=0.23, 95% CI=0.13, 0.39, $p < .0001$, while those conducted in Israel showed the opposite direction, OR=1.48, 95% CI=1.20,1.82, $p < .0001$ (Figure 4B). Both subgroup analyses had an I^2 value of 0%, indicating no heterogeneity.

The overall quality of evidence was very low, with quality issues related to inconsistency and imprecision. The funnel plot presented in Figure 5 displays slight asymmetry, however this is unlikely to be related to publication bias, as most studies included in the review had non-significant results.

Secondary Outcome Measures:

We also reviewed the literature looking for associations between cannabis use and several secondary outcomes – polydrug use, criminal activity, and HIV and HCV risk behaviours. The evidence in all of these areas is inconclusive. Please see Table 1C, Table 1D, and Table 1E (24,27,45,31,33,34,40–44).

Discussion:

We included 23 studies that examined the association between cannabis use and opioid use and retention in MMT. The meta-analysis of six of these studies showed no effect of cannabis on opioid use. Of the 11 studies on the relationship between cannabis use and methadone treatment retention, our pooled meta-analysis of four of these studies showed no significant effect. All meta-analyses had substantial heterogeneity, and the overall quality of evidence was very low, with high risk of bias due to the nature of observational studies.

To our knowledge, this is the first systematic review and meta analyses investigating the use of cannabis during MMT. The results suggest that cannabis has no effect on opioid use in patients on MMT. However, the limitations of this study mean that a true effect of cannabis on opioid use during MMT could have been missed, because of the following limitations.

First, these results come from small to medium sized observational studies with limited data on confounding variables. For example, cannabis is seldom used alone; it's associated with polydrug use, and with comorbid substance use disorders in MMT patients (40,46,47). Both polydrug use and substance use disorders are associated with poorer treatment outcomes in OUD themselves (48).

There were also methodological limitations. Our meta-analyses had substantial heterogeneity, partly because of variability in methodology between studies: there were differences in the delivery and duration of MMT, the definition of cannabis use, and measures of treatment outcomes. Our predefined subgroup analyses based on region and how cannabis use was measured did not explain this heterogeneity. The limited number of studies included in the meta-analyses precluded us from conducting further subgroup analyses to identify possible sources of heterogeneity.

In addition, many of the included studies dichotomized cannabis use in some way, splitting people who used some cannabis from those who used none at all, or splitting those who used more than a certain threshold amount of cannabis from those who used less. This choice was likely made because dosage of cannabis is challenging to quantify (49), but it makes the establishment of a dose-response relationship in any of these studies impossible. It also reduces the sensitivity of any findings. This choice could obscure a significant association, especially considering many of the other health effects of cannabis are only visible with heavy usage (50,51). Although we recognize that it may be difficult, further research should use more sensitive and detailed definitions of cannabis use.

Furthermore, the studies didn't distinguish between cannabis use disorder and recreational cannabis use. Patients with cannabis use disorder (CUD) have high rates of comorbid psychiatric and personality disorders compared to recreational users (52), which are associated with poorer treatment outcomes (53). Some studies suggest cannabis use disorder is associated with less other drug use during MMT, whereas recreational cannabis use is associated with more (54). Again, polydrug use is associated with poorer outcomes, therefore grouping all cannabis users together makes the interpretation challenging.

We need more research to understand the complex relationships between opioid use, OUD treatment outcomes, cannabis use, and other drug use. However, one thing is very clear: there is no evidence to support the use of cannabis as an exit drug. The broad negative health effects of heavy cannabis use have also been well documented in the literature (50,51). We should continue to counsel patients on the potential risks of cannabis use, while emphasizing that we have no evidence to support the use of cannabis to stop opioid use.

Previous studies reported that in states with dispensary-based medical cannabis laws, fewer prescription opioids were dispensed (18,19). We note that those results do not show that this reduction was because cannabis was used as a replacement for opioids. More recently, a national cohort study investigating cannabis use in patients prescribed opioids for chronic non-cancer pain showed that cannabis use did not reduce opioid use or help with opioid discontinuation. Using cannabis was associated with worse pain control and psychiatric symptoms (55). This study supports our findings in a wider population. More investigation is needed to reconcile the findings of the policy-related studies with those of the patient populations.

We conclude based on the current study that cannabis use is not associated with reduced opioid use. Caution must be exercised when evaluating data related to cannabis and opioid use, in order to avoid advocating for cannabis use in the absence of a credible evidence.

References:

1. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities. JAMA [Internet]. 2008;300(22):2613–9. Available from: www.jama.com
2. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid Prescriptions for Chronic Pain and Overdose A Cohort Study. Ann Intern Med [Internet]. 2010;152:85–92. Available from: www.annals.org
3. Paulozzi LJ, Ryan GW. Opioid Analgesics and Rates of Fatal Drug Poisoning in the United States. Am J Prev Med. 2006;31(6):506–11.
4. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report. 2010.
5. National report: Apparent opioid-related deaths in Canada [Internet]. 2018. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-released-march-2018.html
6. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, et al. The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. Annu Rev Public Health. 2015;36:559–74.
7. Han B, Compton WM, Jones CM, Cai R. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. JAMA - J Am Med Assoc. 2015;314(14):1468–78.
8. Connery HS. Medication-assisted treatment of opioid use disorder: Review of the evidence and future directions. Harvard Review of Psychiatry. 2015. p. 63–75.
9. Socias ME, Ahamad K. An urgent call to increase access to evidence-based opioid agonist therapy for prescription opioid use disorders. Can Med Assoc J. 2016;(188):17–8.
10. Farré M, Mas A, Torrens M, Moreno V, Camí J. Retention rate and illicit opioid use during methadone maintenance interventions: A meta-analysis. Drug Alcohol Depend. 2002;(65):283–90.
11. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ. 2012;345(5945).
12. Bruneau J, Ahamad K, Goyer M-È, Poulin G, Selby P, Fischer B, et al. Management of opioid use disorders: a national clinical practice guideline. Can Med Assoc J [Internet]. 2018;190(9):E247–57. Available from: http://www.cmaj.ca/lookup/doi/10.1503/cmaj.170958
13. Shahid, H, Bhatt Meha, Sanger, Nitika, Zielinski, Laura, Luo, Candice, Bantoto, Bianca, Shams, Ieta, Mouravska, Natalia, Lue Tam, Sabrina, Hudson, Jackie, Thabane, Lehana, Samaan Z. Association Between Family Factors and Illicit Polysubstance Use Amongst Methadone Maintenance Patients with Opioid Use Disorder. Int J High Risk Behav Addict. 2018;7(3).
14. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. Am J Addict. 2013;(22):344–51.
15. Zielinski L, Bhatt M, Sanger N, Plater C, Worster A, Varenbut M, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8(1):1–10.

16. Zielinski L, Bhatt M, Eisen RB, Perera S, Bhatnagar N, MacKillop J, et al. Association between cannabis use and treatment outcomes in patients receiving methadone maintenance treatment: A systematic review protocol. Syst Rev. 2016;5(139).
17. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis. 2016;35(1):22–35.
18. Bradford AC, Bradford WD, Abraham A, Adams GB. Association between US state medical cannabis laws and opioid prescribing in the medicare part D population. JAMA Intern Med. 2018;178(5):667–73.
19. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014;174(10):1668–73.
20. Veterans Affairs Medical Marijuana Policy [Internet]. 2017. Available from: https://www.scribd.com/document/367496398/Veterans-Affairs-Medical-Marijuana-Policy#from_embed
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Guidelines and Guidance Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Plos Med [Internet]. 2009;6(7). Available from: http://www.prisma-statement.
22. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014
23. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380–2.
24. Best D, Gossop M, Greenwood J, Marsden J, Lehmann P, Strang J. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. Drug Alcohol Rev. 1999;18(January 1998):31–8.
25. Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend [Internet]. 1998;52(3):183–92. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9839144&retmode=ref&cmd=prlinks%5Cnfile:///Articles/1998/Wasserman/Drug Alcohol Depend 1998 Wasserman.pdf
26. Somers CJ, O'Connor J. Retrospective study of outcomes, for patients admitted to a drug treatment centre board. Irish Medical Journal (IMJ). 2012 Oct 1.
27. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. Addiction. 2003;98(3):269–79.
28. Levine AR, Lundahl LH, Ledgerwood DM, Lisieski M, Rhodes GL, Greenwald MK. Gender-Specific Predictors of Retention and Opioid Abstinence During Methadone Maintenance Treatment. J Subst Abuse Treat [Internet]. 2015;54:37–43. Available from: http://dx.doi.org/10.1016/j.jsat.2015.01.009
29. Lions C, Carrieri MP, Michel L, Mora M, Marcellin F, Morel A, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: An attributable-risk approach (ANRS-Methaville trial). Drug Alcohol Depend [Internet]. 2014;135(1):1–8. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2013.10.018
30. Nava F, Manzato E, Lucchini A. Chronic cannabis use does not affect the normalization

of hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts. Prog Neuro-Psychopharmacology Biol Psychiatry. 2007;31(5):1089–94.
31. Nirenberg TD, Cellucci T, Liepman MR, Swift RM, Sirota AlD. Cannabis versus other illicit drug use among methadone maintenance patients. Vol. 10, Psychology of addictive behaviours. 1996. p. 222–7.
32. Proctor SL, Copeland AL, Kopak AM, Hoffmann NG, Herschman PL, Polukhina N. Outcome predictors for patients receiving methadone maintenance treatment: findings from a retrospective multi-site study. J Subst Use [Internet]. 2016;21(6):601–13. Available from: http://dx.doi.org/10.3109/14659891.2015.1118564
33. Saxon AJ, Calsyn DA, Greenberg D, Blaes P, Haver VM, Stanton V. Urine Screening for Marijuana Among Methadone-Maintained Patients. Am J Addict. 1993;2(3):207–11.
34. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: Implications for opiate dependence and withdrawal. Neuroscience [Internet]. 2013;248:637–54. Available from: http://dx.doi.org/10.1016/j.neuroscience.2013.04.034
35. White WL, Campbell MD, Spencer RD, Hoffman HA, Crissman B, DuPont RL. Patterns of Abstinence or Continued Drug Use Among Methadone Maintenance Patients and Their Relation to Treatment Retention. J Psychoactive Drugs [Internet]. 2014;46(2):114–22. Available from: http://dx.doi.org/10.1080/02791072.2014.901587
36. Joe GW, Dwayne Simpson D, Broome KM. Effects of readiness for drug abuse treatment on client retention and assessment of process. Addiction. 1998;93(8):1177–90.
37. Peles E, Schreiber S, Adelson M. Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. Drug Alcohol Depend. 2006;82(3):211–7.
38. Peles E, Linzy S, Kreek MJ, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: A comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11–25.
39. Schiff M, Levit S, Moreno RC. Retention and illicit drug use among methadone patients in Israel: A gender comparison. Addict Behav. 2007;32(10):2108–19.
40. Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. Australas Psychiatry. 2004;38:42–6.
41. Bleich AVI, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M. Correlates of benzodiazepine abuse in methadone maintenance treatment . A 1 year prospective study in an Israeli clinic. 1999;94(January).
42. Peirce JM, Petry NM, Roll JM, Kolodner K, Krasnansky J, Stabile PQ, et al. Correlates of stimulant treatment outcome across treatment modalities. Am J Drug Alcohol Abuse. 2009;35(1):48–53.
43. Saxon AJ, Wells EA, Fleming C, Jackson TR, Calsyn DA. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. Addiction. 1996;91(8):1197–209.
44. Strain EC, Brooner RK, Bigelow GE. Clustering of multiple substance use and psychiatric diagnoses in opiate addicts. Drug Alcohol Depend. 1991;27(2):127–34.
45. Bell, J, Mattick, R, Hay, A, Chan, J, Hall W. Methadone Maintenance and Drug-Related Crime. J Subst Abuse. 1997;9:15–25.
46. Degenhardt L, Hall W, Lynskey M. The relationship between cannabis use and other substance use in the general population. Drug Alcohol Depend. 2001;64:319–27.

47. Krajicek S. Cannabis Use and Risk of Psychiatric Disorders. JAMA Psychiatry. 2016;73:388–95.
48. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: A survival analysis. Drug Alcohol Depend. 2011;117:170–5.
49. Peggy van der Pol, Nienke Liebregts, Ron de Graaf, Dirk J. Korf, Wim van den Brink M van L. Validation of self-reported cannabis dose and potency: an ecological study. Addiction. 2013;108:1801–1808.
50. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse Health Effects of Marijuana Use. N Engl J Med. 2014;370(23):2219–27.
51. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of cannabis use on human behavior, including cognition,motivation, and psychosis: A review. JAMA Psychiatry. 2016;73(3).
52. Khan SS, Secades-Villa R, Okuda M, Wang S, Pérez-Fuentes G, Kerridge BT, et al. Gender differences in cannabis use disorders: Results from the National Epidemiologic Survey of Alcohol and Related Conditions. Drug Alcohol Depend. 2013;130:101–8.
53. Rosic T, Naji L, Bawor M, Dennis BB, Plater C, Marsh DC, et al. The impact of comorbid psychiatric disorders on methadone maintenance treatment in opioid use disorder: A prospective cohort study. Neuropsychiatr Dis Treat. 2017;
54. Peirce JM, Petry NM, Roll JM, Kolodner K, Krasnansky J, Stabile PQ, et al. Correlates of Stimulant Treatment Outcome Across Treatment Modalities. Alcohol Drug Depend. 2009;35:49–53.
55. Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Heal [Internet]. 2018;3(7):e341–50. Available from: https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(18)30110-5/fulltext

Figure 1. PRISMA flow diagram of included studies

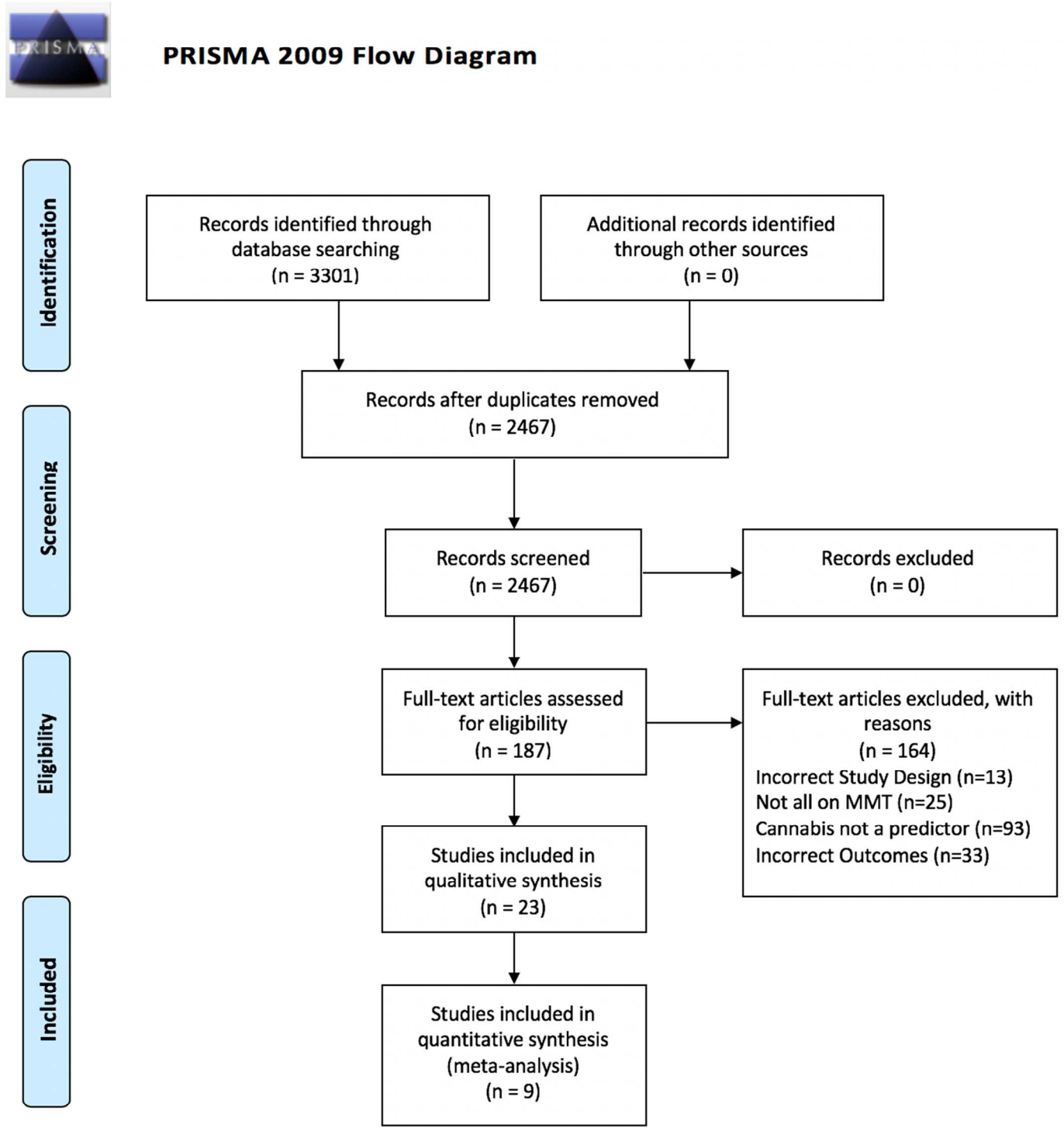
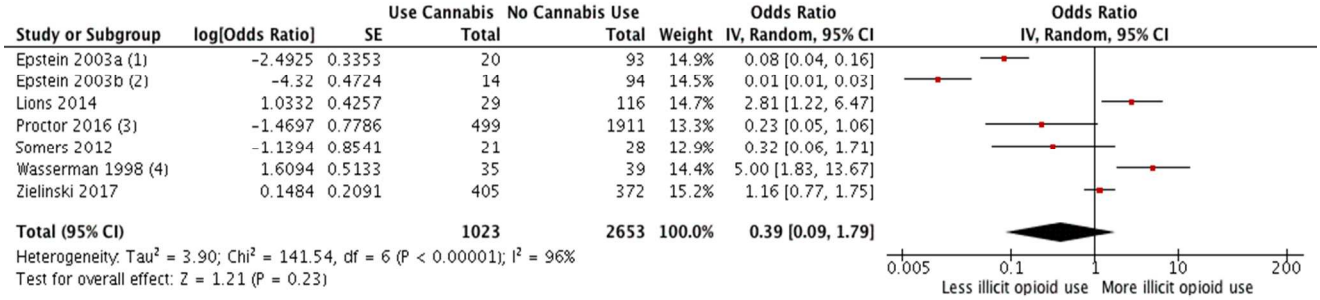


Figure 2. Illicit opioid use during treatment by cannabis use meta-analysis

A. Meta-analysis forest plot for illicit opioid use

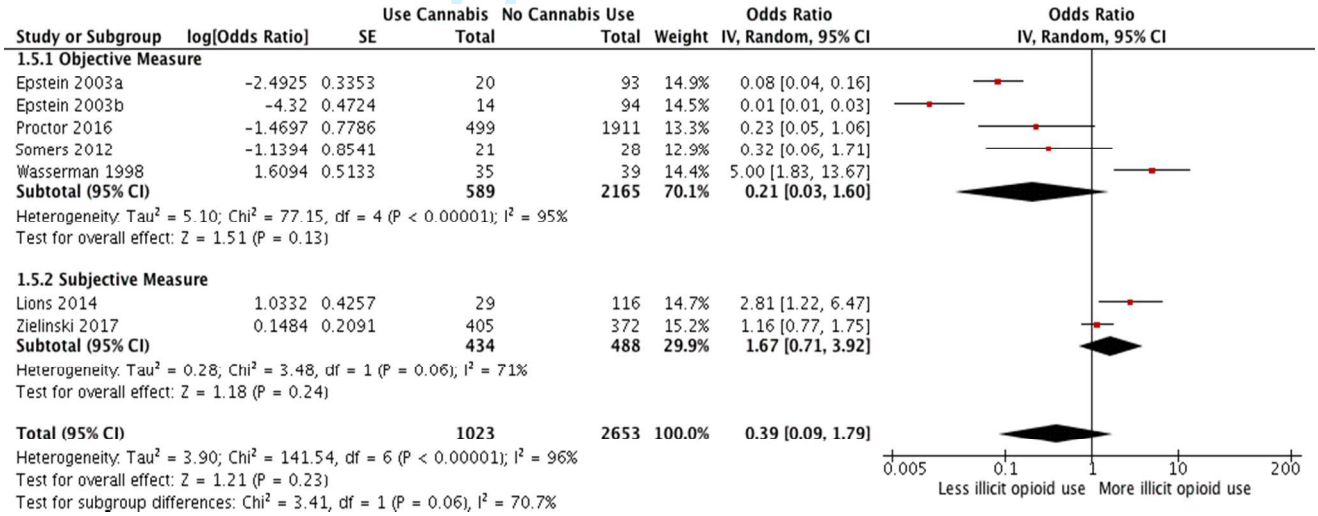


Study or Subgroup	log[Odds Ratio]	SE	Use Cannabis Total	No Cannabis Use Total	Weight	Odds Ratio IV, Random, 95% CI
Epstein 2003a (1)	-2.4925	0.3353	20	93	14.9%	0.08 [0.04, 0.16]
Epstein 2003b (2)	-4.32	0.4724	14	94	14.5%	0.01 [0.01, 0.03]
Lions 2014	1.0332	0.4257	29	116	14.7%	2.81 [1.22, 6.47]
Proctor 2016 (3)	-1.4697	0.7786	499	1911	13.3%	0.23 [0.05, 1.06]
Somers 2012	-1.1394	0.8541	21	28	12.9%	0.32 [0.06, 1.71]
Wasserman 1998 (4)	1.6094	0.5133	35	39	14.4%	5.00 [1.83, 13.67]
Zielinski 2017	0.1484	0.2091	405	372	15.2%	1.16 [0.77, 1.75]
Total (95% CI)			**1023**	**2653**	**100.0%**	**0.39 [0.09, 1.79]**

Heterogeneity: Tau² = 3.90; Chi² = 141.54, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.21 (P = 0.23)

Footnotes
(1) Combined results of two trials which were 8 weeks long
(2) Results from one trial that was 12 weeks long
(3) Prevalence reflects 12-month cannabis use, as baseline prevalence was not reported. Odds ratio reflects baseline cannabis use and 12-month opioid use.
(4) Odds ratio as estimated in Epstein 2003

B. Subgroup meta-analysis stratified by measure of cannabis use



Study or Subgroup	log[Odds Ratio]	SE	Use Cannabis Total	No Cannabis Use Total	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 Objective Measure						
Epstein 2003a	-2.4925	0.3353	20	93	14.9%	0.08 [0.04, 0.16]
Epstein 2003b	-4.32	0.4724	14	94	14.5%	0.01 [0.01, 0.03]
Proctor 2016	-1.4697	0.7786	499	1911	13.3%	0.23 [0.05, 1.06]
Somers 2012	-1.1394	0.8541	21	28	12.9%	0.32 [0.06, 1.71]
Wasserman 1998	1.6094	0.5133	35	39	14.4%	5.00 [1.83, 13.67]
Subtotal (95% CI)			**589**	**2165**	**70.1%**	**0.21 [0.03, 1.60]**
Heterogeneity: Tau² = 5.10; Chi² = 77.15, df = 4 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 1.51 (P = 0.13)						
1.5.2 Subjective Measure						
Lions 2014	1.0332	0.4257	29	116	14.7%	2.81 [1.22, 6.47]
Zielinski 2017	0.1484	0.2091	405	372	15.2%	1.16 [0.77, 1.75]
Subtotal (95% CI)			**434**	**488**	**29.9%**	**1.67 [0.71, 3.92]**
Heterogeneity: Tau² = 0.28; Chi² = 3.48, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)			**1023**	**2653**	**100.0%**	**0.39 [0.09, 1.79]**
Heterogeneity: Tau² = 3.90; Chi² = 141.54, df = 6 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 3.41, df = 1 (P = 0.06), I² = 70.7%						

C. Subgroup meta-analysis stratified by region

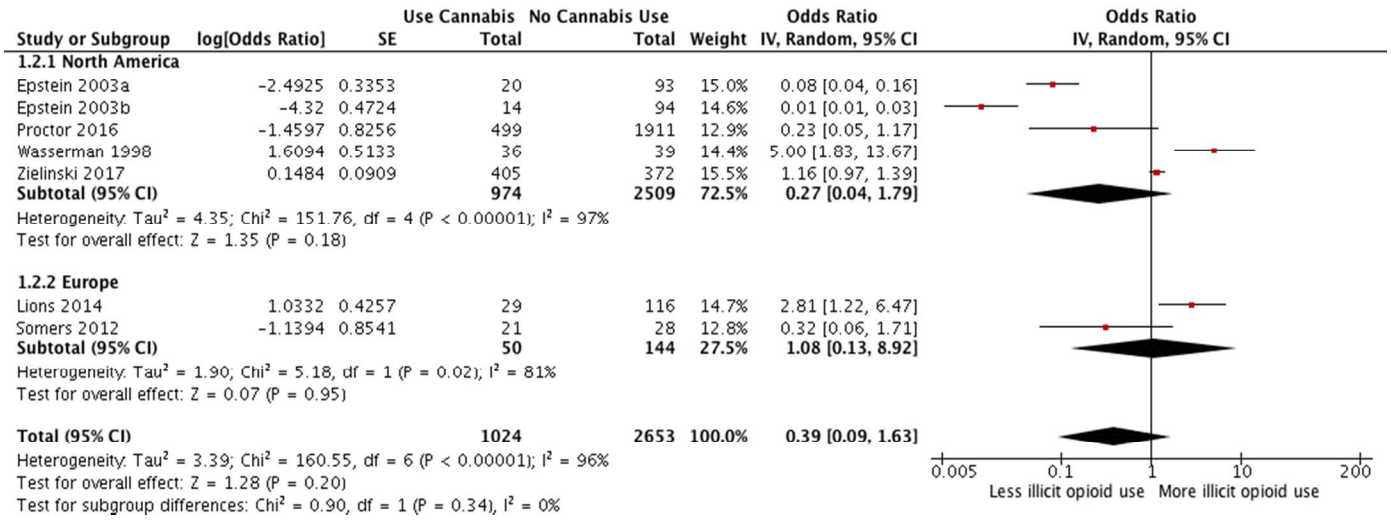


Figure 3. Funnel plot evaluating publication bias for illicit opioid use

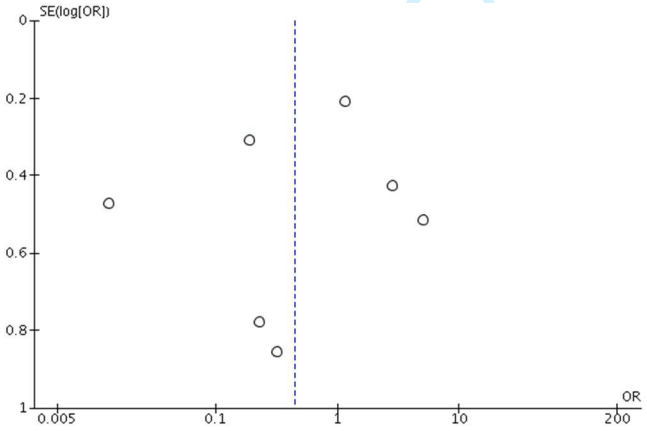
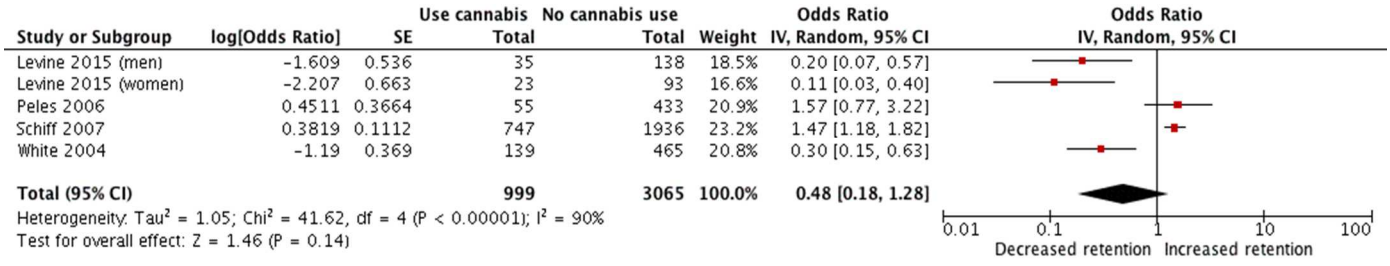


Figure 4. Treatment retention meta-analysis

A. Meta-analysis forest plot for treatment retention



B. Subgroup meta-analysis stratified by country

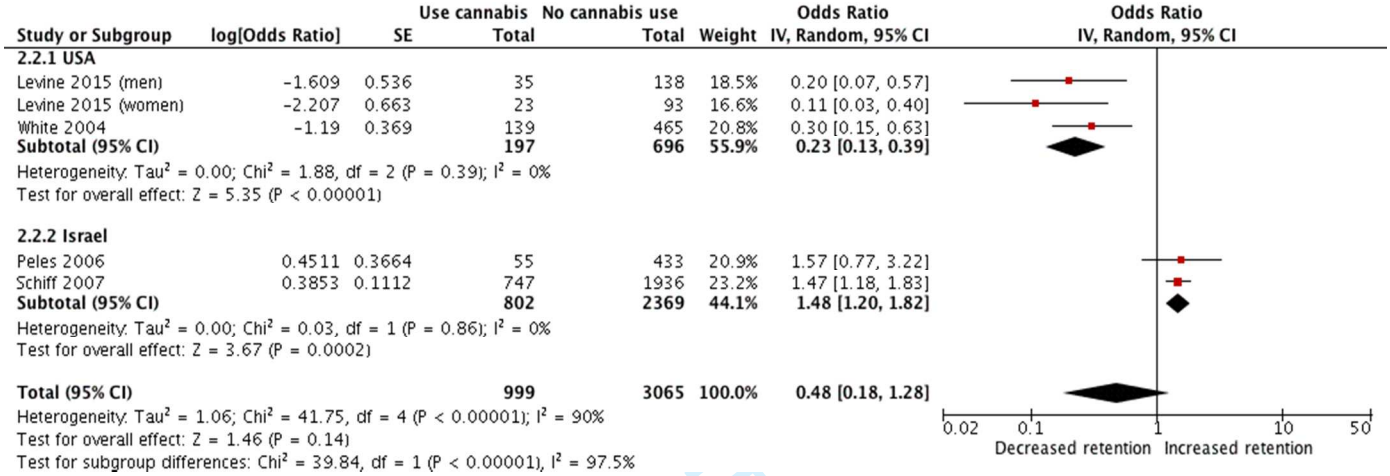


Figure 5. Funnel plot evaluating publication bias for treatment retention.

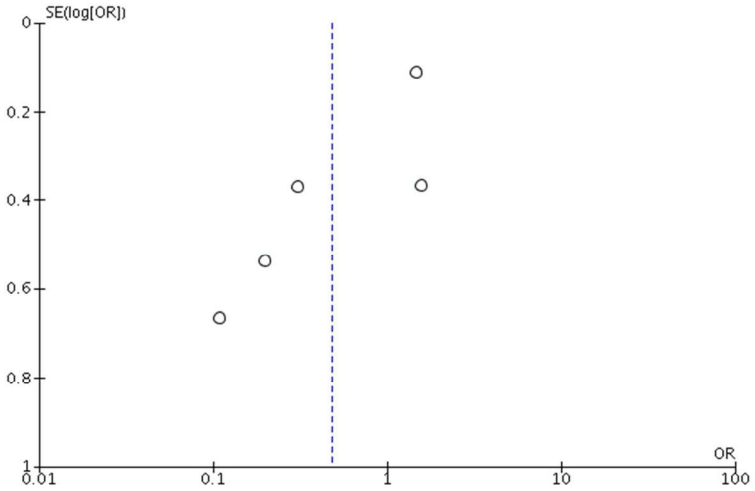


Table 1. Individual Study Characteristics by Outcomes

A. Illicit Opioid Use

Study	Country	Study Design	Sample Size (% Female)	Cannabis Use Definition	Outcome	Statistical Analysis	Results
Best, 1999 (1)	UK	Cross sectional	200 (30%)	**Method:** MAP **Definition:** Categorical; daily users, occasional users (used cannabis but not on all 30 days in previous months), and non-users **Timing:** Baseline	**Method:** MAP **Definition:** Continuous; Mean number of days of heroin use in the past 30 days from MAP **Timing:** Baseline	ANOVA; post-hoc Scheffe test	F=11.07, p<.0001, such that non-users had more occasions of heroin use than occasional and daily users
Epstein, 2003 (2)	USA	Secondary RCT analysis (3 separate analyses), 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Dichotomized cannabis use and cannabis abuse/dependence diagnosis **Timing:** Baseline and 12 months	**Method:** Urinalysis **Definition:** Relapse to heroin among patients who achieved abstinence (3 consecutive weeks of opioid abstinence) **Timing:** Time to lapse	Cox proportional-hazard regression	**Cannabis use:** First two trials: HR = 1.54 (0.93–2.56) ; χ^2=2.78, p=0.095 Third trial: HR = 0.90 (0.48-1.65) ; χ^2=0.13, p=0.72 **Cannabis abuse/dependence:** First two trials: HR = 1.16 (0.63-2.13); χ^2=0.22, p=0.64 Third trial: HR = 2.09 (0.76-5.76); χ^2=1.66, p=0.19
Levine, 2015 (3)	USA	Retrospective cohort, 1 year	290 (40.34%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline within the First month of drug testing upon entry into MMT	**Method:** Urinalysis **Definition:** Continuous; Proportion of UDS results negative for opioids was calculated within the first year **Timing:** 12 months in treatment	Logistic Regression	Not significant, but statistics not reported.
Lions, 2014 (4)	France	Secondary RCT analysis, 45 weeks	158 (15.19%)	**Method:** Opiate Treatment Index **Definition:** Dichotomous; Daily users vs. non-daily users **Timing:** Baseline and 12 months	**Method:** Opiate Treatment Index **Definition:** Dichotomous; Opiate users vs. non-opiate users (used opiates at least once in the past month) **Timing:** 12 months	Multiple logistic regression	**Pre-treatment daily cannabis:** OR=1.46 (0.61-3.77), ns **In-treatment daily cannabis:** OR=2.81 (1.22-6.48), p<.05
Nava, 2007 (5)	Italy	Prospective cohort, 12 months	121 (14%)	**Method:** Self report, Urinalysis **Definition:** Dichotomous; long term users (more than 6 months) and currently smoking at least 7	**Method:** Urinalysis **Definition:** Continuous; Percentage positive opioid screens (missing specimens	Hierarchical linear modelling	**Cannabis users:** z=-3.42, p<.001, such that there was a reduced percentage of positive opioid urines.

				times per week vs. non-users never exposed to marijuana smoking. **Timing:** Baseline	considered positive) **Timing:** Urine samples were collected once a week		**Non-cannabis users:** z=-3.18, p<.001, such that there was a reduced percentage of positive opioid urines.
Nirenberg, 1996 (6)	USA	Prospective cohort, 6 months	70 (1.42%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use; and Categorical 4 groups: Group 1 - cannabis abstainers (0 positive screens); Group 2 - intermittent cannabis users (0%-33.3% positive screens); Group 3 - moderate cannabis users (33.3% to 66.6% positive screens); Group 4 - consistent cannabis users (66.6%-100% positive screens) **Timing:** 45 weeks	**Method:** Urinalysis; **Definition:** Continuous; Percentage positive opioid UDS **Timing**: 45 weeks	ANOVA	**Dichotomized cannabis use:** F(1,68)=0.90, p=.35, ns **Four groups:** F(3,66)=1.13, p=.34, ns
Proctor, 2016* (7)	USA	Retrospective cohort, 12 months	2410 (40.41%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Intake, 3, 6, 9, and 12 months	**Method:** Urinalysis **Definition:** Dichotomous; users vs. nonusers **Timing:** 3, 6, 9, 12 months	Logistic Regression	**3 months:** Intake cannabis: OR=1.17 (0.83-1.63) **6 months:** Intake cannabis: OR=0.59 (0.32-1.10) **9 months**: Intake cannabis: OR=0.63 (0.24-1.66) **12 months:** Intake cannabis: OR=0.23 (0.05-1.16)
Saxon, 1996 (8)	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self report **Definition:** Categorical; seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Timing:** 6 months prior to baseline	**Method:** Urinalysis **Definition**: Dichotomous; Considered opioid users if reported use of any opioid drug other than their prescribed medication, or if they reported having administered their prescribed medication by snorting or injection in the previous 6 months. Percentage of opioid positive urine screens over 18 months **Timing:** 18 months	Cox regression model	r=0.06; B=0.05, ns
Scavone, 2013 (9)	USA	Retrospective cohort, 9 months	91 (36.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized cannabis use	**Method:** Urinalysis **Definition:** Continuous **Timing:** 9 months	ANCOVA	r(82)=.018, p=.873, such that there was no significant relationship between frequency

				Timing: Baseline (self-report) and In-treatment (initial 9 months of MMT enrolment)			of cannabis use in treatment and opiate use.
Somers, 2012 (10)	Ireland	Retrospective cohort, 15 months	123	**Method:** Urinalysis **Definition:** Dichotomous cannabis use **Timing:** Baseline and in-Treatment; intake, 3, 9 and 15 months	**Method:** Urinalysis **Definition:** Dichotomous; Subjects with less than 20 % of samples positive for heroin **Timing:** 3,9,15 months	Logistic regression	**Baseline:** OR: 0.88 (.67-1.15) **3 month:** OR: 0.79 (.58, 1.1) **9 month:** OR: 0.78 (.55, 1.2) **15 months:** OR: 1.45 (.82, 2.5) **Total:** AOR: 0.32 (.06, 1.66)
Wasserman, 1998 (11)	USA	Prospective cohort, 6 months	74 (40.54%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline cannabis (first week) and cannabis as a time-dependent variable included in analyses	**Method:** Self-report or urinalysis; **Definition:** Dichotomous; Participants dichotomized as having used heroin during the period from week 2 through the 6-month follow-up assessment or not. **Timing:** 6 month follow-up	Cox proportional hazards regression	χ^2=8.39, p<0.004., such that baseline cannabis use significantly increased the risk of a lapse to heroin. χ^2=7.62, p<0.006, such that cannabis as a time-dependent variable significantly increased the risk of a lapse to heroin. **6-month follow-up:** χ^2=7.90, p<0.005, such that such that baseline cannabis use significantly increased the risk of a lapse to heroin
Zielinski, 2017 (12)	Canada	Cross-sectional	777 (46.7%)	**Method:** MAP **Definition:** Dichotomized cannabis use in the past 30 days **Timing**: Baseline cannabis	**Method:** Urinalysis **Definition:** Dichotomous; participants with any positive screens of illicit opioids **Timing:** 3 month testing period	Multivariable logistic regression analysis	OR: 1.16, 95%CI: 0.77, 1.75, p=0.49

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified. MAP: Maudsley Addiction Profile; HR: hazard ratio; ANOVA: analysis of variance; RCT: randomized controlled trial; ns: not significant; UDS: urine drug screen; MMT: methadone maintenance treatment; ANCOVA: analysis of covariance; OR: odds ratio. *Proctor et al. (2016) had too many results to present in this table, so we included only intake cannabis values in relation to opioid use at all time points. See study for more results.

B. Treatment Retention

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Epstein, 2003 (2)	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users **Timing:** Time to dropout	**Definition:** Retention in clinical trials up till follow up **Timing:** Did they complete the follow ups to 12 months	Survival analysis for treatment retention for all 3 trials	In all 3 trials, p-values ranged from p=.69 to p=.72 Further statistics not reported.
Joe, 1998 (13)	USA	Prospective cohort, 360 days	981 (39%)	**Method:** Self-report **Definition:** Dichotomous; At least weekly marijuana use or not **Timing:** Baseline	**Definition:** Whether clients stayed at least 360 days in outpatient methadone treatment. **Timing**: 360 days into treatment	Hierarchical linear regression model	b=0.13, SE=0.16, t=0.79, OR=1.14, ns
Levine, 2015 (3)	USA	Retrospective cohort, 1 year	290 (40.34%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline within the First month of drug testing upon entry into MMT	**Definition:** Dichotomized into two groups: less than a year and more than a year **Timing:** 12 months after treatment	Logistic regression	**Men:** cannabis-negative: OR=5.00 (1.61-14.29), p=.01, such that less cannabis use predicted >1 year retention **Women** cannabis-negative: OR=9.09 (2.33-33.33), p<.001, such that less cannabis use predicted >1 year retention
Nava, 2007 (5)	Italy	Prospective cohort, 12 months	121 (13.22%)	**Method:** Self report, Urinalysis **Definition:** Dichotomous; long term users (more than 6 months) and currently smoking at least 7 times per week vs. non-users never exposed to marijuana smoking. **Timing:** Baseline	**Definition:** Percentage dropout from treatment measured **Timing:** 2 weeks, 3 months, and 12 months	Kaplain-Meier survival analysis	No significant association (values not reported).
Peles, 2006 (14)	Israel	Prospective cohort, 11 years	492 (27.24%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** 13 months or month before dropout	**Definition:** Continuous; The number of days in clinic from first admission until the patient quit treatment or until the end of follow-up (11 years) **Timing:** 132 months	Fishers exact test	**Cannabis use on admission:** p=0.3, ns
Peles, 2008 (15)	USA and Israel	Prospective cohort, 12 months	794 (30.98%)	**Method:** Weekly urinalysis; **Definition:** Dichotomized cannabis use	**Definition:** Continuous; Duration in clinic from first admission until the patient stopped treatment or	Kaplan-Meier survival analysis with	**Tel Aviv:** Positive THC on admission: log rank=0.2, p=.8

				Timing: Baseline and in-treatment For follow-up, recorded cannabis use month after completion or one month before if early dropout	until the end of the follow-up **Timing:** Analyzed 6 months retention and 1 year retention in treatment	log rank for cumulative retention.	Positive THC after 1 year: log rank=1.8, p=.2 **Las Vegas:** Positive THC on admission: log rank=4.2, p=.04 Positive THC after 1 year: log rank=0.8, p=.4 Included in multivariate analysis but not significant (values not provided)
Saxon, 1996 (8)	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self report **Definition:** Categorical; seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Timing:** 6 months prior to baseline	**Definition:** subjects remaining in treatment continuously after enrolment and those not remaining **Timing:** 18 months after enrolment	Cox regression analysis	r=0.06; B=1.08 (0.97-1.2), ns
Scavone, 2013 (9)	USA	Retrospective cohort, 9 months	91 (39.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline (self-report) and In-treatment (urinalysis from initial 9 months of MMT enrolment)	**Definition:** Mean number of patients dropped out **Timing:** 9 months into treatment	Pearson correlation, chi square	Unfavourable discharge status: r(80)=.069, p=.567, ns Premature discharge status: χ^2 = 3.009, p=.222, ns
Schiff, 2007 (16)	Israel	Retrospective cohort, 13 months	2,683 (14.07%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** Baseline and in-treatment; 13 months into treatment	**Definition:** Dichotomized patients as 100% retention vs. lower **Timing:** 13 months into treatment	Logistic regression	OR=1.43 (1.15, 1.78), p<.001, such that there was a significant relationship between cannabis use and increased retention.
Weizman, 2004 (17)	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was	**Definition:** Treatment tenure was calculated based upon the overall number of days patients remained in treatment; Continuous **Timing:** 12 months into treatment	Cox regression survival analysis	Non-CAs vs CAs, B=-0.17; SE=0.13; Wald=1.57, p=0.21; r=0.00; Exp(B)=0.84 Analysis with heroin, cocaine, and BZD abuse as covariates did not significantly change the results.

				considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months			
White, 2014 (18)	USA	Retrospective cohort, 15-17 months	604 (39.40%)	**Method:** Urinalysis **Definition:** Dichotomized cannabis use **Timing:** First 3 months	**Definition:** Dichotomized retention as left MMT or remained in MMT **Timing:** 15-17 months	Chi square Fishers Exact Test	**Baseline cannabis use:** OR: 3.3 (1.6-6.8), p<.01, such that cannabis use was significantly associated with increased attrition rates. **Positive ONLY for cannabis at baseline:** 5% OR: 0.5 (0.7-9.8), p=1.00, ns

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified. RCT: randomized controlled trial; SE: standard error; OR: odds ratio; ns: not significant; MMT: methadone maintenance treatment; THC: tetrahydrocannabinol; NR: not reported; SCID: Structured Clinical Interview for DSM disorders; CA: cannabis abuser.

C. Polydrug Use

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Best, 1999 (1)	UK	Cross sectional	200 (30%)	**Method:** MAP **Definition:** Classified participants as daily users, occasional users, and non-users; categorical **Timing:** Baseline	**Method:** MAP **Definition:** Measured alcohol and crack cocaine use; continuous **Timing:** 30 days after MAP	ANOVA; post-hoc Scheffe test	**Alcohol:** F=5.24, p<.01 Scheffe test: significant difference such that non-users of cannabis consumed more alcohol than occasional and daily users **Crack cocaine:** F=4.67, p<.05 Scheffe test: significant difference such that non-users of cannabis consumed more alcohol than occasional and daily users
Bleich, 1999 (19)	Israel	Prospective cohort, 12 months	148 (29.82%)	**Method:** Urinalysis **Definition:** A positive urine test for cannabis. A drug abuser for any substance of abuse was defined as having a positive urine test for that substance during the 12th month of treatment. **Timing:** 12 months into treatment	**Method:** Urinalysis **Definition:** Benzodiazepines; A positive urine test for benzodiazepines non-abusers vs. abusers **Timing:** 12 months into treatment	Chi square	**Benzodiazepine:** χ^2 = 7.77, p=0.005, such that benzodiazepine abusers were more likely to currently abuse cannabis that non abusers of benzodiazepine
Epstein, 2003 (2)	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users **Timing:** Baseline and 12 months	**Method:** Urinalysis **Definition:** Continuous; Cocaine use from urinalysis **Timing:** Entire study duration	Multiple linear regression	**Cocaine abstinence:** Parameter estimate +/- SEM: 11.49 +/- 5.68, t=2.02, p=0.0438
Nirenberg, 1996 (6)	USA	Prospective cohort, 45 weeks	70 (1.43%)	**Method:** Urinalysis **Definition:** Dichotomous and Categorical; 4 groups: Group 1 - cannabis abstainers (0positive screens); Group 2 - intermittent cannabis users (0%-33.3% positive screens); Group 3 - moderate cannabis users (33.3% to 66.6% positive screens); Group 4 - consistent cannabis users	**Method:** Urinalysis **Definition:** Continuous; Cocaine and benzodiazepine use **Timing:** 45 weeks	ANOVA	**Cocaine:** F(3,66)=1.17, p=.33 such that there was no significant difference between the 4 cannabis groups and their use of cocaine. **Benzodiazepines:** F(3,66)=2.10, p=.11, such that there was no significant difference between the 4 cannabis groups and their use of benzodiazepine.

				(66.6%-100% positive screens) **Timing:** 45 weeks			
Peirce, 2009 (20)	USA	Secondary RCT analysis, 12 weeks	386 (44%)	**Method:** Urinalysis. breath sample **Definition:** Cannabis use defined as positive urine/breath sample given at study intake **Timing:** at intake Cannabis use disorder defined as the interview administered checklist of DSM-IV substance use disorder symptoms	**Method:** Urinalysis, breath sample **Definition:** Stimulant use measured as number of stimulant-negative urine results provided **Timing:** Throughout the 12 week study intervention	Mixed-model regression	**Cannabis use at intake:** B(SE) = -3.27 (1.33), p=0.014, such that participants showed more stimulant use (less negative urine tests). **Cannabis use disorder:** B(SE) = 3.89(1.49), p=0.010, such that participants showed less stimulant use (more negative urine tests).
Saxon, 1996 (8)	USA	Prospective cohort, 18 months	353 (38.20%)	**Method:** Self-reported seven-point scale ranging from 0 "never" to 6 "four or more times per day". **Definition:** Categorical; **Timing:** 6 months prior to baseline	**Method:** Urinalysis **Definition:** Continuous; percentage positive urine screens for any drug use then cocaine use, specifically **Timing:** 18 months in treatment	Cox regression model	**Any drug use:** Model 1: r=-0.05; B=0.06 Not included in second model. **Cocaine use:** Model 1: r=-0.08; B=-0.09 Model 2: B=-0.11, p<0.05, such that pre-treatment frequency of cannabis use predicted less cocaine use
Saxon, 1993 (21)	USA	Cross sectional	98 (0%)	**Method:** Urinalysis; **Definition:** Dichotomized cannabis use **Timing:** During the study period, specimens were periodically tested for THC. The number of tests for THC per subject varied from 1 to 17 (median=4). THC testing was generally spread over the duration of the study so that subjects were tested periodically over a span of months.	**Method:** Urinalysis **Definition:** Continuous; screened for opiates, cocaine, and benzodiazepines. **Timing:** Weekly tests during entire treatment	Mann-Whitney U-test	**THC+ vs. THC-:** Percentage of urinalysis positive for other drugs of abuse was not significantly different between THC+ (median=6.5, mean rank=50.74) and THC- patients (median-6.3, mean rank=48.0; z=-0.48). **Consistently THC+:** Participants consistently THC+ had a smaller percentage of urinalysis positive for other drugs of abuse (median=3.25, mean rank=21.7) than those who were intermittently THC+ (median=8.2, mean rank=31.5; z=-2.27, p<0.05).
Scavone, 2013 (9)	USA	Retrospective cohort, 9	91 (39.56%)	**Method:** Self-report, Urinalysis **Definition:** Dichotomized	**Method:** Urinalysis **Definition:** Any illicit	Correlation	**Benzodiazepine:** r(91)=.374, p<.01, such that there

		months		cannabis use **Timing:** Baseline (self-report) and In-treatment (urinalysis from initial 9 months of MMT enrolment)	benzodiazepine use Timing: In-treatment (Initial 9 months of MMT enrolment)		was a positive correlation between rates of cannabis use and illicit benzodiazepine use during the initial nine months in treatment
Strain, 1991 (22)	USA	Cross sectional	66 (45%)	**Method:** Alcohol Research Center Intake Interview **Definition:** Dichotomous; those with versus those without a history of a cannabis use diagnosis **Timing:** Interviews and assessments done in a series of two to three sessions	**Method:** Alcohol Research Center Intake Interview **Definition:** Cocaine, sedative, and alcohol abuse/dependence diagnoses **Timing:** Interviews and assessments done in a series of two to three sessions	Z-Test	**Cocaine diagnosis:** RR=0.69, ns **Sedative diagnosis:** RR=1.67, ns **Alcohol diagnosis:** RR=0.83, ns
Weizman, 2004 (17)	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months	**Method:** Urinalysis; **Definition:** Measured heroin, benzodiazepines, amphetamine, and cocaine abuse (they do not specify if they used SCID or something else to define abuse) **Timing:** 12 months	ANOVA	**Benzodiazepine:** F=18.48, p=0.000, such that CAs abused more benzodiazepines **Amphetamines:** F=9.29, p=0.003, such that CAs abused more amphetamines **Cocaine:** F=4.06, p=0.045, such that CAs abused more cocaine **All abuse and dependency diagnoses:** F=7.5, p=0.007, such that CAs had more other drug abuse and dependency diagnoses

Notes: "Dichotomized cannabis use" means users vs. non-users or at least one positive urine screen vs. none unless otherwise specified. MAP: Maudsley Addiction Profile; ANOVA: analysis of variance; RCT: randomized controlled trial; SEM" standard error of the mean; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; SE: standard error; THC: tetrahydrocannabinol; MMT: methadone maintenance treatment; RR: risk ratio; CA: cannabis abuser; SCID: Structured Clinical Interview for DSM disorders.

D. Criminal Activity, Jail Time

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Bell, 1997 (23)	Australia	Prospective cohort, 12 months	304 (43.09%)	**Method:** Self-report **Definition:** Continuous; average daily use of cannabis in past month **Timing:** Baseline	**Method**: Crime scale of the Opiate Treatment Index; property offenses confirmed using police records **Definition:** Continuous; amount of criminal activity in past month **Timing:** Baseline and 12 months	Multiple linear regression	**Baseline**: Not significant, but statistics not provided **12 months**: Cannabis was a significant predictor, p=0.0001
Epstein, 2003 (2)	USA	Secondary RCT analysis, 12 months	408 (40.44%)	**Method:** Diagnostic Interview and urinalysis **Definition:** Categorical; Non-users, occasional users and frequent users; Cannabis abuse/dependence diagnosis **Timing:** Baseline and 12 months	**Method:** ASI **Definition:** Illegal income, days of illegal activity, days in jail **Timing:** Baseline	Mixed-regression	**Cannabis use:** Cannabis use category not associated with any differences in criminal activity, statistics not provided **Cannabis abuse/dependence:** Days in jail: $F(1,258)=8.58$, $p<0.0037$ Other measures were not significant

Notes: RCT: randomized controlled trial; ASI: Addiction Severity Index.

E. HIV Risk Behaviours (injection drug use, needle sharing, unprotected sex)

Study	Country	Study Design	Sample size (% female)	Cannabis Measurement	Outcome	Statistical Analysis	Results
Weizman, 2004 (17)	Israel	Prospective cohort, 12 months	283 (NR)	**Method:** Urinalysis **Definition:** Dichotomous; Cannabis abuse vs. not; First assessed the percentage of tests positive for a given month (first month and 12th month); second considered that is a patient tested positive for cannabis for any consecutive 3 months during the first year of MMT, was considered a potential cannabis abuser. SCID used to confirm or disconfirm cannabis abuse status. **Timing:** Baseline and 12 months	**Method:** Clinic questionnaire **Definition:** Dichotomous; Whether the patient injected drugs, shared needles, performed safe sex, had sex for drugs, and had a partner who abused drugs during the past year. **Timing:** 12 months	ANOVA	Cannabis abuse was not related to any of the risk behaviours. Statistics not provided.

Notes: NR: not reported; MMT: methadone maintenance treatment; SCID: Structured Clinical Interview for DSM disorders; ANOVA: analysis of variance

Table 2. Risk of bias assessment using modified Newcastle Ottawa Scale (NOS)

	SELECTION BIAS	PERFORMANCE BIAS		DETECTION BIAS		INFORMATION BIAS		
Study	Is the source population representative?	Is the sample size sufficient and is there sufficient power?	Did the study adjust for confounders?	Did the study use appropriate statistical analysis?	Is there little missing data and was it handled appropriately?	Is the outcome measurement appropriate?	Is there an objective assessment of the outcome of interest?	Total Score
Bell 1997	2	2	3	3	2	2	2	**16**
Best 1999	2	3	0	1	1	2	0	**9**
Bleich 1999	1	1	0	1	1	1	3	**8**
Epstein 2003	0	1	2	3	2	3	3	**16**
Joe 1998	3	3	2	3	2	3	3	**19**
Levine 2015	2	2	3	2	1	3	3	**16**
Lions 2014	1	2	0	2	1	3	2	**11**
Nava 2007	0	1	0	2	1	2	3	**9**
Nirenberg 1996	2	1	0	1	1	3	3	**11**
Peirce 2009	1	3	3	3	3	3	3	**19**
Peles 2006	3	3	0	3	3	3	3	**18**
Peles 2008	3	3	1	3	3	3	3	**19**
Proctor 2016	3	3	2	1	1	3	3	**16**
Saxon 1993	1	1	0	1	1	2	3	**9**
Saxon 1996	2	2	3	2	2	2	3	**16**
Scavone 2013	1	1	0	1	2	1	2	**8**
Schiff 2007	3	3	2	3	2	3	3	**19**
Somers 2012	2	1	1	1	2	1	3	**11**
Strain 1991	2	0	0	1	2	2	1	**8**
Wasserman 1998	2	0	3	3	3	3	3	**17**
Weizman 2004	2	2	0	1	1	1	3	**10**
White 2014	2	3	0	1	2	2	3	**13**
Zielinski 2017	3	3	3	3	1	2	3	**19**

Notes: 0=definitely no (high risk of bias); 1=mostly no; 2=mostly yes; 3=definitely yes (low risk of bias). Maximum total score=21.

Table 3. GRADE Evidence Profile for Primary Outcomes

Quality assessment							Quality	Importance
# of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Illicit Opioid Use								
7	observational studies	serious [a]	very serious [b, c]	not serious	very serious [d]	none	⊕◯◯◯ VERY LOW	CRITICAL
Retention								
4	observational studies	not serious	serious [b]	not serious	very serious [d]	none	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

a. Moderate risk of bias across studies

b. Point estimates vary widely across studies, little overlap between individual confidence intervals

c. Heterogeneity not explained by subgroup analyses

d. Small sample sizes, wide pooled 95% confidence interval

References:

1. Best D, Gossop M, Greenwood J, Marsden J, Lehmann P, Strang J. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. Drug Alcohol Rev. 1999;18(January 1998):31–8.

2. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. Addiction. 2003;98(3):269–79.

3. Levine AR, Lundahl LH, Ledgerwood DM, Lisieski M, Rhodes GL, Greenwald MK. Gender-Specific Predictors of Retention and Opioid Abstinence During Methadone Maintenance Treatment. J Subst Abuse Treat [Internet]. 2015;54:37–43. Available from: http://dx.doi.org/10.1016/j.jsat.2015.01.009

4. Lions C, Carrieri MP, Michel L, Mora M, Marcellin F, Morel A, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: An attributable-risk approach (ANRS-Methaville trial). Drug Alcohol Depend [Internet]. 2014;135(1):1–8. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2013.10.018

5. Nava F, Manzato E, Lucchini A. Chronic cannabis use does not affect the normalization of hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts. Prog Neuro-Psychopharmacology Biol Psychiatry. 2007;31(5):1089–94.

6. Nirenberg TD, Cellucci T, Liepman MR, Swift RM, Sirota AlD. Cannabis versus other illicit drug use among methadone maintenance patients. Vol. 10, Psychology of addictive behaviours. 1996. p. 222–7.

7. Proctor SL, Copeland AL, Kopak AM, Hoffmann NG, Herschman PL, Polukhina N. Outcome predictors for patients receiving methadone maintenance treatment: findings from a retrospective multi-site study. J Subst Use [Internet]. 2016;21(6):601–13. Available from: http://dx.doi.org/10.3109/14659891.2015.1118564

8. Saxon AJ, Wells EA, Fleming C, Jackson TR, Calsyn DA. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. Addiction. 1996;91(8):1197–209.

9. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: Implications for opiate dependence and withdrawal. Neuroscience [Internet]. 2013;248:637–54. Available from: http://dx.doi.org/10.1016/j.neuroscience.2013.04.034

10. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. Am J Addict. 2013;(22):344–51.

11. Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend [Internet]. 1998;52(3):183–92. Available from:

http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9839144&retmode=ref&cmd=prlinks%5Cnfile:///Articles/1998/Wasserman/Drug Alcohol Depend 1998 Wasserman.pdf

12. Zielinski L, Bhatt M, Sanger N, Plater C, Worster A, Varenbut M, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8(1):1–10.

13. Joe GW, Dwayne Simpson D, Broome KM. Effects of readiness for drug abuse treatment on client retention and assessment of process. Addiction. 1998;93(8):1177–90.

14. Peles E, Schreiber S, Adelson M. Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. Drug Alcohol Depend. 2006;82(3):211–7.

15. Peles E, Linzy S, Kreek MJ, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: A comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11–25.

16. Schiff M, Levit S, Moreno RC. Retention and illicit drug use among methadone patients in Israel: A gender comparison. Addict Behav. 2007;32(10):2108–19.

17. Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. Australas Psychiatry. 2004;38:42–6.

18. White WL, Campbell MD, Spencer RD, Hoffman HA, Crissman B, DuPont RL. Patterns of Abstinence or Continued Drug Use Among Methadone Maintenance Patients and Their Relation to Treatment Retention. J Psychoactive Drugs [Internet]. 2014;46(2):114–22. Available from: http://dx.doi.org/10.1080/02791072.2014.901587

19. Bleich AVI, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M. Correlates of benzodiazepine abuse in methadone maintenance treatment . A 1 year prospective study in an Israeli clinic. 1999;94(January).

20. Peirce JM, Petry NM, Roll JM, Kolodner K, Krasnansky J, Stabile PQ, et al. Correlates of stimulant treatment outcome across treatment modalities. Am J Drug Alcohol Abuse. 2009;35(1):48–53.

21. Saxon AJ, Calsyn DA, Greenberg D, Blaes P, Haver VM, Stanton V. Urine Screening for Marijuana Among Methadone-Maintained Patients. Am J Addict. 1993;2(3):207–11.

22. Strain EC, Brooner RK, Bigelow GE. Clustering of multiple substance use and psychiatric diagnoses in opiate addicts. Drug Alcohol Depend. 1991;27(2):127–34.

23. Bell, J, Mattick, R, Hay, A, Chan, J, Hall W. Methadone Maintenance and Drug-Related Crime. J Subst Abuse. 1997;9:15–25.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplemental Statistical Methods:

Many of the odds ratios necessary for the meta-analyses were not reported in the publications we've referenced. Here we document how the statistics were calculated.

Formula for Standard Error:

$$SE(\log(OR)) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

a = cannabis positive AND opioid positive

b = cannabis negative AND opioid negative

c = cannabis positive AND opioid negative

d = cannabis negative AND opioid positive

Calculation for Epstein 2003a:

- Opiate study + Cocaine study #1
- State that rate of relapse is 80% in non-users of cannabis
- N cannabis users = 126 (frequent + non-frequent users in cocaine study 1 and opiate study)
- N non-cannabis users = 89
- 113 absent from illicit opioids

OR = 0.189, SE = 0.307

2x2 Table

	+ opioids	- opioids	Total
+ cannabis	31	95	126
- cannabis	71	18	89
Total	102	113	215

Calculation for Epstein 2003b:

- Cocaine study #2
- Rate of relapse is 90% in non-users
- N cannabis users = 94
- N non-cannabis users = 99
- 94 absent from illicit opioids in total

OR = 0.013376, SE = 0.4724

OR = a*d/b*c

100/7476 = 0.013376

	+ opioids	- opioids	Total
+ Cannabis	10	84	94
- Cannabis	89	10	99
Total	99	94	193

Calculation for Wasserman 1998:

- **Information and relative risk calculation collected from Epstein et al., 2003**
- 35 people tested positive for cannabis
- Sample size is 74
- Opioid positives detected in 30 patients
- N non-cannabis users = 39
- 44 absent from illicit opioids
- Relative risk is (21/35)/(9/36) = 2.6
  OR = 5.00, SE = 0.5133