Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies

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Summary

Background Opioid dependence is associated with substantial health and social burdens, and opioid agonist treatment (OAT) is highly effective in improving multiple outcomes for people who receive this treatment. Methadone and buprenorphine are common medications provided as OAT. We aimed to examine buprenorphine compared with methadone in the treatment of opioid dependence across a wide range of primary and secondary outcomes.

Methods We did a systematic review and meta-analysis in accordance with GATHER and PRISMA guidelines. We searched Embase, MEDLINE, CENTRAL, and PsycINFO from database inception to Aug 1, 2022; clinical trial registries and previous relevant Cochrane reviews were also reviewed. We included all RCTs and observational studies of adults (aged ≥18 years) with opioid dependence comparing treatment with buprenorphine or methadone. Primary outcomes were retention in treatment at 1, 3, 6, 12, and 24 months, treatment adherence (measured through doses taken as prescribed, dosing visits attended, and biological measures), or extra-medical opioid use (measured by urinalysis and self-report). Secondary outcomes were use of benzodiazepines, cannabis, cocaine, amphetamines, and alcohol; withdrawal; craving; criminal activity and engagement with the criminal justice system; overdose; mental and physical health; sleep; pain; global functioning; suicidality and self-harm; and adverse events. Single-arm cohort studies and RCTs that collected data on buprenorphine retention alone were also reviewed. Data on study, participant, and treatment characteristics were extracted. Study authors were contacted to obtain additional data when required. Comparative estimates were pooled with use of random-effects meta-analyses. The proportion of individuals retained in treatment across multiple timepoints was pooled for each drug. This study is registered with PROSPERO (CRD42020205109).

Findings We identified 32 eligible RCTs (N=5808 participants) and 69 observational studies (N=323 340) comparing buprenorphine and methadone, in addition to 51 RCTs (N=11 644) and 124 observational studies (N=700 035) that reported on treatment retention with buprenorphine. Overall, 61 studies were done in western Europe, 162 in North America, 14 in north Africa and the Middle East, 20 in Australasia, five in southeast Asia, seven in south Asia, two in eastern Europe, three in central Europe, one in east Asia, and one in central Asia. 1 040 827 participants were included in these primary studies; however, gender was only reported for 572 111 participants, of whom 377 991 (66·1%) were male and 194 120 (33·9%) were female. Mean age was 37·1 years (SD 6·0). At timepoints beyond 1 month, retention was better for methadone than for buprenorphine: for example, at 6 months, the pooled effect favoured methadone in RCTs (risk ratio 0·76 [95% CI 0·67–0·85]; I^2=74·2%; 16 studies, N=3151) and in observational studies (0·77 [0·68–0·86]; I^2=98·5%; 21 studies, N=155 111). Retention was generally higher in RCTs than observational studies. There was no evidence suggesting that adherence to treatment differed with buprenorphine compared with methadone. There was some evidence that extra-medical opioid use was lower in those receiving buprenorphine in RCTs that measured this outcome by urinalysis and reported proportion of positive urine samples (over various time frames; standardised mean difference –0·20 [–0·29 to –0·11]; I^2=0·0%; three studies, N=841), but no differences were found when using other measures. Some statistically significant differences were found between buprenorphine and methadone among secondary outcomes. There was evidence of reduced cocaine use, cravings, anxiety, and cardiac dysfunction, as well as increased treatment satisfaction among people receiving buprenorphine compared with methadone; and evidence of reduced hospitalisation and alcohol use in people receiving methadone. These differences in secondary outcomes were based on small numbers of studies (maximum five), and were often not consistent across study types or different measures of the same constructs (eg, cocaine use).

Interpretation Evidence from trials and observational studies suggest that treatment retention is better for methadone than for sublingual buprenorphine. Comparative evidence on other outcomes examined showed few statistically significant differences and was generally based on small numbers of studies. These findings highlight the imperative for interventions to improve retention, consideration of client-centred factors (such as client preference) when selecting between methadone and buprenorphine, and harmonisation of data collection and reporting to strengthen future syntheses.

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Introduction

Opioid dependence, as defined by the ICD, involves a cluster of symptoms that include impaired control over opioid use, prominence of use of a substance in a person's life, and physiological symptoms including tolerance and withdrawal. In North America, the DSM-5 term opioid use disorder is often used. We use the term opioid dependence as the ICD is the predominant classification system used globally. It was estimated that there were 40·5 million (95% uncertainty interval 34·3–47·9) people with opioid use disorder globally in 2017.[1]

Fatal opioid overdose is a major adverse outcome of extra-medical opioid use,[2] as is non-fatal overdose.[3] People who inject drugs are at risk of HIV and hepatitis C virus (HCV) infection,[4] in addition to skin and soft tissue infections and infective endocarditis.[5] Other outcomes associated with opioid dependence include poorer quality of life,[6] physical and mental health problems,[7] criminal

Research in context

Evidence before this study

Methadone and buprenorphine are the most commonly used medications for opioid agonist treatment and have both been recommended as first-line treatments for opioid dependence by different organisational guidelines. There is discussion around, and clinical imperative to understand, which medication is preferable and in what contexts. Retention in treatment has been identified as an especially important outcome. A 2014 Cochrane review collated evidence from randomised controlled trials (RCTs) published up to January, 2013, comparing buprenorphine maintenance treatment with either methadone maintenance treatment or placebo for the treatment of opioid dependence on a wide range of outcomes. The review found that retention in treatment was superior with methadone than with buprenorphine when dosing was flexible. For the remainder of outcomes, there was minimal evidence of differences between methadone and buprenorphine and often small numbers of eligible studies. The authors noted that more evidence on outcomes, including criminal activity, mortality, and adverse events would be advantageous but is unlikely to emerge from RCTs due to the short duration of these studies.

More recent reviews have compared buprenorphine and methadone maintenance treatments for specific outcomes or populations, including RCTs and non-RCT studies.

A systematic review capturing studies published until 2020 found that overall mortality risk was comparable between methadone and buprenorphine. However, the rate of mortality was increased in the first 4 weeks of treatment compared with the remainder for methadone (rate ratio 2·81 [95% CI 1·55–5·09]) but not buprenorphine (0·58 [0·18–1·85]). A systematic review of studies published between 2001 and 2019 reported median proportions of individuals retained in buprenorphine and methadone treatment followed up for a minimum of 6 months. The largest pooled estimate was reported for the 12-month follow-up and was a median retention rate of 60·7% (range 20·3–94·0; 24 studies) for methadone and 45·4% (range 11·7–61·6; six studies) for buprenorphine. 2019–20 reviews have also compared methadone and buprenorphine maintenance treatment for opioid dependence during pregnancy, looking at outcomes specific to this subpopulation.

Added value of this study

The current study is, to our knowledge, the first since the 2014 Cochrane review to report the availability and data on a comprehensive range of outcomes in opioid dependence, and the first to do so for both RCTs and non-RCT studies. In addition to providing an update of evidence examined in the 2014 review, the current investigation includes a large number of clinically important outcomes not examined in any previous review. The inclusion of these outcomes and a range of study designs was done in response to the acknowledged limitations of RCTs in providing data for some important outcomes, and has a large impact on data availability. We identified 101 eligible studies comparing buprenorphine and methadone, of which 32 (including N=5808 participants) were RCTs and 69 (N=323 340) were observational studies. The current review contributes comprehensive data on treatment retention, including direct comparisons (risk ratios) of the proportion of individuals retained in treatment for methadone and buprenorphine at specific timepoints from 1 month onwards for both RCTs and non-RCTs studies, which has not been done in any of the described reviews. Our review also included analysis of retention rates in buprenorphine regardless of the study comparator, which meant inclusion of an additional 124 observational studies (N=700 035) and 51 RCTs (N=11 644). In the context of growing use and study of extended-release formulations of buprenorphine, this is also the first review of retention for extended-release buprenorphine.

Implications of all the available evidence

Evidence suggests better retention in treatment with methadone than with buprenorphine, although retention for both medications, particularly over the long term, is suboptimal. There were few clear differences identified between the medications on most other outcomes, but these comparisons were hampered by limited numbers of studies for which consistent data were available. This review highlights the importance of interventions to improve retention on opioid agonist treatment and of harmonisation of data collection for future evidence syntheses.

activity,[8] and involvement with the criminal justice system.[8]

Opioid agonist treatment (OAT) is an effective treatment for opioid dependence that reduces harms across multiple health outcomes.[3] A range of opioids have been used in OAT, but the two most common are buprenorphine and methadone, both of which are included in the WHO Model List of Essential Medicines. There has been considerable discussion about whether and which of these two medications should be preferred, and in which contexts. Methadone is a full opioid agonist with no ceiling for respiratory depression, whereas buprenorphine is a partial agonist with a ceiling effect for respiratory depression at higher doses.[9] Previous reviews of the evidence comparing methadone and buprenorphine for the treatment of opioid dependence have been done. A 2014 Cochrane review[10] examined randomised controlled trials (RCTs) comparing methadone and buprenorphine in terms of treatment retention, use of other drugs, criminal activity, mortality, physical and psychological health, and adverse events. Treatment retention was better for methadone than for buprenorphine, but for the remainder of the outcomes there was minimal evidence of differences between methadone and buprenorphine, and often minimal eligible data.[10] That review did not include non-RCT studies. Differences in mortality risk have been reviewed, with evidence for lower risk of death during induction onto buprenorphine compared with methadone in observational studies, but no clear differences in other periods of treatment.[11] Reviews of buprenorphine versus methadone for women who are pregnant have found low-quality evidence that retention was superior with methadone than with buprenorphine[12] and low-quality evidence of improved birth outcomes for children of mothers receiving buprenorphine.[3] There are several formulations of buprenorphine available: a mono-buprenorphine formulation and buprenorphine–naloxone formulations, administered sublingually, and, more recently, extended-release depot formulations (which can last for 1 week or 1 month, depending on the product). No systematic reviews have yet included extended-release buprenorphine formulations.

We sought to review evidence of the effectiveness of buprenorphine compared with methadone for people who are opioid dependent, including evidence from RCTs and non-RCT studies, and examining retention in treatment; medication adherence; extra-medical use of opioids; use of benzodiazepines, cannabis, cocaine, amphetamines, and alcohol; withdrawal; craving; criminal activity and engagement with the criminal justice system; overdose; mental and physical health; sleep; pain; global functioning; suicidality and self-harm; and adverse events. We also sought to collate all available evidence on rates of retention in buprenorphine treatment, including retention on extended-release buprenorphine, examining both RCT and observational study designs.

Methods

Overview

We did a systematic review and meta-analysis in accordance with GATHER[13] and PRISMA[14] guidelines (appendix pp 3–5). This study was registered with PROSPERO (CRD42020205109).

See **Online** for appendix

Search strategy and selection criteria

Full details of the search strategy are presented in the appendix (pp 6–16). Searches were conducted by EZ, BC, GM, and OL with input from the wider team. We searched MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Clinical Trials via Ovid, from database inception to Aug 1, 2022, for studies comparing buprenorphine and methadone, as well as studies reporting on retention in treatment for buprenorphine. Searches for all databases combined terms related to buprenorphine, opioid dependence, and a range of eligible study types. To identify ongoing or unpublished studies, we also searched ClinicalTrials.gov, the ISRCTN Registry, the EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry, using the keywords "buprenorphine" and "opioid" and the condition "opioid-use disorder" on Sept 28, 2021. Additionally, we hand-searched the reference lists of included studies and topical reviews for potentially relevant articles. No restrictions were placed on language, publication status, or publication type.

Two reviewers (EZ, SN, LD, JK, BL, MF, BC, GM, OL, and DMB) independently examined titles and abstracts using the Covidence tool. Relevant articles were obtained in full and assessed for inclusion in the review independently by two authors (EZ, SN, LD, BC, GM, OL, and DMB). Inter-reviewer disagreement was resolved via team discussion (EZ, BC, GM, OL, DMB, LD, MF, SN, BL, and MH), where consensus was not reached by the two initial reviewers.

For more on **Covidence** see https://www.covidence.org/

Inclusion criteria for the study population were adults (aged ≥18 years) with opioid dependence, including participants dependent on illicit or pharmaceutical opioids. We included inpatient and outpatient settings (eg, prisons, residential rehabilitation, and primary care facilities). Exclusion criteria were people younger than 18 years, trials exclusively including pregnant women (which have recently been reviewed elsewhere),[12,15] and use of buprenorphine for detoxification.

Eligible studies were RCTs of buprenorphine versus methadone as therapies for opioid dependence; cohort studies that examined buprenorphine versus methadone for opioid dependence; cohort studies that examined retention in buprenorphine treatment; case-control studies of buprenorphine treatment in which cases were defined by the opioid agonist received and any of the treatment outcomes were reported separately for cases and controls; cross-sectional studies of people receiving buprenorphine compared with methadone treatment; and clinical trials of buprenorphine for

	Randomised controlled trials					Observational studies				
	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured
Primary outcomes										
Retention in treatment										
1 month	22 (4124)	16–37	RR 0·95 (0·90 to 1·00)	87·0%	Neither	19 (140 888)	38–56	RR 0·97 (0·90 to 1·05)	99·2%	Neither
3 months	23 (4285)	16–36,57–59	RR 0·88 (0·82 to 0·95)	73·9%	Methadone	23 (155 673)	38,39,42,54–57, 60–63	RR 0·80 (0·73 to 0·88)	98·7%	Methadone
6 months	16 (3151)	16,18–20,23,25–27, 29,32–34,58,64–66	RR 0·76 (0·67 to 0·85)	74·2%	Methadone	21 (155 111)	39,41–46,48–51, 54–57,60,67–70	RR 0·77 (0·68 to 0·86)	98·5%	Methadone
12 months	3 (1238)	20,26,29	RR 0·82 (0·68 to 0·98)	57·5%	Methadone	16 (142 549)	39,41–46,52, 55–57,60,71–73	RR 0·73 (0·63 to 0·85)	99·0%	Methadone
24 months	0	..	..	..	..	8 (98 308)	39–42,45,55,56,60	RR 0·65 (0·51 to 0·84)	98·6%	Methadone
Adherence to treatment										
Doses taken as prescribed	1 (147)	74	RR 0·98 (0·87 to 1·10)	NA	Neither	1 (83)	75	RR 0·96 (0·87 to 1·05)	NA	Neither
Dosing visits attended	2 (215)	35,36	RR 1·13 (0·58 to 2·22)	0·0%	Neither	0	..	..	..	..
Adherence confirmed via biological measures	0	..	..	..	..	1 (456)	76	RR 0·85 (0·55 to 1·31)	NA	Neither
Extra-medical opioid use										
Measured by urinalysis (categorical)	17 (3041)	18,20,22–25,28, 33–37,64,65,77–79	RR 1·09 (0·93 to 1·28)	77·5%	Neither	10 (1106)	38,43,49,51, 63,67,80–83	RR 0·75 (0·56 to 1·01)	66·6%	Neither
Measured by urinalysis (continuous)	3 (841)	21,28,66	SMD −0·20 (−0·29 to −0·11)	0·0%	Buprenorphine	0	..	..	..	..
Measured by self-report (categorical)	3 (962)	65,77,84	RR 1·78 (0·29 to 10·86)	99·2%	Neither	9 (5283)	39,75,85–91	RR 0·64 (0·35 to 1·17)	97·0%	Neither
Measured by self-report (continuous)	8 (1165)	21,24,28,64,78, 92–94	SMD −0·15 (−0·35 to 0·06)	58·7%	Neither	2 (277)	75,90	SMD −0·16 (−0·42 to 0·09)	0·0%	Neither
Secondary outcomes										
Use of other drugs										
Self-reported use of cocaine (continuous)	3 (666)	28,32,95	SMD −0·26 (−0·74 to 0·23)	48·0%	Neither	1 (204)	90	SMD 0·20 (−0·11 to 0·50)	NA	Neither
Self-reported use of cocaine (categorical)	1 (699)	84	RR 0·61 (0·49 to 0·77)	NA	Buprenorphine	3 (558)	85,90,96	RR 0·81 (0·26 to 2·47)	66·6%	Neither
Positive urine test for cocaine use (categorical)	10 (919)	18,22,32–36, 65,81,95	RR 0·98 (0·73 to 1·31)	63·7%	Neither	3 (320)	51,67,80	RR 0·56 (0·19 to 1·65)	50·3%	Neither
Self-reported use of cannabis (continuous)	2 (474)	28,94	SMD 0·06 (−0·36 to 0·49)	68·9%	Neither	1 (204)	90	SMD −0·04 (−0·34 to 0·27)	NA	Neither
Self-reported use of cannabis (categorical)	0	..	..	..	..	4 (642)	75,85,90,96	RR 0·93 (0·78 to 1·12)	12·9%	Neither
Positive urine test for cannabis use (categorical)	3 (182)	25,34,94	RR 0·81 (0·44 to 1·49)	5·35%	Neither	0	..	..	..	..
Self-reported use of amphetamine (continuous)	2 (474)	28,94	SMD −0·06 (−0·24 to 0·12)	0·0%	Neither	0	..	..	..	..
Self-reported use of amphetamine (categorical)	0	..	..	..	..	4 (590)	75,90,91,96	RR 0·64 (0·23 to 1·78)	86·4%	Neither

(Table 1 continues on next page)

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	Randomised controlled trials					Observational studies				
	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured
(Continued from previous page)										
Positive urine test for amphetamine use (categorical)	3 (164)	25,94	RR 1·50 (0·18 to 12·46)	72·0%	Neither	1 (53)	67	RR 2·32 (0·10 to 54·52)	NA	Neither
Self-reported use of benzodiazepines (continuous)	2 (474)	28,94	SMD −0·09 (−0·27 to 0·09)	0·0%	Neither	0	..	..	..	..
Self-reported use of benzodiazepines (categorical)	0	..	..	..	..	5 (1629)	75,85,89,90,96	RR 0·73 (0·50 to 1·07)	81·3%	Neither
Positive urine test for benzodiazepine use (categorical)	7 (537)	18,25,34–36,81,94	RR 1·09 (0·73 to 1·64)	28·1%	Neither	1 (53)	67	RR 1·11 (0·58 to 2·13)	NA	Neither
Self-reported use of alcohol (continuous)	1 (80)	94	SMD 0·41 (−0·04 to 0·85)	NA	Neither	1 (204)	90	SMD −0·02 (−0·36 to 0·31)	NA	Neither
Self-reported use of alcohol (categorical)	0	..	..	..	..	2 (528)	90,91	RR 1·50 (1·01 to 2·24)	41·8%	Methadone
Craving assessed by validated scales	4 (272)	30,78,79,94	SMD 0·77 (−1·02 to 2·55)	93·7%	Neither	1 (60)	97	SMD −2·22 (−2·87 to −1·57)	NA	Buprenorphine
Change in withdrawal symptoms assessed by validated scale	2 (185)	64,98	SMD −0·06 (−0·98 to 0·87)	88·5%	Neither	0	..	..	..	..
Sleep quality	0	..	..	..	..	1 (56)	99	SMD 0·04 (−0·49 to 0·56)	NA	Neither
Pain										
Severity or intensity assessed by validated scale	0	..	..	..	..	2 (264)	90,97	SMD −0·77 (−2·39 to 0·86)	95·9%	Neither
Interference assessed by validated scale	0	..	..	..	..	1 (204)	90	SMD −0·04 (−0·34 to 0·27)	NA	Neither
Measures of global functioning	3 (423)	66,78,81	SMD −0·05 (−0·49 to 0·39)	6·3%	Neither	4 (642)	63,67,100,101	SMD −0·21 (−1·03 to 0·61)	82·0%	Neither
Mean treatment satisfaction as measured by validated scale	0	..	..	..	..	1 (135)	61	SMD 0·51 (0·16 to 0·86)	NA	Buprenorphine
Engagement with criminal justice system										
Arrest as measured by self-report	1 (116)	102	RR 1·06 (0·83 to 1·34)	NA	Neither	0	..	..	..	..
Arrest as measured by data linkage (police records)	1 (303)	103	SMD −0·03 (−0·26 to 0·20)	NA	Neither	0	..	..	..	..
Incarceration as measured by self-report	1 (303)	103	RR 0·86 (0·66 to 1·11)	NA	Neither	0	..	..	..	..
Mental health										
Prevalence of a depressive disorder assessed by validated scales	0	..	..	..	..	3 (651)	38,90,96	RR 1·00 (0·82 to 1·23)	0·0%	Neither
Depressive symptoms assessed by validated scales	3 (281)	30,74,78	SMD −0·88 (−4·83 to 3·07)	96·5%	Neither	3 (520)	87,90,100	SMD −0·26 (−0·75 to 0·24)	27·4%	Neither
Prevalence of an anxiety disorder assessed by validated scales	0	..	..	..	..	3 (623)	86,90,104	RR 1·46 (0·34 to 6·31)	97·5%	Neither
Anxiety symptoms assessed by validated scales	1 (72)	78	SMD −0·44 (−0·91 to 0·02)	NA	Neither	2 (417)	90,100	SMD −0·32 (−0·52 to −0·12)	0·0%	Buprenorphine
Prevalence of non-fatal opioid overdose	0	..	..	..	..	3 (15 967)	73,105,106	RR 1·21 (0·23 to 6·36)	92·5%	Neither

(Table 1 continues on next page)

	Randomised controlled trials					Observational studies				
	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured	Studies (participants), n	References	Pooled effect*	I^2	Treatment favoured
(Continued from previous page)										
Physical health										
Change in physical health assessed by validated scales	0	..	..	..	..	3 (429)	63,82,101	SMD −0·16 (−1·71 to 1·40)	88·5%	Neither
Cardiac dysfunction (QT intervals measured by ECG)	1 (110)	107	RR 0·04 (0·00 to 0·62)	NA	Buprenorphine	5 (890)	108–112	RR 0·17 (0·05 to 0·54)	30·7%	Buprenorphine
Sexual dysfunction measured by self-report	1 (80)	81	RR 0·81 (0·45 to 1·46)	NA	Neither	7 (2416)	67,82,113–117	RR 0·67 (0·43 to 1·04)	88·7%	Neither
Hospitalisation	0	..	..	..	..	1 (21 311)	118	SMD 0·16 (0·09 to 0·24)	NA	Methadone
Adverse events										
All-cause adverse events	4 (651)	21,27,66,119	RR 1·10 (0·41 to 2·95)	84·6%	Neither	3 (401)	61,82,100	RR 0·85 (0·31 to 2·40)	86·8%	Neither
All-cause serious adverse events	5 (843)	16,23,79	RR 1·37 (0·47 to 4·00)	9·5%	Neither	1 (805)	108	RR 1·50 (0·78 to 2·92)	NA	Neither
All-cause treatment-related adverse events	1 (96)	23	RR 0·73 (0·32 to 1·65)	NA	Neither	0	..	..	..	..
Study withdrawals due to adverse events	1 (140)	34	RR 2·38 (0·45 to 12·55)	NA	Neither	0	..	..	..	..

Data on extended-release buprenorphine versus methadone were available from only one study,[54] to facilitate meaningful interpretation, those data were not synthesised here, and data in this table represent sublingual buprenorphine only. The Hartung–Knapp–Sidik–Jonkman method for random-effects meta-analyses was used where k≥3, as per Cochrane review recommendations.[120] Analyses involving only one or two studies were done with the DerSimonian–Laird method, with heterogeneity estimates based on the Mantel–Haenszel model. Only outcomes for which we found at least one study are included in this table. In instances where the number of studies is very small, an I^2 of 0% reflects these sparse data and should be interpreted with considerable caution. NA=not applicable. RR=risk ratio. SMD=standardised mean difference. *Pooled effects for buprenorphine compared with methadone are presented as RR for comparison of categorical data and SMD for comparison of continuous data.

Table 1: **Summary of evidence for the use of sublingual buprenorphine versus methadone for the treatment of opioid dependence**

opioid dependence in which treatment outcomes were reported.

We excluded case reports or case series of treatment episodes (because of the inability to draw comparisons); cohorts not receiving buprenorphine for opioid dependence; studies that did not report on eligible outcomes including those focused only on mortality (which is not an outcome in this review and is explored in a separate review);[11] works that did not present original data (eg, editorials or commentaries); conference abstracts of studies reported in full elsewhere; systematic reviews; studies in which it was unclear what medication the participants in the cohort received, or in which outcome data were not reported by medication type; and studies with fewer than 50 individuals.

Data extraction

Full details of the data extracted are listed in the appendix (pp 84–94). For each eligible study, we (BC, GM, DMB, and OL) extracted data on study characteristics, characteristics of people in the study, and treatment received. Summary data for eligible outcomes was extracted. Country regions were coded according to those used by the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[1] All extracted data were checked again by a second person (LD, BC, SN, JK, BL). Authors of included studies were contacted for additional information if primary outcome data appeared to have been collected but had not been reported on as required for studies published within the past 10 years with at least 20 individuals receiving buprenorphine for opioid dependence.

Outcomes

Outcomes are defined in the appendix (pp 82–83) and listed in table 1. Primary outcomes were retention in opioid agonist treatment at 1, 3, 6, and 12 months (with data also extracted for proportion retained at any timepoints other than those prespecified, with the aim of synthesising where data were sufficient); adherence to opioid agonist treatment (proportion of doses taken as prescribed, proportion of dosing visits attended, and biological measures); and extra-medical opioid use (including use of heroin, pharmaceutical opioids or fentanyl, and illicit or synthetic fentanyl) as measured by self-report and urinalysis. Secondary outcomes encompassed use of other drugs (cocaine, cannabis, amphetamines, benzodiazepines, and alcohol); opioid craving; precipitated withdrawal (change in withdrawal symptoms); criminal activity; engagement with the criminal justice system (arrest or incarceration); mental health (prevalence of diagnosis and symptoms of depression and anxiety, and prevalence of suicidality and self-harm); non-fatal overdose (of opioids or other drugs); physical health (including change on validated scales, HIV and HCV infection, cardiac and sexual dysfunction, and hospitalisation); sleep quality; pain; global functioning, including treatment satisfaction; and adverse events.

Assessment of risk of bias and grading of evidence

Two reviewers assessed each study independently (GM and OL) and conflicts between reviewers were resolved by a third party (BC, LD, MF, and MH), if necessary. For RCTs, we used the RoB 2 tool[121] to assess risk of bias across five domains. RoB 2 identifies sources of bias arising from the randomisation procedure, deviations from assigned interventions, missing data, outcome measurement, and the selection of reported results. We used ROBINS-I,[122] a tool for assessing risk of bias in studies of non-randomised interventions, to estimate risk of bias for each observational study across seven domains. Domains include signalling questions regarding risk of bias due to confounding, participant selection, intervention classification, deviation from intended intervention, outcome measurement, missing data, and selection of reported results.[122] For single-arm cohort studies of buprenorphine treatment, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist[123] was used to determine risk of bias, with "include" or "exclude" as the overall appraisal. This checklist covers clear criteria for inclusion in the study, valid measurement, identification of condition for participants included, consecutive and complete inclusion of participants, clear reporting of participant demographics, clinical information (eg, comorbidities), the follow-up outcome (ie, retention in treatment), clear reporting of the participating sites and clinics, demographic information, and use of appropriate statistical analysis. For cross-sectional studies, an adapted version of the Newcastle-Ottawa Quality Assessment Scale (appendix p 226)[124] was used to estimate risk of bias on the basis of selection (sample size, representativeness of sample, proportion of non-respondents, and method of ascertaining exposure), controlling of confounders across treatment groups, outcome assessment method, and appropriateness of statistical tests used.

Publication bias was assessed with use of Egger's test and Harbord's test (appendix pp 227–228).

Data analysis

All outcome data were extracted separately for the buprenorphine maintenance therapy and methadone maintenance therapy groups of each study. For pooled estimates of retention in buprenorphine treatment at each timepoint (1, 3, 6, and 12 months, and any other commonly reported timepoints), all study designs were included, including RCTs and observational studies comparing buprenorphine and methadone treatment and single-arm cohort studies of buprenorphine treatment. For all other outcomes, only RCTs and observational studies that compared methadone and buprenorphine were included. For binary outcomes, proportions were calculated as the number of participants in each group who did or did not experience a given outcome. For continuous outcomes, group means and SDs were extracted. When not provided directly, SD was calculated from available data such as standard error or CI if possible.

Data for each outcome were pooled through meta-analyses and 95% CIs were calculated, with data from RCTs and observational studies considered separately. Continuous measures were compared between buprenorphine and methadone and pooled across studies using Cohen's method (standardised mean differences) with a random-effects model, using the Hartung-Knapp-Sidik-Jonkman[125] method for analyses with data from at least three studies.[120] The DerSimonian-Laird method[126] was used for syntheses of fewer than three studies. Binary outcomes were compared between buprenorphine and methadone and pooled across studies with risk ratios (RRs), calculated with use of the random-effects models specified above. For both types of data, meta-analysis was done in Stata 16.1 using the meta and metan commands for meta-analyses. For retention, the proportion retained in treatment with buprenorphine at each specified timepoint was pooled across studies, stratified by route of administration and study type, with use of the metaprop command in Stata 16.1. A continuity correction was incorporated so that studies reporting 0% or 100% retention contributed to the proportion retained at various timepoints. We did not apply inverse probability weighting for pooled estimates of proportions. For all analyses, heterogeneity was quantified with the I^2 statistic.

To quantify any variance in key findings according to sample and study, planned meta-regressions were run for primary outcomes with sufficient data (k>10, where k is the number of studies; note, number of people is denoted by N throughout this Article). Meta-regressions were run with use of the metareg command in Stata 16.1 with a random-effects model for aggregate-level data. We tested assumptions of linearity for quantitative predictors where appropriate (ie, where we had not log-transformed the predictors); results suggested that these assumptions were met. The specific outcome and explanatory variables included in this analysis are shown in tables 2 and 3.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The PRISMA flowchart showing the identification and selection of studies for inclusion is shown in the appendix (p 30). The combined search, conducted on Aug 18, 2020, and updated on Aug 1, 2022, identified 11 333 records, from which 3004 duplicates were removed. 8329 unique records were screened for relevance by title and abstract. The 847 studies excluded at the full-text screening stage are listed in the appendix (pp 31–78). We identified 101 studies comparing methadone and buprenorphine: 32 RCTs (N=5808) and 69 observational studies (N=323 340; appendix pp 95–171). Additionally, 124 cohort

	Retention at 1 month		Retention at 3 months		Retention at 6 months		Retention at 12 months		Extra-medical opioid use via urinalysis	
	exp(b) (95% CI)	p value	exp(b) (95% CI)	p value	exp(b) (95% CI)	p value	exp(b) (95% CI)	p value	exp(b) (95% CI)	p value
Study type*	1·00 (0·88–1·12)	0·95	0·89 (0·76–1·05)	0·15	0·98 (0·80–1·21)	0·86	0·86 (0·51–1·45)	0·57	0·83 (0·63–1·09)	0·17
Study year	1·00 (0·99–1·01)	0·45	1·00 (0·99–1·01)	0·37	1·01 (1·00–1·02)	0·055	1·02 (0·99–1·04)	0·17	1·00 (0·98–1·02)	0·90
Proportion of women	0·99 (0·99–1·00)	0·18	0·99 (0·99–1·00)	0·14	0·99 (0·98–1·00)	0·42	0·98 (0·96–1·00)	0·070	1·00 (0·99–1·01)	0·38
Mean age	1·01 (1·00–1·03)	0·040	1·02 (1·00–1·04)	0·094	0·99 (0·96–1·01)	0·30	1·02 (0·99–1·05)	0·16	1·00 (0·94–1·08)	0·87
Mean buprenorphine dose	1·00 (0·99–1·02)	0·62	1·01 (0·98–1·03)	0·64	0·99 (0·95–1·03)	1·03	1·03 (0·93–1·14)	0·48	1·00 (0·97–1·03)	0·98
Study region										
Western Europe	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Australasia	0·98 (0·68–1·42)	0·91	0·79 (0·65–0·94)	0·011	0·79 (0·63–0·98)	0·035	0·70 (0·50–0·97)	0·031	1·37 (0·91–2·06)	0·13
Central Asia	..	..	1·19 (0·61–2·34)	0·61	..	..	..	..	..	..
Eastern Europe	1·12 (0·83–1·49)	0·46	1·20 (0·75–1·92)	0·43	1·27 (0·83–1·93)	0·26	1·31 (0·61–2·84)	0·48	..	..
High-income North America	1·03 (0·90–1·17)	0·68	1·01 (0·83–1·22)	0·94	0·87 (0·68–1·10)	0·23	0·69 (0·46–1·05)	0·082	1·46 (1·11–1·92)	0·009
North Africa and Middle East	1·00 (0·71–1·39)	0·99	0·89 (0·58–1·38)	0·60	1·03 (0·58–1·83)	0·93	0·94 (0·26–3·42)	0·93	..	..
Southeast Asia	..	..	..	..	..	..	..	..	1·30 (0·82–2·07)	0·26
Recruitment setting										
Database	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Community	1·09 (0·79–1·50)	0·60	1·36 (0·92–2·00)	0·12	0·99 (0·48–2·06)	0·99	..	..	1·00 (0·49–2·02)	0·99
Drug treatment clinic(s)	0·98 (0·86–1·10)	0·70	1·15 (0·99–1·35)	0·069	1·14 (0·94–1·39)	0·16	1·35 (0·92–1·97)	0·12	0·89 (0·52–1·53)	0·65
Primary care centre(s)	1·06 (0·69–0·62)	0·80	1·38 (0·79–2·38)	0·25	1·49 (0·82–2·73)	0·19	2·23 (0·67–7·38)	0·18	1·51 (0·41–5·52)	0·51
Country coverage										
National	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..	..	..
Subnational	0·87 (0·75–1·01)	0·069	0·67 (0·56–0·81)	<0·001	0·68 (0·54–0·86)	<0·001	0·67 (0·47–0·94)	0·021	1·22 (0·98–1·53)	0·070
City	0·87 (0·73–1·03)	0·11	0·76 (0·58–1·00)	0·048	0·68 (0·47–0·98)	0·039	0·96 (0·51–1·83)	0·91	1·73 (0·98–3·04)	0·057
Single centre	0·92 (0·78–1·08)	0·29	0·90 (0·72–1·12)	0·32	0·84 (0·61–1·18)	0·31	0·99 (0·55–1·77)	0·96	1 (ref)	
Risk of bias	1·02 (0·83–1·26)	0·85	1·24 (0·96–1·60)	0·10	1·42 (1·02–1·98)	0·038	1·44 (0·90–2·31)	0·13	1·25 (1·00–1·58)	0·053
Cross-sectional studies†	..	..	..	..	..	..	..	..	..	..
RCTs	..	..	1·22 (0·73–2·04)	0·42	..	..	..	..	1·27 (1·00–1·61)	0·047
Observational studies	1·02 (0·79–1·31)	0·87	1·27 (0·93–1·72)	0·13	1·44 (1·00–2·07)	0·051	1·47 (0·90–2·40)	0·12	0·81 (0·18–3·71)	0·74
Proportion positive for HIV	1·00 (0·99–1·01)	0·57	1·01 (1·00–1·03)	0·071	1·01 (1·00–1·03)	0·088	1·03 (0·95–1·11)	0·25	1·00 (0·99–1·02)	0·70
Proportion positive for HCV	1·00 (0·99–1·02)	0·52	1·00 (0·99–1·02)	0·41	1·00 (0·99–1·02)	0·52	..	..	1·00 (0·97–1·04)	0·75

exp(b) is the exponentiated regression coefficient which is interpreted as an odds ratio. A one unit increase in the predictor variable multiplies the odds of the outcome by the amount exp(b), such that exp(b)<1 indicates decreased odds of the outcome with an increase in the predictor variable; exp(b)>1 indicates increased odds of the outcome given a one unit increase in the predictor variable; exp(b)=1 indicates no change in the odds of the outcome given a one unit increase in the predictor variable. HCV=hepatitis C virus. RCTs=randomised controlled trials. *RCTs *vs* observational studies. †All cross-sectional studies (assessed with the Newcastle-Ottawa scale) were at a low risk of bias; as such, meta-regressions that included Newcastle-Ottawa scores as a covariate could not be calculated.

Table 2: **Meta-regressions of variables potentially associated with variations in retention and extra-medical opioid use in buprenorphine compared with methadone treatment**

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	Retention at 1 month		Retention at 3 months		Retention at 6 months		Retention at 12 months	
	b (95% CI)	p value	b (95% CI)	p value	b (95% CI)	p value	b (95% CI)	p value
Study type*	0·03 (<0·01 to 0·05)	0·025	0·02 (<0·01 to 0·05)	0·10	−0·01 (−0·02 to 0·04)	0·55	<0·01 (−0·90 to 0·94)	0·97
Study year	−0·01 (−0·01 to <0·01)	0·004	<0·01 (−0·01 to <0·01)	0·98	<0·01 (−0·01 to <0·01)	0·42	<0·01 (−0·01 to 0·01)	0·93
Proportion of women†	0·19 (−0·09 to 0·48)	0·19	0·12 (−0·04 to 0·30)	0·16	0·11 (−0·10 to 0·32)	0·30	0·05 (−0·18 to 0·29)	0·65
Mean age	<0·01 (−0·01 to <0·01)	0·36	<0·01 (>−0·01 to <0·01)	0·58	<0·01 (−0·01 0·01)	0·48	−0·01 (−0·03 to <0·01)	0·050
Mean buprenorphine dose‡	0·07 (−0·03 to 0·16)	0·15	−0·06 (−0·19 to 0·07)	0·34	0·04 (−0·11 to 0·18)	0·63	0·16 (−0·06 to 0·37)	0·14
Region								
Western Europe	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Australasia	−0·09 (−4·0 to 0·22)	0·57	−0·22 (−0·32 to −0·12)	<0·001	0·22 (0·34 to −0·10)	<0·001	−0·32 (−0·46 to −0·18)	<0·001
Central Asia	..	..	0·19 (−0·06 to 0·45)	0·13	..	..	..	..
Central Europe	0·9 (−0·32 to 0·15)	0·45	−0·07 (−0·42 to 0·28)	0·13	−0·22 (−0·61 to 0·18)	0·28	..	..
Eastern Europe	0·16 (−0·03 to 0·34)	0·97	0·18 (>−0·01 to 0·36)	0·052	0·21 (0·04 to 0·38)	0·017	0·21 (−0·01 to 0·42)	0·063
North America	−0·04 (−0·11 to 0·03)	0·28	−0·06 (−0·13 to 0·2)	0·13	−0·09 (−0·19 to −0·01)	0·035	−0·18 (−0·29 to −0·07)	0·002
North Africa and Middle East	0·06 (−0·13 to 0·26)	0·52	−0·09 (−0·29 to 0·10)	0·35	−0·12 (−0·37 to 0·13)	0·35	−0·27 (−0·74 to 0·20)	0·26
Southern sub-Saharan Africa	..	..	−0·03 (−0·39 to 0·32)	0·85	..	..	..	..
South Asia	−0·03 (−0·35 to 0·30)	0·88	−0·16 (−0·32 to 0·01)	0·067	−0·13 (−0·30 to 0·05)	0·15	−0·21 (−0·51 to 0·09)	0·18
Southeast Asia	0·14 (−0·17 to 0·45)	0·36	0·14 (−0·20 to 0·48)	0·42	..	..	..	..
Recruitment setting								
Database	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Community	0·01 (−0·16 to 0·19)	0·86	0·11 (0·04 to 0·26)	0·14	0·13 (−0·10 to 0·37)	0·26	−0·29 (−0·76 to 0·18)	0·22
Drug treatment clinic(s)	0·02 (−0·06 to 0·09)	0·62	0·10 (0·03 to 0·16)	0·006	0·12 (0·04 to 0·20)	0·002	0·21 (0·10 to 0·32)	<0·001
Primary care centre(s)	−0·04 (−0·22 to 0·14)	0·69	−0·20 (−0·37 to −0·03)	0·019	−0·25 (−0·49 to <0·01)	0·047	0·09 (−0·35 to 0·54)	0·68
Country coverage								
National	0 (ref)	..	0 (ref)	..	0 (ref)	..	0 (ref)	..
Subnational	−0·04 (−0·14 to 0·06)	0·47	−0·07 (−0·17 to 0·04)	0·22	−0·01 (−0·13 to 0·11)	0·87	−0·06 (−0·20 to 0·07)	0·35
City	−0·06 (−0·16 to 0·05)	0·31	−0·06 (−0·19 to 0·06)	0·32	−0·05 (−0·20 to 0·11)	0·56	−0·12 (−0·34 to 0·10)	0·29
Single centre	−0·03 (−0·13 to 0·06)	0·48	−0·01 (−0·12 to 0·10)	0·83	<0·01 (−0·13 to 0·12)	0·95	0·04 (−0·10 to 0·18)	0·58
Risk of bias	−0·01 (−0·10 to 0·08)	0·82	0·05 (−0·07 to 0·16)	0·42	0·11 (−0·06 to 0·29)	0·19	0·22 (0·02 to 0·43)	0·034
Cross-sectional studies§	..	..	..	..	..	..	..	..
RCTs	..	..	0·20 (−0·07 to 0·48)	0·14	..	..	..	..
Observational studies	0·03 (−0·08 to 0·14)	0·61	0·08 (−0·05 to 0·21)	0·24	0·15 (−0·04 to 0·33)	0·12	0·23 (0·02 to 0·44)	0·032
Proportion positive for HIV	<0·01 (>−0·01 to <0·01)	0·38	<0·01 (>−0·01 to <0·01)	0·53	<0·01 (>−0·01 to <0·01)	0·20	<0·01 (>−0·01 to <0·01)	0·46
Proportion positive for HCV	<0·01 (>−0·01 to 0·01)	0·041	<0·01 (>−0·01 to <0·01)	0·12	<0·01 (>−0·01 to <0·01)	0·17	<0·01 (>−0·01 to <0·01)	0·045
Incarceration history	<0·01 (>−0·01 to 0·02)	0·034	0·01 (>−0·01 to 0·02)	0·056	<0·01 (−0·01 to 0·03)	0·27	..	..

b is the unstandardised regression coefficient which is interpreted in the change in the outcome variable given a one unit increase in the predictor variable. b<0 indicates a decrease of b units in the outcome variable with a one unit increase in the predictor; b>0 indicates increase of b units in the outcome variable with a one unit increase in the predictor; b=0 indicates no change in the outcome with a one unit increase in the predictor. >−0·01 denotes a value between −0·01 and 0·00. <0·01 denotes a value between 0·00 and 0·01. HCV=hepatitis C virus. RCTs=randomised controlled trials. *RCTs *vs* observational studies. †Compares studies with >50% women to those with ≤50% women. ‡Compares studies with mean dose >16 mg/day to the remainder. §All cross-sectional studies (assessed with the Newcastle-Ottawa scale) were at a low risk of bias; as such, meta-regressions that included Newcastle-Ottawa scores as a covariate could not be calculated.

Table 3: **Meta-regressions of variables potentially associated with variation in the proportion of patients retained in buprenorphine treatment**

and cross-sectional studies of buprenorphine (N=700 035) and 51 RCTs of buprenorphine (N=11 644; appendix pp 95–171) reported on the proportions of people retained in treatment at specified timepoints (which were included in pooled estimates of retention rates). Among studies reporting gender (note: we use "gender" throughout to encompass gender or sex as reported in primary studies, which often did not distinguish between them; as most data were collected via self-report, we typically assumed gender was being reported), there were 377 991 (66·1%) male and 194 120 (33·9%) female participants. The overall mean age was 37·1 years (SD 6·01). Characteristics of included studies are presented in the appendix (pp 95–171). 13 RCTs were done in western Europe, 49 in North America, ten in north Africa and the Middle East, seven in Australasia, one in central Asia, and three in southeast Asia. Of the observational studies, 48 were done in western Europe, 113 in North America, four in north Africa and the Middle East, 13 in Australasia, seven in south Asia, two in southeast Asia, two in eastern Europe, three in central Europe, and one in east Asia.

In addition, we identified 15 studies (two RCTs and 13 observational studies) that examined the initiation of buprenorphine during hospitalisation. Characteristics

of these studies are presented in the appendix (pp 172–174).

Seven studies (three RCTs and four observational studies) were identified that examined the initiation of buprenorphine during incarceration or post-release from incarceration. Characteristics of these studies are presented in the appendix (pp 175–177).

The amount of evidence (from both RCTs and observational studies) located for each of the primary and secondary outcomes is shown in the appendix (pp 79–81). Many fewer studies reported on extra-medical use of opioids (most commonly heroin) than on retention in treatment, and adherence to treatment was rarely studied. Among the secondary outcomes, cocaine and benzodiazepine use were the most studied drug use outcomes. Few studies examined non-fatal overdose (and no RCTs examined this outcome), criminal activity, criminal justice system contact, pain, or sleep. Several studies assessed depression and anxiety, but no studies examined risk of non-fatal suicidality or self-harm. One study examined buprenorphine versus methadone with regard to satisfaction with treatment. Quality of life, when assessed (k=9 studies), was assessed mostly among observational studies.

Table 1 summarises the findings across primary and secondary outcomes (forest plots are presented in the appendix pp 179–208). All comparisons reported in table 1 are between methadone and sublingual buprenorphine. Only one study[54] included direct comparison between methadone and extended-release buprenorphine and for consistency this data was included only in pooled retention analyses presented in figure 1. For RCTs and non-RCT studies, retention in treatment did not differ significantly between methadone and sublingual buprenorphine at 1 month,[16–56] but methadone typically had better retention at subsequent timepoints, up to 24 months post-treatment entry in non-RCT studies (pooled RR 0·65 [95% CI 0·51–0·84]).[16–36,38–46,48–52,54–73] The proportions of individuals retained in treatment across timepoints and by study design are plotted in figure 1 and reported in the appendix (p 212). Beyond the first month of treatment, retention was consistently better for methadone than for sublingual buprenorphine. For example, at 6 months, retention was better in methadone than buprenorphine in RCTs (pooled RR 0·76 [95% CI 0·67–0·85], k=16, N=3151) and non-RCT studies (0·77 [0·68–0·86], k=21, N=155 111; table 1). In observational studies, at 6-month follow-up, the pooled estimate of retention was 52% (95% CI 50–55) for sublingual buprenorphine compared with 56% (49–63) for methadone. At 12 months, the pooled estimate of retention in observational studies of sublingual buprenorphine was 43% (39–47) compared with 47% (38–56) for methadone. The available retention data for extended-release buprenorphine from observational studies (figure 1; appendix p 212) indicated a pooled estimate of retention of 66% (36–96) at 6 months and 74% (69–79) at 12 months; however, data were obtained from a small number of studies (k=5 at 6 months,[54,127–130] k=2 at 12 months[127,128]), with high levels of uncertainty around these estimates. When pooled analyses were limited to observational studies (k=2) that reported 12-month retention,[127,128] treatment retention for extended-release buprenorphine was 98% at 1 month, 87% at 3 months, 79% at 6 months, and 74% at 12 months.

There was no evidence that adherence to treatment differed between buprenorphine and methadone (table 1).[35,36,74] Evidence from three RCTs (N=841)[21,28,66] showed that extra-medical opioid use as measured by urinalysis was lower for people being treated with buprenorphine, but no other measure of extra-medical opioid use showed a difference between the treatments in either RCTs or observational studies.[18,20–25,28,33–39,43,49,51,63–65,67,75–94]

In general, there were few studies and insufficient evidence of differences in secondary outcomes between buprenorphine and methadone (table 1). One RCT suggested lower prevalence of cocaine use in people receiving buprenorphine compared with those receiving methadone (N=699).[84] Two observational studies (N=528) suggested higher prevalence of alcohol use in people

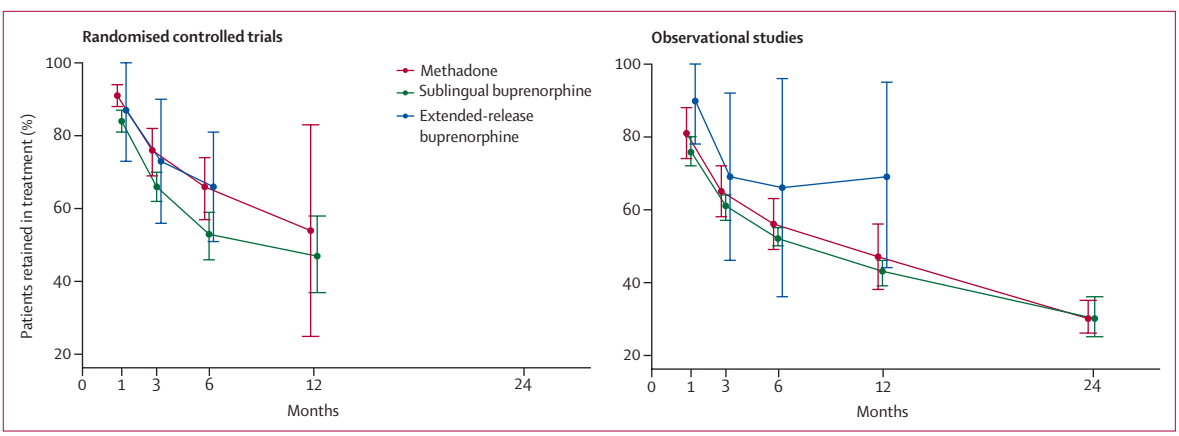

Figure 1: **Retention in treatment with buprenorphine versus methadone at 1, 3, 6, 12, and 24 months**
Buprenorphine data are stratified by route of administration. Error bars are 95% CIs.

Figure 2: **Risk of bias assessments for primary outcomes of retention in treatment and extra-medical opioid use**
Graphs show the percentages of RCTs (A, C) and observational studies (B, D) rated as having each risk level of bias in the treatment retention outcome (A, B) and the extra-medical opioid use outcome (C, D). RCTs were assessed with the Rob 2 tool and observational studies with the ROBINS-I tool. RCTs=randomised controlled trials. k=number of studies.

receiving buprenorphine compared with those receiving methadone.[90,91] Prevalence of other types of substance use did not differ between treatments, whether examined in RCTs or observational studies. A single observational study (N=60) reported lower intensity of craving in buprenorphine compared with methadone,[97] and another (N=135) reported higher treatment satisfaction in people receiving buprenorphine.[61] Two observational studies (N=417) indicated lower severity of anxiety symptoms in people receiving buprenorphine compared with those receiving methadone.[90,100] Risk of cardiac dysfunction was lower for buprenorphine compared with methadone in an RCT (N=110)[107] and in observational studies (N=890).[108–112] One large observational study (N=21 311) suggested a lower risk of hospitalisation among those receiving methadone than among those receiving buprenorphine.[118]

We conducted a series of meta-regressions to explore potential reasons for variability across studies on the primary outcomes, and on the percentage of people retained in treatment with buprenorphine (tables 2, 3). Few variables were consistently associated with variations in retention in buprenorphine compared with methadone treatment (table 2). Retention in buprenorphine compared with methadone treatment was poorer at some timepoints in studies done in Australasia, and in studies with subnational or city-wide geographical coverage. For retention of individuals in buprenorphine treatment, the proportions retained were higher at some timepoints in eastern European studies and in more circumscribed recruitment settings (eg, clinics) compared with databases which tend to cover broader populations (table 3).

Risk of bias assessments are summarised in figure 2 for primary outcomes and detailed in the appendix (pp 213–228), along with publication bias assessments.

RoB 2 assessment of RCTs with data on retention in buprenorphine compared with methadone (k=27), found that nine (33%) had an overall low risk of bias. Bias arising from the randomisation process led to 17 (63%) RCTs being rated as having some concerns regarding bias, and one (4%) RCT was found to be at high risk of bias, with this bias resulting from missing outcome data (figure 2A). The ROBINS-I assessment of observational studies with retention data for buprenorphine and methadone treatment (k=31) found that bias occurred as a result of confounding in all studies, with 21 (68%) studies rated as having a moderate risk of bias and ten (32%) having a serious risk of bias (figure 2B). Risk of bias among studies contributing data only on proportion retained in buprenorphine treatment at various timepoints is described in the appendix (pp 220–225).

Of 21 RCTs comparing buprenorphine and methadone on extra-medical opioid use, ten (48%) were at a low risk of bias, five (24%) were at a high risk of bias overall as a result of missing outcome data, and six (29%) were rated as having some concern regarding bias, attributable to the randomisation process (figure 2C). Among non-randomised observational studies that examined extra-medical opioid use (k=13), three (23%) were found to be at serious risk of bias due to confounding, and the remaining ten (77%) had a moderate risk of bias, resulting from bias due to confounding, bias due to missing data, and bias in the measurement of outcomes (figure 2D). In all six cross-sectional studies that had data on extra-medical opioid use, bias due to representativeness of the sample, comparability of the groups, and assessment of the outcome resulted in a moderate risk of bias.

Of the three RCTs that reported data on adherence to treatment, two were assessed as having some concerns of bias due to bias arising from the randomisation process. The third study was rated as having a low risk of bias. Of the two observational studies with adherence data, both were rated as moderate risk of bias due to confounding.

We conducted a sensitivity analysis of the proportion of people retained in treatment, comparing all studies with studies at a low risk of bias, by timepoint, study type, and medication type; no significant differences were found (appendix pp 229).

Discussion

Long-term retention on OAT in trials and observational studies is suboptimal, which limits the effect of OAT with regard to reducing drug-related deaths.[131] There was consistent evidence that retention was slightly better on methadone than buprenorphine across RCTs and observational studies at timepoints beyond 1 month, although few RCTs examined long-term retention.

The amount and reporting of other outcome data for comparisons between buprenorphine and methadone were inconsistent. There was inconsistent evidence that extra-medical opioid use and use of cocaine might be lower among people prescribed buprenorphine. Limited evidence (typically from single studies) suggested that some other outcomes might differ between buprenorphine and methadone, more commonly favouring buprenorphine, but overall there remains considerable scope for expanding evidence for many outcomes.

Previous reviews have shown good evidence that, compared with methadone, sublingual buprenorphine has a lower risk of death due to overdose during the first month of treatment, but not after that time,[11] which might be linked to differences in effects on respiratory depression.[9] Despite that risk, given the poorer retention in treatment and the absence of clear evidence of strong benefits in other areas, it is not clear that buprenorphine should yet be recommended as a first-line treatment.

Only one observational study[54] has directly compared methadone with extended-release buprenorphine, and few studies have been published on retention in treatment with this new formulation of buprenorphine. Despite small study numbers and an absence of well powered RCTs, there are indications that retention might be higher with extended-release than sublingual

buprenorphine, suggesting that the changed formulation might partly address issues related to retention; however, large-scale RCTs and real-world data showing outcomes from large-scale implementation are needed.

Many outcomes showed no statistically significant difference between medications. Given that few differences were found between methadone and buprenorphine, other factors such as patient preference,[132] access to unsupervised dosing, and cost[133] to the individual are important factors to consider. Studies should also examine the effect of an individual's medication preference on treatment outcomes, particularly retention.

Long-term retention in treatment is crucial to maximise the benefits of OAT at the individual and population levels, but low rates of retention have be found in the observational studies done to date. New studies should examine strategies to increase retention in treatment. Options to be investigated include examination of increasing the flexibility of dosing; a Cochrane review[134] found, on the basis of six studies, insufficient evidence to make a clear decision about the effect of supervised versus unsupervised dosing on retention, adherence, and other outcomes. Observational evidence (eg, from Ward and colleagues[135] and Gomes and colleagues[106]) during COVID-19 restrictions showed that the increased flexibility of OAT provision during the pandemic might have increased retention. Further work is needed to ascertain whether these effects continue outside this context.

Clinical practice with buprenorphine has changed over time in some settings, given evidence of the importance of adequate dosing of buprenorphine for the improvement of retention,[10] especially during induction onto buprenorphine. Our meta-regressions found that study year was a statistically significant predictor of proportion retained in buprenorphine at 1 month. However, study year was not a significant predictor of any other measure of either retention in buprenorphine treatment or differences in retention between methadone and buprenorphine, suggesting that these changes in clinical practice might not have occurred in all settings. Furthermore, in many studies, dose was not recorded, which limited our capacity to examine the potential effects of dose on retention. In studies that did report mean buprenorphine dose, our meta-regressions did not find this variable to be associated with either retention in buprenorphine treatment or differences in retention between methadone and buprenorphine. Future studies should ensure recording of dose.

The rapid changes in the North American illicit opioid market, with the influx of illicitly manufactured fentanyl into the market,[136] bear mentioning. Existing studies rarely specified the opioids being used by participants in the research, and at any rate most research evidence was generated before those market changes. It is possible that retention in OAT—as well as other outcomes during OAT—differ among people dependent on fentanyl, and that such differences are not consistent across buprenorphine and methadone. Future studies, particularly in North America, could attempt to better measure and assess these possibilities.

We prespecified a wide range of structured primary and secondary outcomes. Nonetheless, many studies, even large-scale RCTs, measured only one or two outcomes. In some instances, idiosyncratic measures of our specified outcomes were used, and we could therefore not include those studies in the quantitative syntheses. Therefore, for many outcomes, few data exist. Future studies could consider measuring a wider range of outcomes and reporting those in a more standardised way to permit syntheses from more studies in future reviews of this topic.

RCTs were often substantially limited by small sample sizes and low statistical power to detect differences between groups. The observational studies, although in some cases very large and well powered, were constrained by the very high likelihood of selection bias and confounding due to probable differences in characteristics of people receiving buprenorphine compared with methadone. The potential effect of confounding needs to be considered when reviewing the synthesised evidence from observational studies. Additionally, reporting of preregistration of studies and outcomes for observational studies was rare, further enhancing the potential for post hoc analyses and selective reporting of outcomes. Future studies would do well to undertake this step and to improve the quality and comprehensiveness of data.

Some limitations in the available data encountered in the current review inform recommendations for future primary research. Few studies have investigated extended-release buprenorphine, and only one has directly compared extended-release buprenorphine with methadone. Future research could explore whether there are benefits for retention and other health outcomes in key subpopulations such as adolescents and older adults. We were unable to synthesise data on participants' ethnicity. In future primary studies could look to collect and report ethnicity data more consistently to facilitate synthesis in future reviews. The limited data on outcomes such as treatment satisfaction and quality of life demonstrate a need for patient-centred non-consumption outcomes to be included in future studies to investigate the real-world effectiveness of OAT. As few studies have focused on the needs of different populations, future primary studies focusing on strategies to increase retention would help to address this evidence gap.

There is consistent evidence across timepoints and study types that retention is better for methadone than buprenorphine after the first month of treatment, although retention for both medications, particularly over the longer term, is suboptimal. We identified few statistically significant differences between these treatments for most other outcomes. Where differences were identified they were generally based on a small

number of available studies and were not consistent across metrics and study types. This review highlights the importance of interventions to improve retention on OAT as well as of harmonisation of data collection for future evidence syntheses.

Contributors

LD, MF, EZ, BL, and SN contributed to conceptualisation and data curation. EZ, BC, DM-B, OL, and GM contributed to literature searches and data extraction. OL, BC, and GM conducted the formal analyses. LD led the writing of the manuscript. LD, OL, EZ, BC, MF, and GM contributed to writing the original draft and review and editing. All authors commented and contributed text to the manuscript.

Declaration of interests

In the past 3 years, LD and MF have received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior and Seqirus. MH reports speaker honoraria and travel expenses in the past 3 years from Gilead and MSD. SN has received untied investigator-initiated research grants from Seqirus, and is a named investigator on a buprenorphine depot implementation study funded by Indivior.

Data sharing

People interested in obtaining further information on the data presented in this manuscript can contact the corresponding author. Our protocol and approach to statistical analysis are available to be shared at any stage. We are open to discussion regarding any additional collaboration related to this review with those interested.

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