

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

## INTRODUCTION

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.

## AIMS

We aimed to examine buprenorphine compared with methadone in the treatment of opioid dependence across a wide range of primary and secondary outcomes.

## METHODS

### PRIMARY OUTCOMES

### RETENTION

### ADHERENCE TO TREATMENT

### EXTRA-MEDICAL OPIOID USE

- Secondary measures included a range of substance use, criminal justice, physical and mental health outcomes.
- We searched Embase, MEDLINE, CENTRAL, and PsycINFO through August 2022; clinical trial registries, and previous relevant Cochrane reviews.
- All RCT and observational studies among people with opioid dependence treated with buprenorphine compared to methadone that collected data on our primary or secondary outcomes, were included.
- Single arm cohort studies and randomised controlled trials that collected data on buprenorphine retention rates were also collected.
- Study authors were contacted to obtain additional data as needed. Data on study, participant and treatment characteristics were extracted.
- Comparative estimates were pooled using random-effects meta-analyses. Retention across multiple time points was pooled, stratified by medication and study types.
- Meta-regressions examined potential reasons for variation in observed effects.
- This study aligned with GATHER and PRISMA guidelines and was registered with PROSPERO (CRD42020205109).

## RESULTS

### WE IDENTIFIED

- 32 eligible RCTs (N=5808 participants) and 69 observational studies (N=323 340) comparing buprenorphine and methadone.
- An additional 51 RCTs (N=11 644) and 124 observational studies (N=700 035) that reported on treatment retention with buprenorphine.

### PRIMARY OUTCOMES

Data from studies directly comparing methadone and buprenorphine showed that 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<sup>2</sup>=74.2%; 16 studies, N=3151) and in observational studies (0.77 [0.68–0.86]; I<sup>2</sup>=98.5%; 21 studies, N=155 111).

There was some evidence that EXTRA-MEDICAL OPIOID USE was lower in those receiving buprenorphine, however this evidence was specific to RCTs that measured opioid use by urinalysis and reported results as a proportion of positive urine samples (SMD -0.20 [-0.29 to -0.11]; I<sup>2</sup>=0.0%; three studies, N=841), and no differences were found on other metrics for this outcome.

There was no evidence of differences in ADHERENCE between buprenorphine and methadone.

	Randomised controlled trials					Observational studies				
	Studies (participants), n	References	Pooled effect*	I <sup>2</sup>	Treatment favoured	Studies (participants), n	References	Pooled effect*	I <sup>2</sup>	Treatment favoured
<b>Primary outcomes</b>										
<b>Retention in treatment</b>										
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
<b>Adherence to treatment</b>										
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
<b>Extra-medical opioid use</b>										
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

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

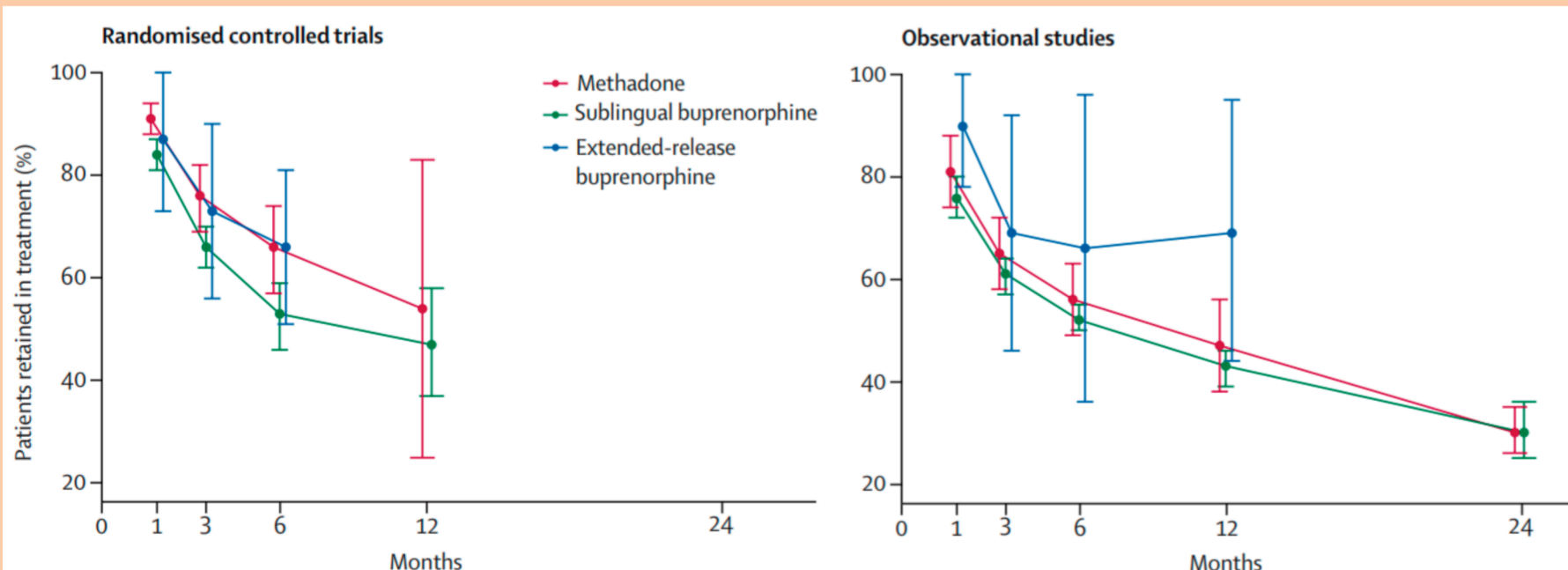


Figure 1: Retention in treatment with buprenorphine or methadone at 1, 3, 6, 12, and 24 months in RCTs (panel A) or observational studies (panel B). Buprenorphine data are stratified by route of administration. Error bars are 95% CIs. These estimates include data from studies comparing buprenorphine and methadone, as well as studies reporting retention in buprenorphine alone.

### SECONDARY OUTCOMES

There were relatively few statistically significant differences between buprenorphine and methadone among secondary outcomes. Pooled evidence favoured buprenorphine treatment for COCAINE USE, CRAVINGS, ANXIETY, TREATMENT SATISFACTION, and CARDIAC DYSFUNCTION; and evidence favoured methadone for HOSPITALISATION and ALCOHOL USE. 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.

## IMPLICATIONS

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. 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.

## PUBLICATION