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Opioid agonist treatment for pharmaceutical opioid dependent people (Review)

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Abstract

Background There are increasing concerns regarding pharmaceutical opioid harms including overdose and dependence, with an associated increase in treatment demand. People dependent on pharmaceutical opioids appear to differ in important ways from people who use heroin, yet most opioid agonist treatment research has been conducted in people who use heroin. **Objectives** To assess the effects of maintenance agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence. **Search methods** The search included the Cochrane Drugs and Alcohol Group's Specialised Register of Trials; the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 5); PubMed (January 1966 to May 2015); EMBASE (Ovid) (January 1974 to May 2015); CINAHL (EBSCOhost) (1982 to May 2015); ISI Web of Science (to May 2014); and PsycINFO (Ovid) (1806 to May 2014). **Selection criteria** We included randomised controlled trials examining maintenance opioid agonist treatments that made the following two comparisons: 1. full opioid agonists (methadone, morphine, oxycodone, levo-alpha-acetylmethadol (LAAM), or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment and 2. full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment). **Data collection and analysis** We used standard Cochrane methodological procedures. **Main results** We identified six randomised controlled trials that met inclusion criteria (607 participants). We found moderate quality evidence from two studies of no difference between methadone and buprenorphine in self reported opioid use (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.08 to 1.63) or opioid positive urine drug tests (RR 0.81, 95% CI 0.56 to 1.18). There was low quality evidence from three studies of no difference in retention between buprenorphine and methadone maintenance treatment (RR 0.69, 95% CI 0.39 to 1.22). There was moderate quality evidence from two studies of no difference between methadone and buprenorphine on adverse events (RR 1.10, 95% CI 0.64 to 1.91). We found low quality evidence from three studies favouring maintenance buprenorphine treatment over detoxification or psychological treatment in terms of fewer opioid positive urine drug tests (RR 0.63, 95% CI 0.43 to 0.91) and self reported opioid use in the past 30 days (RR 0.54, 95% CI 0.31 to 0.93). There was no difference on days of unsanctioned opioid use (standardised mean difference (SMD) -0.31, 95% CI -0.66 to 0.04). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on retention in treatment (RR 0.33, 95% CI 0.23 to 0.47). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on adverse events (RR 0.19, 95% CI 0.06 to 0.57). The main weaknesses in the quality of the data was the use of open-label study designs. **Authors' conclusions** There was low to moderate quality evidence supporting the use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence. Methadone or buprenorphine appeared equally effective. Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments. Due to the overall low to moderate quality of the evidence and small sample sizes, there is the possibility that the further research may change these findings.

Keywords

people, dependent, agonist, (review), opioid, pharmaceutical, treatment

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[Intervention Review]

Opioid agonist treatment for pharmaceutical opioid dependent people

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ABSTRACT

Background

There are increasing concerns regarding pharmaceutical opioid harms including overdose and dependence, with an associated increase in treatment demand. People dependent on pharmaceutical opioids appear to differ in important ways from people who use heroin, yet most opioid agonist treatment research has been conducted in people who use heroin.

Objectives

To assess the effects of maintenance agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence.

Search methods

The search included the Cochrane Drugs and Alcohol Group's Specialised Register of Trials; the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 5); PubMed (January 1966 to May 2015); EMBASE (Ovid) (January 1974 to May 2015); CINAHL (EBSCOhost) (1982 to May 2015); ISI Web of Science (to May 2014); and PsycINFO (Ovid) (1806 to May 2014).

Selection criteria

We included randomised controlled trials examining maintenance opioid agonist treatments that made the following two comparisons:

1. full opioid agonists (methadone, morphine, oxycodone, levo-alpha-acetylmethadol (LAAM), or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment and

2. full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment).

Data collection and analysis

We used standard Cochrane methodological procedures.

Main results

We identified six randomised controlled trials that met inclusion criteria (607 participants).

We found moderate quality evidence from two studies of no difference between methadone and buprenorphine in self reported opioid use (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.08 to 1.63) or opioid positive urine drug tests (RR 0.81, 95% CI 0.56 to 1.18). There was low quality evidence from three studies of no difference in retention between buprenorphine and methadone maintenance treatment (RR 0.69, 95% CI 0.39 to 1.22). There was moderate quality evidence from two studies of no difference between methadone and buprenorphine on adverse events (RR 1.10, 95% CI 0.64 to 1.91).

We found low quality evidence from three studies favouring maintenance buprenorphine treatment over detoxification or psychological treatment in terms of fewer opioid positive urine drug tests (RR 0.63, 95% CI 0.43 to 0.91) and self reported opioid use in the past 30 days (RR 0.54, 95% CI 0.31 to 0.93). There was no difference on days of unsanctioned opioid use (standardised mean difference (SMD) -0.31, 95% CI -0.66 to 0.04). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on retention in treatment (RR 0.33, 95% CI 0.23 to 0.47). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on adverse events (RR 0.19, 95% CI 0.06 to 0.57).

The main weaknesses in the quality of the data was the use of open-label study designs.

Authors' conclusions

There was low to moderate quality evidence supporting the use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence. Methadone or buprenorphine appeared equally effective. Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments.

Due to the overall low to moderate quality of the evidence and small sample sizes, there is the possibility that the further research may change these findings.

PLAIN LANGUAGE SUMMARY

Opioid maintenance medicines for the treatment of dependence on opioid pain medicines

Background

Use of pharmaceutical opioids (medicines that are used to treat pain) has increased dramatically in some parts of the world since the mid-1990s. With the increased use, there has been increasing numbers of people seeking treatment for dependence (addiction) on pharmaceutical opioids. Currently, most treatment guidelines are based on research that was conducted in people who were dependent on heroin (a highly addictive opioid). This review sought to compare different opioid agonist maintenance treatments (i.e. treatments such as methadone or buprenorphine that are given for at least 30 days to help the person to reduce their unsanctioned drug use) for the treatment of pharmaceutical opioid dependence. We also compared results from maintenance treatment to short term treatments such as detoxification (removal of the drug from the body) or psychological treatments (e.g. talking therapy, counselling).

Study characteristics

We examined the scientific literature up to May 2015. We identified six randomised controlled trials (studies where people were allocated at random to one of two or more treatment or control conditions) involving 607 people who were dependent on pharmaceutical opioids. The people in the study were 77% male and had an average age of 31.6 years. The average duration of the studies comparing different opioid maintenance treatments (three studies that compared methadone to buprenorphine) was 24 weeks, and the average duration of studies comparing a maintenance treatment (three studies with buprenorphine maintenance) to detoxification or psychological treatment was 10 weeks. Five of the six studies were conducted in the US, with one study from Iran.

We looked at opioid use and leaving treatment early.

Five of the studies were funded by the National Institute of Health (USA), with one study not reporting the funding source. Four studies reported that a drug company provided the medicine.

Key results

We found that there is probably little or no difference between how well methadone and buprenorphine worked to keep people in treatment, to reduce opioid use, or side effects. We found that buprenorphine probably keeps more people in treatment, may reduce use of opioids, and has fewer side effects compared to detoxification or psychological treatment alone.

Quality of the evidence

Overall, the evidence was of low to moderate quality. All studies put people into treatment groups randomly, but the participants and researchers knew which medication the participants were taking, which could bias the results and lower the quality of the evidence. Some of the studies had reasonable numbers of people who did not finish the study in both treatment groups, which means there are some missing results, but the number of people with missing results was similar in both treatment groups of the study for most studies. Most of the studies were similar in design and results were collected in a way that allowed them to compare opioid use and number of people completing the study.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Full opioid agonists versus different full opioid agonists or partial opioid agonists (methadone versus buprenorphine) for maintenance

Patient or population: pharmaceutical opioid dependent people
Intervention: methadone
Comparison: buprenorphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with buprenorphine	Risk with methadone				
Opioid use assessed with: days of unsanctioned opioid use at end of study period Scale from: 0 to 30 follow-up: mean 24 weeks	The mean opioid use was 2.92 days	The mean opioid use in the intervention group was 1.41 days lower (3.37 lower to 0.55 higher)	-	129 (1 RCT)	⊕⊕⊕◯ Moderate[1]	-
Opioid use assessed with: positive urine drug screen for opioids at end of treatment	Study population		RR 0.81 (0.56 to 1.18)	196 (2 RCTs)	⊕⊕⊕◯ Moderate[1]	For 1 study (Saxon 2013) missing urine drug screens were coded as positive; however, sensitivity analyses were conducted and results were not changed if this assumption was not made
	436 per 1000	353 per 1000 (244 to 514)				
	-					
	414 per 1000	335 per 1000 (232 to 488)				
Opioid use assessed with: self reported opioid use at the end of the study period follow-up: mean 24	Study population		RR 0.37 (0.08 to 1.63)	155 (2 RCTs)	⊕⊕⊕◯ Moderate[1]	-

weeks						
	382 per 1000	141 per 1000 (31 to 623)				
	-					
	519 per 1000	192 per 1000 (42 to 846)				
Retention assessed with: proportion of participants retained in treatment follow-up: mean 20 weeks	Study population		RR 0.69 (0.39 to 1.22)	360 (3 RCTs)	⊕⊕◯◯ Low[1,2]	-
	631 per 1000	436 per 1000 (246 to 770)				
	-					
	382 per 1000	264 per 1000 (149 to 467)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] All studies were open label. In addition, one study presented limited information meaning that we were unable to assess risk of bias
[2] Significant heterogeneity, P value = 0.04; I^2 = 68% when the meta-analyses included Ahmadi 2003. This is not apparent (1^2 = 2%) when the meta-analyses included only results from Neumann 2013 and Saxon 2013.

BACKGROUND

Description of the condition

The non-medical use of, and dependence to, pharmaceutical drugs has been described as a major health problem. An estimated 26 to 36 million people were using opioids in 2010, with around half using pharmaceutical opioids (UNODC 2012). There are an estimated 15.6 million opioid dependent people worldwide, with the global consumption of opioids considered to be increasing (WHO 2009). Opioid dependence is a chronic relapsing condition with significant cost to human life (Hser 2001; Grella 2011).

Dependence on pharmaceutical opioids has been well established as a problem in the US and Canada (Fischer 2012; Manchikanti 2012). In the USA, pharmaceutical opioids are increasingly used by young people, and pain medications are second to marijuana as the drug used by new illicit drug initiates (NSDUH 2011).

Globally, illicit opioid use is a major cause of mortality from both acute effects of intoxication (e.g. overdose and traffic accidents) and transmission of blood-borne disease associated with injection drug use (such as human immunodeficiency virus (HIV) and hepatitis C) (Degenhardt 2011). In the USA, where pharmaceutical opioid use has been described as an epidemic, pharmaceutical opioid overdose is one of the leading cause of mortality, with deaths from pharmaceutical opioids exceeding the number of deaths from heroin and cocaine (Compton 2015). In the USA in 2007, more people died from prescription opioid overdose than motor vehicle accidents and suicides (Manchikanti 2012). A more recent trend of declining mortality from prescription opioids was observed in young people, while among older adults, mortality has continued to increase (West 2015). Similarly high rates of pharmaceutical opioid use have been described in Canada (Fischer 2012). Although other countries are yet to reach the magnitude of the problems seen in the USA and Canada, there is evidence of increased pharmaceutical opioid use and harms. One global review identified that pharmaceutical opioid diversion, non-medical use and injection was a considerable problem in the USA, South Asia, South East Asia, and some European countries (Degenhardt 2007). In Europe, non-medical use of prescription opioids is documented, including the problematic use of non-prescription codeine in the UK and France. However, the risk of a prescription opioid epidemic on the scale of what was observed in North America is thought to be low (van Amsterdam 2015). An estimated 1.6% to 1.7% of the German population are thought to be dependent on prescription drugs (Casati 2012). Increasing treatment presentations with prescription and over-the-counter (non-prescription) codeine opioids are reported in South Africa, where 5% to 8% of treatment presentations are now associated with over-the-counter opioid dependence (Weich 2008). Increasing reports of use and harms with pharmaceutical opioids are also reported in Australia, with increasing mortality due to oxycodone, and increasing hospital presentations for pharmaceutical opioids including over-the-counter codeine (Frei 2010; Rintoul 2010; Roxburgh 2011). The number of hospital poisonings in Australia from pharmaceutical opioids exceeded heroin in 2004 and has continued to grow every year, and the number of treatment episodes are increasing, though heroin dependence remains the main opioid people seek treatment for (Roxburgh 2011; Nielsen 2015a).

Description of the intervention

Opioid agonist treatments are established to be effective in the treatment of heroin dependence (Clark 2002; Faggiano 2003; Mattick 2009; Mattick 2014). The two main opioid agonist treatments that are most widely available are methadone and buprenorphine.

Methadone is well established as a treatment and has a strong evidence base demonstrating its effectiveness in reducing mortality and substance use, improving physical and mental health outcomes, reducing criminal activity, and reducing HIV risk and risk behaviours (Caplehorn 1996; Amato 2005; Gowing 2011; Gowing 2012; Gowing 2013; Mattick 2014).

Methadone is a synthetic μ-opioid agonist, and an N-methyl-D-aspartate (NMDA) antagonist. It has a half-life of 24 to 36 hours and has close to 100% oral bioavailability. Methadone is generally given as a single daily dose in the treatment of opioid dependence. Methadone doses of 60 to 100 mg are more effective in retaining people in treatment compared with lower doses (Faggiano 2003).

Buprenorphine is a partial opioid agonist, having a lower intrinsic activity at the opioid receptor, but, due to its high affinity for the opioid receptor, buprenorphine has antagonist actions, blocking the effect of other opioids. Buprenorphine has a favourable safety profile due to its ceiling on respiratory effects (Walsh 1994), with mortality in treatment appearing to be relatively less common with buprenorphine compared with methadone in naturalistic study designs in Australia and France (Auriacombe 2001; Degenhardt 2009). Buprenorphine has poor oral bioavailability, and is available in sublingual formulations for the treatment of opioid dependence. Due to its pharmacological properties, buprenorphine is able to be given as larger doses every second or third day (Amass 2000).

Levo-alpha-acetylmethadol (LAAM) was concluded to be more effective than methadone for reducing heroin use (Clark 2002), but it is currently not commercially available. Other therapies such as slow release oral morphine have also been explored.

How the intervention might work

Opioid agonist treatment, also known as opioid maintenance treatment, involves prescribing maintenance doses of an opioid medication in place of the drug of dependence. Most of the original research into opioid maintenance treatment involved prescribing a legal opioid such as methadone or buprenorphine to treat illicit opioid (e.g. heroin) dependence. The provision of a regular

dose of a legal opioid treatment enables a reduction in illicit or unsanctioned opioid use, with improvements in health and social stability. The dose of the medication is adjusted to a level that reduces withdrawal and craving without causing excessive sedation. Regular dosing maintains a fairly constant blood level, so that the sense of euphoria or intoxication usually associated with each dose of the drug (either illicit or prescribed) is lessened. Maintenance treatment decreases the frequency and intensity of the cycle of intoxication and withdrawal, allowing the client to address the associated issues necessary for recovery better. Psychosocial support provided in conjunction with medication can help to address the psychological health and social problems that can be associated with opioid use, and therefore help to improve quality of life and prevent premature mortality (WHO 2009).

Opioid agonist treatment works by provision of a regular dose of μ-opioid agonist that binds at the μ-opioid receptor, alleviating opioid withdrawal symptoms. Providing a stable dose of opioid agonist has been demonstrated to lead to numerous health and social benefits for opioid dependent people, specifically though reducing illicit opioid use (Amato 2005; Mattick 2009; Mattick 2014), HIV risk behaviour (Gowing 2011), HIV seroconversion (MacArthur 2012), and criminality (Amato 2005; Mattick 2009). It has been confirmed to improve physical and mental health, and social functioning (Padaiga 2007; Mattick 2009; Mattick 2014), and reduce mortality (Degenhardt 2011).

Why it is important to do this review

Opioid agonist treatment is commonly initiated as a first-line treatment for people with pharmaceutical opioid dependence, even though much of the evidence base for the use of pharmacotherapy in opioid dependence has been derived from studies conducted primarily or exclusively with heroin-dependent samples. People who use pharmaceutical opioids (i.e. both prescription opioids and over-the-counter opioids such as codeine) have been described in the literature to be a patient population with a number of characteristics that differ from heroin-using populations, including being more likely to be white, employed, less likely to use drugs by injection, and having a higher prevalence of physical and mental health co-morbidities (Brands 2004; Moore 2007; Fischer 2008; Nielsen 2011; Nielsen 2015a). How these characteristics may impact on treatment outcomes is not well understood. Further, studies that have compared treatment outcomes for people who use pharmaceutical opioids and heroin have had mixed results, with some studies finding better treatment outcomes for people using pharmaceutical opioids, and other studies finding no difference (Banta-Green 2009; McCabe 2013; Nielsen 2013; Nielsen 2015b).

Pharmaceutical opioid dependence is at epidemic levels in the USA and is increasing globally. Establishing an evidence base for treatment of prescription opioid dependence is therefore timely and critical. An emerging evidence base exists for the use of opioid agonist treatments in prescription opioid dependence, but a systematic review is yet to be conducted to determine whether similar outcomes can be expected for this new population of opioid dependent people. This review will fill an evidence gap informing clinicians about effective approaches using agonist pharmacotherapies for pharmaceutical opioid dependence.

OBJECTIVES

To assess the effects of maintenance agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

We included studies with people who were assessed by study staff to meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), or other validated criteria for pharmaceutical opioid dependence, or were assessed by a clinician to meet criteria for pharmaceutical opioid dependence (i.e. a population meeting criteria for 'addiction' rather than just physiological neuro-adaptation in the absence of other behaviours suggesting dependence).

Pharmaceutical opioid dependent people did not include those who were solely taking pharmaceutical opioids in the context of opioid substitution treatment (e.g. studies of people who were already in methadone treatment). Where participants were reported to be 'opioid dependent', as opposed to specifically dependent on pharmaceutical opioids, the main opioid used prior to treatment entry must have been a pharmaceutical opioid. We excluded studies examining opioid treatments primarily for pain and not for the treatment of opioid dependence.

Where study populations were not exclusively comprised of primary pharmaceutical opioid dependent people, at least 80% of the study participants must have reported pharmaceutical opioids as their primary substance for the parent study data to be included in the analysis. Where subpopulations of pharmaceutical opioid dependent people do not comprise 80% of the study population, we requested data for sub-analysis, with only participants meeting the above criteria (i.e. dependent on pharmaceutical opioids, or

opioid dependent with the main opioid used being a pharmaceutical opioid) included in the analysis. We contacted study authors where necessary to confirm levels of use of pharmaceutical opioids. Studies with mixed populations of opioid dependent people must have recruited at least 10 people who were dependent on pharmaceutical opioids for re-analyses of data to be included in the review.

Types of interventions

We included studies of maintenance opioid agonist treatments, where maintenance was defined as at least 30 days of opioid agonist treatment. We included trials that made the following comparisons:

1. full opioid agonists (methadone, morphine, oxycodone, LAAM, or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment;
2. full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment).

Types of outcome measures

Outcome measures were not considered as part of the eligibility criteria.

Primary outcomes

1. Illicit opioid use, as measured by: days of unsanctioned opioid use at the end of the intervention period.
2. Illicit opioid use at end of treatment completion (defined as point prevalence of opioid use at end of treatment by self report and with urine drug screen).
3. Retention.

Secondary outcomes

1. Pain, assessed by validated scales such as the Brief Pain Inventory (Cleeland 1991), and the McGill Pain Questionnaire (Melzack 1975).
2. Risk behaviours (injecting, sexual, polydrug use, overdoses, or hospital admissions).
3. Adverse effects (participants experiencing any adverse event, or serious adverse event).
4. Aberrant opioid related behaviours (e.g. seeing multiple doctors for extra opioid medication, lost medication, unauthorised dose escalations).
5. Employment.
6. Quality of life, as assessed by validated scales such the World Health Organization Quality of Life (WHOQOL) or WHOQOL-BREF (WHO 1997).
7. Physical health, as assessed by validated scales such as the 36-item Short Form (SF-36) (Ware 1992)
8. Psychological health, as assessed by validated scales such as the SF-36 (Ware 1992), Kessler Psychological Distress Scale (K10) (Kessler 2002), or Depression and Anxiety Stress Scale (DASS) (Lovibond 1995).

Outcomes were either self reported or objectively measured.

Search methods for identification of studies

Electronic searches

A search strategy was developed in consultation with a drug and alcohol research information specialist, and search terms revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules (Appendix 1).

We searched:

1. Cochrane Drugs and Alcohol Group's Specialised Register of Trials; May 2015;
2. the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 5);
3. PubMed (January 1966 to May 2015);
4. EMBASE (Ovid) (January 1974 to May 2015);
5. CINAHL (EBSCOhost) (1982 to May 2015);
6. ISI Web of Science (1900 to May 2014);
7. PsycINFO (Ovid) (1806 to May 2014).

Searching other resources

We search abstracted databases including the National Institute on Drug Abuse/College on Problems of Drug Dependence (NIDA/CPDD) abstracts, as well as clinical trial registers ClinicalTrials.gov (www.clinicaltrials.gov); World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en).

We searched the reference lists of all relevant papers to identify further studies, in addition to contacting the authors of all included studies to enquire if there were other relevant published or unpublished studies. All searches included English and non-English language literature.

Data collection and analysis

Selection of studies

One review author reviewed the titles and abstracts identified by the above searches. We requested the full text of each potentially relevant article, and two review authors independently assessed the studies for inclusion. Where the two review authors were unable to reach agreement following their independent review of the full text, a third review author assessed the studies to assist in reaching consensus.

Data extraction and management

Two review authors independently extracted data using a data collection form, with a third review author involved where there was disagreement to assist in reaching consensus.

We extracted information about the number of participants treated; drug and dosing regimen; study design; study duration and follow-up; and outcomes listed at including pain, substance use measures, treatment retention, risk behaviours, employment, quality of life, physical and psychological health, and adverse events (participants experiencing any adverse event, or serious adverse event) from each study and recorded them on a data extraction sheet.

We attempted to collect and utilise the most detailed numerical data that might have facilitated similar analyses of included studies. Where 2×2 tables or means and standard deviations were not available, we used effect estimates (e.g. odds ratios, regression coefficients), confidence intervals (CI), test statistics (e.g. t, F, Z, Chi^2) or P values in the analyses (see also Measures of treatment effect).

Assessment of risk of bias in included studies

We performed the risk of bias assessment for RCTs using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This comprises a two-part tool addressing seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high, or unclear risk. To make these judgements, we used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), adapted to the addiction field. See Appendix 2 for details.

The tools addressed the domains of sequence generation and allocation concealment (avoidance of selection bias) by a single entry for each study.

We considered blinding of participants, personnel, and outcome assessor (avoidance of performance bias and detection bias) separately for objective outcomes (e.g. retention, substance use measured by urine analysis, participants relapsed at the end of follow-up, participants engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, participant self reported use of substance, adverse effects, social functioning as integration at school or at work, family relationship).

We considered incomplete outcome data (avoidance of attrition bias) for all outcomes except for retention, which is often the primary outcome measure in trials on addiction.

Grading the evidence

We assessed the overall quality of the evidence for the primary outcome using the Grading of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) system. GRADE developed a system for grading the quality of evidence that takes into account issues not only related to internal validity but also to external validity, such as directness, consistency, imprecision of results, and publication bias (GRADE 2004; Guyatt 2008; Guyatt 2011). We presented the main findings of the review in the 'Summary of findings' tables, which present results in a transparent and simple tabular format. In particular, the tables provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons.

1. Serious (-1) or very serious (-2) limitation to study quality.
2. Important inconsistency (-1).
3. Some (-1) or major (-2) uncertainty about directness.
4. Imprecise or sparse data (-1).
5. High probability of reporting bias (-1).

Grading is increased for the following reasons.

1. Strong evidence of association - significant risk ratio (RR) of greater than 2 (less than 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1).
2. Very strong evidence of association - significant RR of greater than 5 (less than 0.2) based on direct evidence with no major threats to validity (+2).
3. Evidence of a dose response gradient (+1).
4. All plausible confounders would have reduced the effect (+1).

Measures of treatment effect

Where possible, we expressed the treatment effect for each dichotomous outcome as a risk ratio (RR) with 95% confidence intervals (CI). Where there was a comparable consistent outcome measure (e.g. days of opioid use), we expressed the treatment effect for each continuous outcome as a mean difference (MD) with

95% CIs. Where there was variability in outcome measure (e.g. quality of life scales, risk behaviour measures, or pain scales), we expressed the treatment effect for each continuous outcome as a standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

For trials with multiple treatment arms, we combined groups to allow single pair-wise comparisons.

Dealing with missing data

Where there appeared to be an important amount of missing data, we described the possible effects of the missing data in the 'Discussion' section and 'Summary of findings' tables.

Assessment of heterogeneity

We considered clinical heterogeneity (variability in the participants, interventions, and outcomes studied) and methodological heterogeneity (variability in study design and risk of bias), which we discussed in the 'Summary of findings' tables.

We conducted meta-analysis were studies were sufficiently homogeneous in terms of participants, interventions, and outcomes to provide a meaningful summary. Where this was not the case, and the heterogeneity of the included studies precluded a meta-analysis being performed, we described the relevant studies separately.

To assess heterogeneity, initially we inspected the results graphically. A P value of the test lower than 0.10 or an I^2 statistic of at least 50% indicated significant statistical heterogeneity.

Assessment of reporting biases

We planned to use funnel plots (plots of the effect estimate from each study against the standard error) to assess the potential for bias related to the size of the trials, which could indicate possible publication bias. As the search identified too few studies to be included in a meta-analysis, we did not use funnel plots. In future updates of this review if sufficient studies are included in meta-analyses (i.e. more than 10), we will use funnel plots.

Data synthesis

We summarised the key findings of studies descriptively before considering if studies were appropriate for quantitative meta-analysis. We contacted study authors where we required additional information to enable inclusion of studies in meta-analyses.

We undertook statistical analysis using Review Manager 5 (RevMan 2012).

We combined the outcomes of the individual trials through meta-analysis where possible (depending on the comparability of interventions and outcomes between trials) using of a random-effects model as variability was expected between the studies. Where meta-analysis was not possible, we reported a narrative synthesis of the findings.

Subgroup analysis and investigation of heterogeneity

The search did not identify a sufficient number of studies to enable planned subgroups of participants to be examined and investigated for potential sources of heterogeneity:

1. with and without chronic pain;
2. with and without a history of heroin use;
3. with and without a history of injecting drug use;
4. with and without mental health problems.

We will consider the possibility of subgroup analyses when we update the review and additional studies are available.

Sensitivity analysis

Where the effect of a decision on the outcome of the review was uncertain (e.g. the decision to include or exclude a study remained unclear, or the impact of unavailable data on the findings was uncertain), we conducted a sensitivity analysis with the results described in text.

To incorporate risk of bias assessment in the review process, we planned to plot intervention effect estimates for different outcomes stratified for risk of bias for each item; however, we found insufficient numbers of studies to warrant this process for the two planned comparisons. For future updates of this review, if differences in results are present among studies at different risk of bias, we will perform sensitivity analysis, excluding studies at a high risk of bias. We will also perform subgroup analysis for studies at a low and unclear risk of bias.

RESULTS

Description of studies

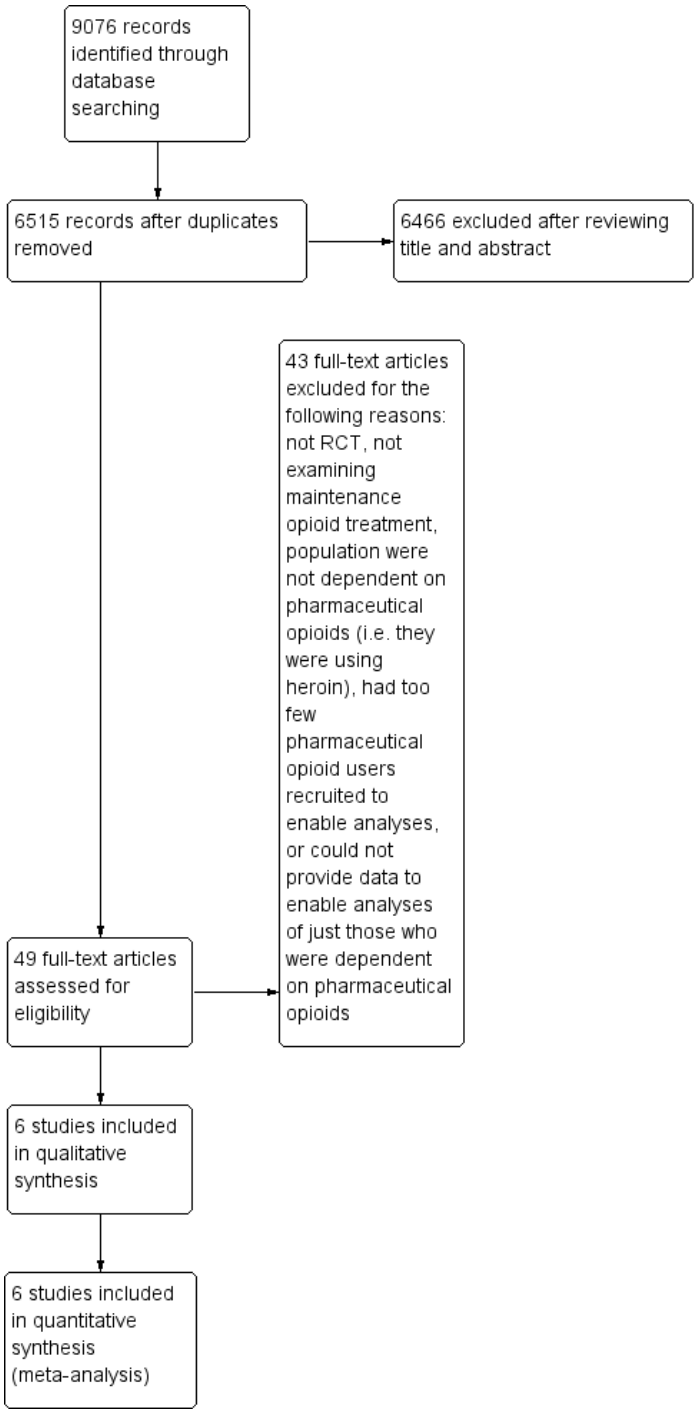
See Characteristics of included studies table.

Results of the search

We identified 9076 studies through the electronic and other searches. After removing duplicates, 6515 titles and abstracts remained. We examined the full text or contacted study authors (or both) of 49 records, excluding 43 records at this stage, identifying six studies to be included in the analysis (See Figure 1). Several full texts that were reviewed indicated studies had recruited populations of 'opioid dependent people' without specifying the primary opioid used (e.g. whether the participant was dependent on a pharmaceutical opioid, heroin, or opium). In each of these papers, where the full text did not explicitly indicate that the participants were dependent on pharmaceutical opioids, the review

authors (SN, BL) contacted the study authors to determine if the study met eligibility criteria with respect to the opioid used being a pharmaceutical opioid. We included studies where the primary opioid of concern was clearly identified as a pharmaceutical opioid or where the study population included at least 10 participants that were dependent on pharmaceutical opioids and data were available to enable analyses of the study data only for those participants that were dependent on pharmaceutical opioids. Where authors were unable to provide further information on the primary drug of concern (other than being an opioid), or where we received no response, we did not include the study.

Figure 1. Study flow diagram.



Included studies

We identified six RCTs that met the inclusion criteria (607 participants). Three studies compared methadone and buprenorphine (Ahmadi 2003; Neumann 2013; Saxon 2013), and three studies compared buprenorphine maintenance to either buprenorphine taper (in addition to psychological treatment) (Woody 2008; Fiellin 2014) or brief intervention and referral to treatment (D'Onofrio 2015). The mean duration of the trials was 105 days. Five of the six studies were conducted in an outpatient setting. One study recruited participants who were admitted to hospital, with one group randomised to commence buprenorphine as an inpatient while the other two groups offered a brief intervention and treatment referral information (D'Onofrio 2015). Neumann 2013 recruited a population of people with chronic non-cancer pain and opioid dependence. All other studies recruited participants with dependence on pharmaceutical opioids, and one study specifically recruited participants that were injecting buprenorphine (Ahmadi 2003).

Data from three studies were re-analyses of parent studies to include only data from participants who were dependent on pharmaceutical opioids; two studies provided data for analyses through the CTN data share website (Woody 2008; Saxon 2013), and for one study, the study statistician provided the data for participants who were dependent on pharmaceutical opioids (D'Onofrio 2015). Fiellin 2014 also provided additional data to facilitate analyses with comparable outcome measures across the studies. Data for two studies were drawn directly from the published papers (Ahmadi 2003; Neumann 2013).

Five studies were conducted in the US and one study was conducted in Iran (Ahmadi 2003). Five studies recruited adults, and one study examined young people aged 15 to 21 years (Woody 2008).

Overall, the participants in the studies were 77% male and had a mean age of 31.6 years. The mean duration of the studies comparing different opioid maintenance treatments (three studies that compared methadone to buprenorphine) was 24 weeks, and the mean duration of studies comparing a maintenance treatment (three studies with buprenorphine maintenance) to detoxification or psychological treatment was 10 weeks.

Excluded studies

Of the studies that we excluded during full text review, we excluded three studies because all participants received the same opioid agonist (or partial agonist) medication, meaning that no comparison was possible: one study of buprenorphine for prescription opioid dependence because the study was an adaptive study design where the randomised trial component compared adjunctive counselling to standard care, and all participants received buprenorphine (resulting in there being no non-opioid agonist comparison group) (Weiss 2011). Fiellin 2006 described that all participants received buprenorphine, hence there was no non-agonist arm for comparison. Chopra 2009 also examined different psychosocial adjunct treatments where all participants received buprenorphine.

Four studies contained prescription opioid dependent people in their population, but the number was too small (e.g. two or three participants) to permit meaningful analyses of the prescription opioid dependent participants across different treatment conditions (Liebschutz 2013), or dependence to pharmaceutical opioids was unable to be confirmed where participants were using multiple opioids (Strain 1996; Kristensen 2005; Piralishvili 2015). Two further studies recruited pharmaceutical opioid dependent participants to the study; we requested data to perform analyses for only those dependent on pharmaceutical opioids but they were not available at the time of this review (Ling 2010; Rosenthal 2013).

Three studies did not administer maintenance opioid agonists (Stitzer 1983; Amass 1994; Sigmon 2013), and three studies were not RCTs (Batki 1998; Gossop 2001; Hoffmann 2014).

The remainder of the excluded studies had populations of opioid dependent people primarily using heroin (see Excluded studies).

Risk of bias in included studies

Figure 2 and Figure 3 present a summary of the assessed risk of bias for each of the included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

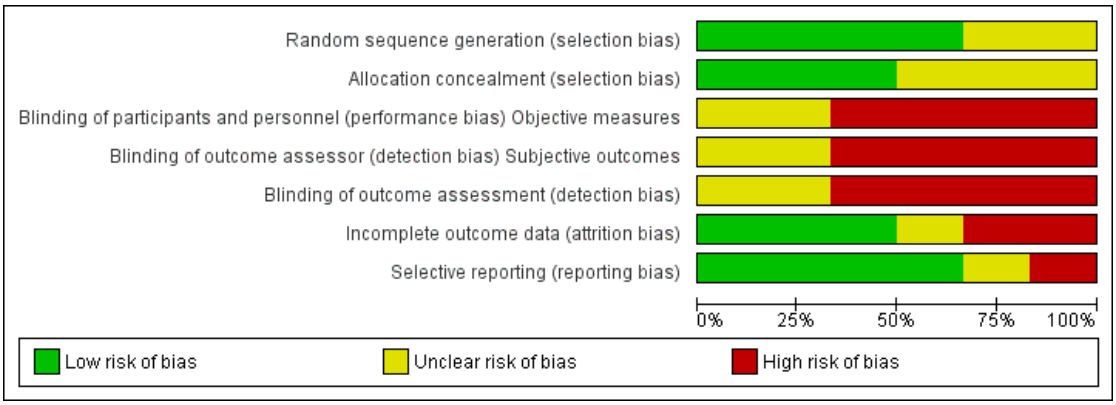
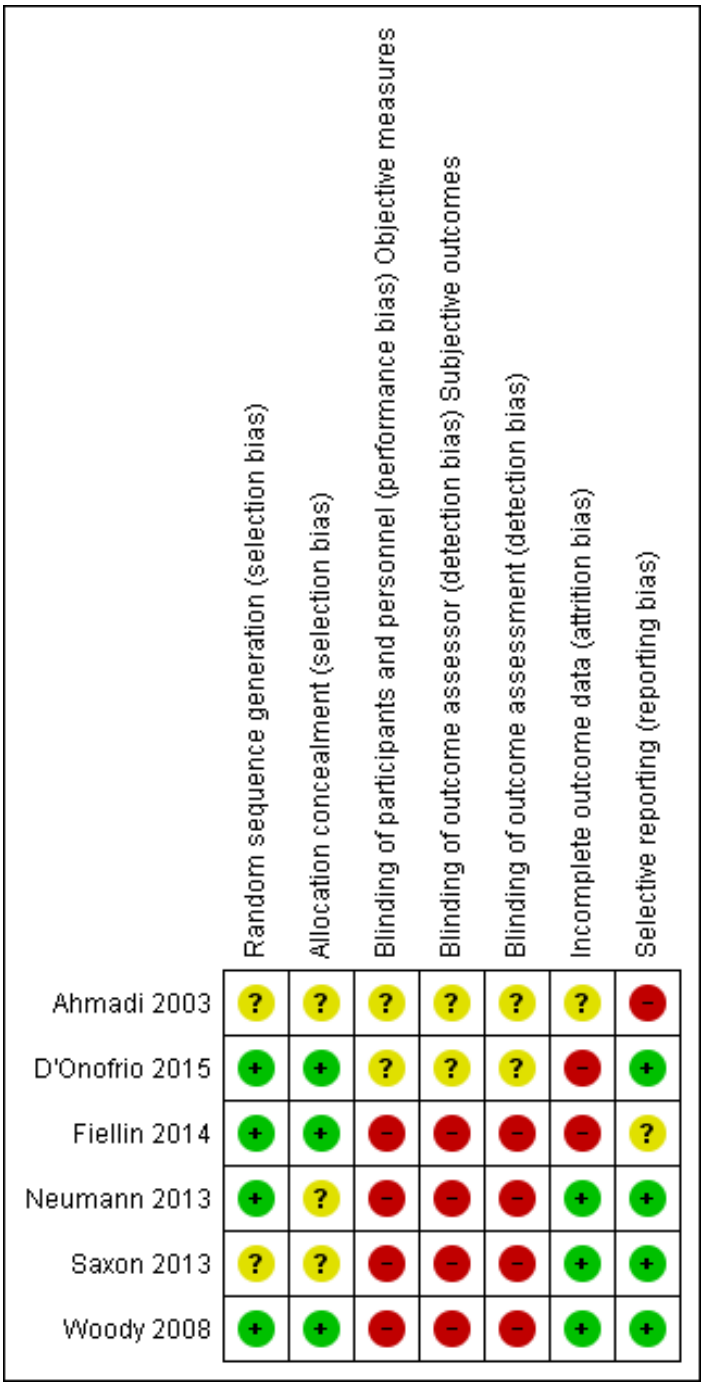


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

No studies had high risk of selection bias. All included studies were RCTs. For two studies, the method of sequence generation was unclear (Ahmadi 2003; Saxon 2013), and for three studies, the method of allocation concealment was unclear (Ahmadi 2003; Neumann 2013; Saxon 2013). The remaining studies had low risk of random sequence or allocation bias.

Blinding

None of the studies were double blinded studies (most studies were described as open-label studies), with all studies having either a high or unknown risk of bias.

Incomplete outcome data

All studies reported data on retention. For other outcomes measures, some studies only presented data on treatment completers (Neumann 2013), or had differences in the number of participants retained across groups, which potentially introduced bias (Fiellin 2014; D'Onofrio 2015). Two studies had a low risk of bias (Woody 2008; Saxon 2013).

Selective reporting

Four studies had a low risk of reporting bias, with prospectively published protocols available or prospective clinical trial registration including describing main outcome measures or data published on open access websites, or a combination of these (Woody 2008; Neumann 2013; Saxon 2013; D'Onofrio 2015). One study only reported on one outcome measure, retention (Ahmadi 2003).

Effects of interventions

See: **Summary of findings for the main comparison** Full opioid agonists versus different full opioid agonists or partial opioid agonists (methadone versus buprenorphine) for maintenance; **Summary of findings 2** Full or partial opioid agonist maintenance versus placebo, detoxification only or psychological treatment (buprenorphine maintenance compared to taper or treatment as usual)

See Summary of findings for the main comparison; Summary of findings 2. We presented results for the two main comparisons:

1. opioid agonists versus other opioid agonists (or partial agonists) for maintenance treatment;
2. full or partial opioid agonists versus placebo, detoxification, or psychological treatment (without maintenance agonist treatment).

The results in the 'Summary of findings' tables include the primary outcomes measures of opioid use and retention in treatment.

Full opioid agonists versus different full opioid agonists or partial opioid agonists

We found three studies, all comparing methadone versus buprenorphine (with or without naloxone) (Ahmadi 2003; Neumann 2013; Saxon 2013). We found no studies examining opioids agonists other than methadone or buprenorphine.

Primary outcomes

Illicit opioid use

There was no significant difference in days of unsanctioned opioid use (MD -1.41 days, 95% CI -3.37 to 0.55; one study; 129 participants) (Analysis 1.1).

There was no significant difference in point prevalence use at the end of treatment (urine-analysis results) (RR 0.81, 95% CI 0.56 to 1.18; two studies; 196 participants) (Analysis 1.2).

There was no significant difference in point prevalence use at the end of treatments (self reported)(RR 0.37, 95% CI 0.08 to 1.63; two studies; 155 participants) (Analysis 1.3).

Retention

There was no significant difference in retention (number of participants retained at end of treatment) (RR 0.69, 95% CI 0.39 to 1.22; three studies; 360 participants) (Analysis 1.4).

Secondary outcomes

Pain

Two studies with 152 participants found no significant difference in pain using different measures (improvement from baseline pain and mean bodily pain). They found no significant difference (SMD 0.11, 95% CI -0.22 to 0.43) (Analysis 1.5).

Risk behaviours

One study with 170 participants found no significant difference in risk behaviours (RR 0.52, 95% CI 0.02 to 12.64) (Analysis 1.6).

Adverse effects

Two studies examined adverse effects but in different ways: Neumann 2013 described self reported adverse effects and serious adverse events, Saxon 2013 examined serious adverse effects. The two studies, with data from 196 participants, found no significant difference (RR 1.10, 95% CI 0.64 to 1.91) (Analysis 1.7).

Aberrant opioid related behaviours

None of the studies reported aberrant opioid related behaviours.

Employment

None of the studies reported on employment.

Quality of life

None of the studies reported an overall quality of life score.

Physical health

One study found no significant difference in mean physical functioning (SF-36) (MD 1.28, 95% CI -3.83 to 6.39; 127 participants) (Analysis 1.8).

Psychological health

One study found no significant difference in mental health functioning (SF-36) (MD -2.13, 95% CI -10.06 to 5.80; 127 participants) (Analysis 1.9).

Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment)

We found three studies, all comparing buprenorphine maintenance treatment to a control condition. We found no studies using other opioid agonist treatment compared to a non-agonist control group.

Primary outcomes

Illicit opioid use

There was no significant difference in days of unsanctioned opioid use (reported as mean days in past 7 or 30 days: SMD -0.31; 95% CI -0.66 to 0.04; two studies; 133 participants) (Analysis 2.1).

There was a significant difference in favour of buprenorphine maintenance treatment for point prevalence use at the end of treatment (urine-analysis results) (RR 0.63, 95% CI 0.43 to 0.91; three studies, 206 participants) (Analysis 2.2).

There was a significant difference in favour of buprenorphine maintenance treatment for point prevalence use at the end of treatments (self reported) RR 0.54, 95% CI 0.31 to 0.93; three studies, 204 participants). When the analysis excluded results from Woody 2008 due to evidence of heterogeneity (degrees of freedom (df) = 2; P value = 0.12; I^2 = 52%) the result of the meta-analyses was unchanged favouring buprenorphine maintenance (RR 0.66, 95% CI 0.49 to 0.89; two studies; 177 participants; P value = 0.81; I^2 = 0%) (Analysis 2.3).

Retention

There was a significant difference in favour of buprenorphine maintenance treatment for retention (number of participants retained at end of treatment) (RR 0.33, 95% CI 0.23 to 0.47; three studies; 247 participants) (Analysis 2.4).

Secondary outcomes

Pain

There was no significant difference in the proportion of participants who reported 'moderate' or 'extreme' pain or discomfort at week eight (RR 0.52, 95% CI 0.27 to 1.01; one study; 36 participants)(Analysis 2.5).

Risk behaviours

There was no significant difference in events of injecting risk behaviour (RR 0.38, 95% CI 0.04 to 3.54; two studies; 98 participants) (Analysis 2.6).

Adverse effects

Outcomes were measured differently across two studies, one study reported protective transfers Fiellin 2014 and one study reported serious adverse events Woody 2008. 166 participants: with findings favouring the buprenorphine maintenance (RR 0.19, 95%CI 0.06, 0.57). See Analysis 2.7.

Aberrant opioid related behaviours

None of the studies reported aberrant opioid related behaviours.

Employment

None of the studies reported on employment.

Quality of life

None of the studies reported an overall quality of life measure.

Physical health

There was a significant difference in favour of buprenorphine maintenance treatment for mean ratings of physical health on the EQ Visual Analogue Scale (a scale of self reported health state out of 100) at week eight (MD 31.08, 95% CI 12.40 to 49.76; one study; 36 participants) (Analysis 2.8).

Psychological health

There was no significant difference in proportions of participants reporting moderate or extreme anxiety and depression (as measured with the EQ-5D (EuroQol five dimensions questionnaire)) at week eight (RR 0.89, 95% CI 0.53 to 1.50; one study; 36 participants) (Analysis 2.9).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Full or partial opioid agonist maintenance versus placebo, detoxification only or psychological treatment (buprenorphine maintenance compared to taper or treatment as usual)

Patient or population: pharmaceutical opioid dependent people
Intervention: opioid agonist
Comparison: detoxification/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with detoxification/placebo	Risk with Opioid agonist				
Days of unsanctioned opioid use assessed with: number of days of unsanctioned use (as number of days/30 or days/7) Scale from: 0 to 7 or 30 follow-up: mean 10 weeks	The mean days of unsanctioned opioid use was 1.06 days	The mean days of unsanctioned opioid use in the intervention group was 0.31 standard deviations days lower (0.66 lower to 0.04 higher)	-	133 (2 RCTs)	⊕⊕◯◯ Low[1,2]	-
Self reported opioid use at treatment completion follow-up: mean 10 weeks	Study population		RR 0.54 (0.31 to 0.93)	204 (3 RCTs)	⊕⊕◯◯ Low[1,2]	Some heterogeneity in results, which is likely to be attributed to the different populations (i.e. non-treatment seeking), and indirect nature of substance use outcomes in the study by D'Onofrio 2015
	596 per 1000	322 per 1000 (185 to 554)				
	-					
	737 per 1000	398 per 1000 (228 to 685)				

Opioid use assessed with: urine drug screens follow-up: mean 10 weeks	Study population		RR 0.63 (0.43 to 0.91)	206 (3 RCTs)	⊕⊕◯◯ Low[12]	-
	615 per 1000	387 per 1000 (264 to 559)				
	-					
	500 per 1000	315 per 1000 (215 to 455)				
Retention assessed with: proportion of participants retained in treatment follow-up: mean 10 weeks	Study population		RR 0.33 (0.23 to 0.47)	247 (3 RCTs)	⊕⊕⊕◯ Moderate[1]	Some heterogeneity was identified in populations, of note is that the study by Ahmadi 2003 recruited people who were injecting buprenorphine, and predominantly had histories of opium or heroin use prior to buprenorphine. Results were not changed when the analyses excluded this study (i.e. no difference between buprenorphine and methadone when this study was included or excluded)
	631 per 1000	208 per 1000 (145 to 297)				
	-					
	769 per 1000	254 per 1000 (177 to 362)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Studies were open label, differences in retention were reported between the groups resulting in differences in missing data on some variables.

[2] One study was examining different methods of referral to treatment in non-treatment seeking people who presented to hospital. Substance use was an indirect outcome of the study as this was not the primary focus.

DISCUSSION

Summary of main results

The studies identified compared methadone versus buprenorphine maintenance treatment (three studies), and buprenorphine maintenance treatment versus detoxification or psychological treatment (without maintenance agonist treatment); two studies where the comparison was buprenorphine taper and one study where the control condition was brief intervention and referral). In total, the review included six studies with 604 participants. The quality of the evidence was generally low to moderate (see Summary of findings for the main comparison; Summary of findings 2) with all studies being RCTs that were not double blind. Sample sizes were generally small, from 53 to 204 participants. The meta-analyses included data for both comparisons for the primary outcomes of opioid use and retention.

There was moderate quality evidence finding no significant differences in self reported opioid use or opioid positive urine drug tests between methadone and buprenorphine. There was low quality evidence that there was no difference in retention between methadone and buprenorphine. These are commonly considered some of the important outcomes for treatment of pharmaceutical opioid dependence. As evidence did not favour either of these treatments, other clinician or treatment system factors may contribute to the choice of pharmacotherapy for patients, including patient preference, safety, and availability of medications.

Where buprenorphine maintenance was compared with detoxification or other psychological treatment (in the absence of maintenance opioid pharmacotherapy), low to moderate quality evidence favoured maintenance buprenorphine treatment with less self reported opioid use and fewer opioid positive urine tests combined with greater retention. These findings suggest that where retention and substance outcomes are important to patient and clinician, there appear to be advantages in maintenance agonist treatment.

Overall completeness and applicability of evidence

There was enough consistency in the way the studies collected and reported primary outcome measures to enable pooling data on the key outcomes measures. Missing data introduced the potential for bias in opioid use outcome measures. An important limitation to generalisability is study location. Five of the six studies were conducted in the US, making it difficult to know how these findings may apply to people dependent on pharmaceutical opioids in other settings.

Quality of the evidence

The studies in this review were generally either small or the sample size was small once the population was restricted to only people that were dependent on pharmaceutical opioids. Two studies had larger sample sizes; Saxon 2013 (170 participants in the analyses of only pharmaceutical opioid dependent people) and Ahmadi 2003 (204 participants, although this study reported only one outcome). The study by Ahmadi 2003 contributed around one-third of the sample size, and represented a population of buprenorphine injectors. As such, the population in this study may differ from the populations of the other two studies. Sensitivity analyses confirmed that the exclusion of this study did not change the overall result of the meta-analyses. No studies had high risk of selection bias, though none of the studies were double blinded. Four out of six studies had low risk of reporting bias. See Figure 2 and Figure 3.

One of the studies had the primary outcome of 'enrolment in addiction treatment 30 days after randomisation', as the study was examining commencing buprenorphine as an inpatient versus two other conditions where participants received some form of brief intervention and referral to addiction treatment (these two other non-buprenorphine groups were combined in the present analyses) (D'Onofrio 2015). As such, the evidence from this study on opioid use outcomes could be considered indirect as the study did not directly aim to reduce opioid use. Finally, data for three of the six studies were drawn from existing larger studies of opioid dependent people, rather than from studies specifically developed to examine the effectiveness of these interventions for pharmaceutical opioid dependent people (Woody 2008; Saxon 2013; D'Onofrio 2015).

Potential biases in the review process

There is the possibility that studies with negative findings on pharmacotherapy may be less likely to be published, which could potentially favour the finding of published studies that demonstrate an effect of pharmacotherapy treatments. We identified no conference abstracts of unpublished studies to confirm if this is the case.

Agreements and disagreements with other studies or reviews

The finding of no difference in retention between methadone and buprenorphine is in contrast to findings reported in studies of predominantly people dependent on heroin, where Mattick 2014 found evidence in favour of methadone retaining more participants in treatment. Due to the small sample sizes in this review, there is the possibility that the review was underpowered to detect a difference.

Findings appear consistent with a larger adaptive study design that also appeared to favour longer periods of buprenorphine

treatment, with poorer outcomes following buprenorphine taper among pharmaceutical opioid dependent people (Weiss 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There was low quality evidence supporting the use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence. The current data suggest that methadone or buprenorphine are equally effective. As evidence did not favour either of these treatments over the other, other clinician or treatment system factors may contribute to the choice of pharmacotherapy for patients, including patient preference, safety, and availability of medications.

Maintenance treatment with buprenorphine may be more effective than detoxification or psychological treatments (or both).

Due to the overall low to moderate quality of the evidence and smaller sample sizes, there is the possibility that the further research may change these findings.

Implications for research

There is a high prevalence of chronic pain among pharmaceutical opioid dependent people (Lusted 2013); however, only one small study examined outcomes among people with concurrent pain and opioid dependence (Neumann 2013). Larger studies are needed to examine all outcomes, and particularly for people with pain and opioid dependence, in addition to including standardised measures of pain severity and pain interference as secondary outcomes measures in randomised controlled trials of opioid treatments where populations with pain are recruited (Turk 2008). Growing evidence supports the use of multi-modal treatment strategies for pain, as opposed to relying solely on opioids for pain management. Expanding the evidence for non-drug and adjuvant medication strategies to reduce the reliance on opioids for pain management will be important areas for future work. In addition, studies that specifically recruit pharmaceutical opioid dependent people will add to the evidence base that is currently formed in large part by secondary data analyses from previously completed clinical trials.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Ahmadi 2003

Methods	Open label randomised controlled trial
Participants	Participants had reported daily buprenorphine injection for at least 6 months. Most (80%) had a history of heroin or opium dependence prior to buprenorphine injection. All participants were male, mean age of 31.2 years (range 17-53). No current use of substances was reported
Interventions	Methadone 50 mg (n = 68) Buprenorphine 5 mg (n = 68) Naltrexone 50 mg (n = 68) For 12 weeks
Outcomes	Retention
Notes	No other outcome measures reported. A second publication appeared to report findings from the same study. Included only the first publication on the study. Funding for the study not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided to enable assessment
Allocation concealment (selection bias)	Unclear risk	Insufficient information was provided to enable assessment
Blinding of participants and personnel (performance bias) Objective measures	Unclear risk	Insufficient information was provided to enable assessment
Blinding of outcome assessor (detection bias) Subjective outcomes	Unclear risk	Insufficient information was provided to enable assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information was provided to enable assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information was provided to enable assessment
Selective reporting (reporting bias)	High risk	Information was only reported on retention

Woody 2008

Methods	Open label randomised controlled trial of buprenorphine (+ naloxone) maintenance compared with buprenorphine detoxification
Participants	Opioid dependent youths (aged 15-21 years). Analyses from unpublished data reported represents only those participants (n = 53) who reported that a pharmaceutical opioid was their main drug problem. Mean age of participants reporting pharmaceutical opioid as a main drug problem 20.0 (SD 1.3) years old, and 64% male
Interventions	Buprenorphine-naloxone + counselling (n = 27) for 12 weeks Buprenorphine detoxification + counselling (n = 26) for 14 days
Outcomes	Main outcome measure was opioid positive urine tests at weeks 4, 8, and 12
Notes	All outcomes reported in this analysis were for week 8 as buprenorphine taper began in week 9, meaning at week 12 participants were no longer in maintenance treatment Disclosures: Quote: "Dr Woody reported being a member of the RADARS [Researched Abuse, Diversion and Addiction-Related Surveillance] postmarketing study external advisory group whose job is to assess abuse of prescription medications. Denver Health administers RADARS and Abbott, Cephalon, Endo, Pricara/Ortho-McNeil, Purdue Pharma, and Shire subscribe to its data. Dr Woody reported that Ortho-McNeil and Purdue Pharma funded similar work by him prior to his joining RADARS. Dr Woody reported that Schering-Plough, the European distributor for buprenorphine-naloxone, funded his travel costs to meetings in Sweden and Finland in June 2008 to present data from this study. Dr Bogenschutz reported receiving research funding from Forest and Lilly and having a confidentiality agreement with Lilly. Dr Forman reported being a faculty member at the University of Pennsylvania and co-principal investigator with Dr Woody on the Delaware Valley Node of the NIDA Clinical Trials Network until December 2005 when he joined Alkermes. Dr Patkar reported being a consultant to Bristol-Meyers Squibb, GlaxoSmithKline, and Reckitt Benckiser and being on the speakers' bureau for and receiving honoraria from Bristol-Meyers Squibb, Forest, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals Lundbeck, McNeil Consumer & Specialty Inc, Organon, and Pfizer. Dr Publicker reported having been a speaker for Cephalon, Forest, and Reckitt Benckiser. Dr McNicholas reported having conducted training programs to certify physicians in the use of buprenorphine. Her expenses have been paid by unrestricted grants to universities that were often provided by Reckitt Benckiser. Dr Fudala reported having been employed by the University of Pennsylvania and Philadelphia VA Medical Center from 1991 until he joined Reckitt Benckiser in June 2005 and reported having been a consultant to Johnson & Johnson and Purdue Pharma" This study was supported by the NIDA and Reckitt Benckiser provided medication for the study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization occurred through an automated 24-hour service at the Veterans Affairs Cooperative Studies Program in Perry Point, Maryland, that was pro-

Woody 2008 (*Continued*)

		grammed to randomise patients separately by site"
Allocation concealment (selection bias)	Low risk	Central randomisation procedures described above, condition could not be foreseen by staff
Blinding of participants and personnel (performance bias) Objective measures	High risk	Quote: "Research assistants likely know group assignments because the study was not blinded" Open label study
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	Quote: "Research assistants likely know group assignments because the study was not blinded" Open label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Research assistants likely knew group assignments because the study was not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Investigators used multiple statistical approaches to examine the impact of missing data on their results and it appears the results of these analyses did not alter the results of the study findings Quote: "A pattern-mixture model was used to assess the impact of missing data on urine test results. Pattern mixture models extend the basic repeated measures by including a variable that describes the main patterns of missing data as a main effect and an interaction with other variables (week and group). Significant interactions with the missing data indicator on the main variables suggest that its effects differ across levels of missing data and that missing data may not be ignorable. Following suggested guidelines,23 we used time of last data provision (a categorical variable representing week 4, 8, or 12) as the missing variable. Another approach often taken is to impute missing tests as positive. If results obtained for the original and imputed models differ substantially, missing data may not be ignorable. Both methods were used to evaluate the effects of data on the primary outcome wherein miss-

		ing urine test results were counted as opioid positive. A GEE [generalised estimating equation] model that ignored missing data showed a marginal group × time interaction (= 4.93, P = .09). While not attaining the usual 5% significance, it likely reflected a lack of power for interaction effects rather than constant treatment effects at each time point." "Because there were no interactions pertaining to dropout time, results suggested that missing data were not invalidating the group effect"
Selective reporting (reporting bias)	Low risk	Protocol and data were available on an open access datashare website

Saxon 2013

Methods	Open label randomised controlled trial of methadone vs. buprenorphine
Participants	Reported analyses of unpublished data only for participants that used only pharmaceutical opioids in the 30 days prior to the study (n = 170). Sample was 61% (n = 104) male, mean age 34.4 years (SD 10.1) at baseline and 83% white with no difference between randomisation groups on demographic characteristics. Participants who were randomised to the buprenorphine group were less likely to report a history of heroin use (odds ratio 0.465, 95% confidence interval 0.25 to 0.88). Past year dependence on other substance was as follows: alcohol 7% (n = 11), cannabis 7% (n = 12), cocaine 8% (n = 14), amphetamines 7% (n = 11), sedatives 7% (n = 12)
Interventions	Methadone (n = 66) Buprenorphine (n = 104) 24 weeks in a flexible dose schedule
Outcomes	Primary outcome of the parent study was liver function at 24 weeks
Notes	Financial interests disclosed. Quote: "Andrew Saxon: Paid consultant to Reckitt Benckiser Pharmaceuticals; Walter Ling: Paid consultant to Reckitt Benckiser Pharmaceuticals; R. Douglas Bruce: Research grant support from Gilead Sciences, Inc., Merck & Co., Bristol Myers Squibb, Boehringer Ingelheim, Reckitt Benckiser Pharmaceuticals, Abbott Laboratories, Pfizer, Inc., and honorarium from Reckitt Benckiser Pharmaceuticals; Yuliya Lokhnygina: Paid consultant to Johnson & Johnson Reckitt Benkiser provided some initial advice on the study design and supplied Suboxone. The main study funding came from the NIDA through the Clinical Trials Network

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Saxon 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Study stated randomisation, no additional information reported on sequence generation
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding of participants and personnel (performance bias) Objective measures	High risk	Study reported to be an open label study
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	Study reported to be an open label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study reported to be an open label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Figure 1 of the publication indicated that there was more missing data from the buprenorphine group; however, in the sub-analyses, retention was comparable across the groups suggesting that this was less likely to influence the results presented in this review
Selective reporting (reporting bias)	Low risk	Study protocol was available and expected results were reported. Further, study data available on datashare website

Neumann 2013

Methods	Open label randomised controlled trial
Participants	Participants eligible for randomisation were men and women aged ≥ 18 years with well documented chronic non-malignant pain related to the spine or a large joint (e.g. hip, knee, shoulder) and an addiction to prescription opioids. The sample (n = 54) was 54% (n = 29) men, mean age 38.3 years (SD 9.7). 7 participants reported cocaine use at baseline and 20 (36%) had a urine drug test that was positive for any other drug at baseline
Interventions	Sublingual buprenorphine/naloxone 4-16 mg/1-4 mg/day (experimental group) (n = 26) Oral methadone tablets 10-60 mg/day (active comparator group) (n = 28); doses were divided 1-4 times daily
Outcomes	Pain and opioid use
Notes	Results were reported for treatment completers only The study was supported, in part, by a grant from the NIDA. Conflicts of interest were not reported in the manuscript

Neumann 2013 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised into 1 of 2 groups that were pre-determined by drawing lots using a 3:3 ratio block randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding of participants and personnel (performance bias) Objective measures	High risk	Quote: "This is a preliminary study ...that was not a double-blind and double-dummy study." "This was an open-label trial without a placebo and a control group. The outcomes might have been different, if a placebo had been used and the treatment conditions were masked to the participants, to the clinicians who provided care, and to the investigators who collected the follow-up data" No blinding was described
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	As above, open label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above, open label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses only for completers; however, missing data balanced across the 2 intervention groups (n = 15/28 missing for methadone group and n = 13/26 missing for buprenorphine group), 13 completers in each group
Selective reporting (reporting bias)	Low risk	Outcomes were consistent with those prospectively reported on clinicaltrials.gov NCT00879996

Fiellin 2014

Methods	Open label office-based trial of buprenorphine taper compared to buprenorphine maintenance
Participants	People who were prescription opioid dependent, mean age 30.35 years (SD 9.16), 58% male. At baseline cocaine abuse was reported by 12% (n = 13)

Fiellin 2014 (*Continued*)

Interventions	Buprenorphine stabilisation for 6 weeks followed by 3-week taper (n = 57) Maintenance buprenorphine (n = 56) for 14 weeks
Outcomes	Illicit opioid use, retention, and re-initiation of buprenorphine treatment
Notes	Quote: "Dr Fiellin has received honoraria for serving on expert advisory boards to monitor for diversion, misuse, and abuse of buprenorphine for Pinney Associates and ParagonRx and has received honoraria from the American Society of Addiction Medicine to serve as the medical director of the Physician Clinical Support Systems for Buprenorphine and Primary Care and from the American Academy of Addiction Psychiatry to serve as a consultant to the Physician Clinical Support Systems for Buprenorphine and Opioids. Drs Schottenfeld and Moore received support from the Connecticut Mental Health Center, State of Connecticut. Dr Barry has received compensation for expert testimony addressing addiction and pain. No other disclosures were reported" Funding was received from NIDA and a pharmaceutical company, Reckitt-Benckiser Pharmaceuticals, provided buprenorphine through the NIDA

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After the induction and stabilization period, patients were randomly assigned in a 1:1 ratio to receive taper or maintenance therapy (each described below). An urn randomisation procedure under the control of an investigator (B.A.M.) who was not involved with enrolment or assessment for eligibility was used to ensure that the groups were similar with regard to current cocaine abuse and urine samples with findings negative for opioids and cocaine at the time of randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was communicated by an investigator not involved in assessment for eligibility or randomization who notified each patient of his or her treatment assignment in a sequential manner"
Blinding of participants and personnel (performance bias) Objective measures	High risk	Quote: "Open label randomized clinical trial"
Blinding of outcome assessor (detection bias) Subjective outcomes	High risk	Quote: "Open label randomized clinical trial"

Fiellin 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open label randomized clinical trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Patients in the taper group provided fewer urine samples than those in the maintenance group (57.3% vs 78.2%; P = .001). The results regarding the patient-reported frequency of illicit opioid use are based on 1044 assessments of the 1582 total possible assessments (66.0%) had all patients remained in treatment for the entire 14-week trial. Patients in the taper group completed fewer patient-reported assessments than those in the maintenance group (56.9% vs 76.3%; P < .001)"
Selective reporting (reporting bias)	Unclear risk	Clinicaltrials.gov indicated some measures that were collected were not included in the primary outcome paper (e.g. reductions in HIV risk; patient satisfaction, costs of services). The main outcomes that would be expected to be reported in a study of this type were included in the main outcome paper, suggesting that this may not represent bias

D'Onofrio 2015

Methods	Randomised controlled trial (open label) of opioid dependent people presenting at emergency departments
Participants	Included in analyses were unpublished data for participants where a pharmaceutical opioid was the primary opioid used (n = 82). The main study recruited participants who were 75% male with a mean age of 31.4 years (SD 10.6). Data on other substance use for the subset that used pharmaceutical opioids were not available
Interventions	Referral to addiction treatment (n = 31) Brief intervention and referral to addiction treatment (n = 24) Brief intervention and commenced on buprenorphine as an inpatient (n = 27)
Outcomes	Primary outcome was engagement in addiction treatment on the 30th day following randomisation. Secondary outcomes collected at 30 days included self reported number of days of illicit opioid use in the past 7 days, urine toxicology for illicit opioid use, HIV risk taking behaviour, and use of addiction treatment services

D'Onofrio 2015 (*Continued*)

Notes	Quote: "The study was supported by grant 5R01DA025991 from the National Institute on Drug Abuse (NIDA), and Reckitt-Benckiser Pharmaceuticals provided buprenorphine through NIDA" Dr Fiellin reported having received honoraria from Pinney Associates "for serving on an external advisory board monitoring the diversion and abuse of buprenorphine"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computerized stratified randomization procedure under the control of an investigator (M.C.C.) who was not involved with enrolment or assessment for eligibility was used to ensure that the groups were balanced with regard to sex, cocaine use in the last 30 days, and primarily prescription opioid or heroin use"
Allocation concealment (selection bias)	Low risk	Quote: " A computerized stratified randomization procedure under the control of an investigator (M.C.C.) who was not involved with enrolment or assessment..."
Blinding of participants and personnel (performance bias) Objective measures	Unclear risk	Quote: "Data on all outcomes were collected by research associates not involved in the patients' ED [emergency department] care" Not enough details were available to assess risk (i.e. just because the participants were not aware of the care in the ED did not mean that they were not aware of the study treatment)
Blinding of outcome assessor (detection bias) Subjective outcomes	Unclear risk	Quote: "Data on all outcomes were collected by research associates not involved in the patients' ED [emergency department] care" Not enough details were available to assess risk (i.e. just because the participants were not aware of the care in the ED did not mean that they were not aware of the study treatment)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Data on all outcomes were collected by research associates not involved in the patients' ED [emergency department] care"

		Not enough details were available to assess risk (i.e. just because the participants were not aware of the care in the ED did not mean that they were not aware of the study treatment)
Incomplete outcome data (attrition bias) All outcomes	High risk	For the main outcome paper, most data would not have been affected by attrition due to the statistical methods used Quote: "We used the mixed-models procedure repeated measures linear models to evaluate the differences between baseline and 30-day follow-up in the number of days per week of illicit opioid use, HIV risk behaviors, and inpatient addiction services across the study groups. This analytical approach uses all available data on each randomized patient; therefore, all study patients, including those with missing data, were included in the analyses; no imputations were required" This suggests that for the main outcome paper low risk would exist; however, authors reported that there were more missing data for the non-opioid agonist group, suggesting analyses presented in this review may be affected by attrition bias
Selective reporting (reporting bias)	Low risk	All measures prospectively reported on Clinicaltrials.gov were reported in the main outcome paper, in addition to those that would be usually expected in this type of study

HIV: human immunodeficiency virus; n: number of participants; NIDA: National Institute on Drug Abuse; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amass 1994	No opioid maintenance condition as per definition of maintenance in protocol
Anglin 2007	Participants were heroin dependent

(*Continued*)

Batki 1998	Study was not a randomised controlled trial
Cameron 2006	Unable to determine if participants were dependent on pharmaceutical opioids
Chopra 2009	All participants received buprenorphine (i.e. not randomised to different opioid agonists, and no non-agonist group), randomised to different conditions of contingency management to promote abstinence from illicit opioid use
Eder 1998	Study participants were primarily heroin dependent
Fiellin 2006	All groups received buprenorphine, that is there was no non-agonist comparison group
Fischer 1999	Study participants were primarily heroin dependent
Fudala 2003	Study participants were primarily heroin dependent
Gossop 2001	Study was not a randomised controlled trial design
Gruber 2008	Participants were primarily using heroin
Hoffmann 2014	Observational study (not a randomised controlled trial)
Johnson 1992	Participants were primarily using heroin
Johnson 1995	Participants were primarily using heroin
Johnson 2000	Participants were primarily using heroin
Kakko 2003	Participants were primarily using heroin
Karp-Gelernter 1982	Participants were primarily using heroin
Kristensen 2005	Sub-analyses of participants that used only pharmaceutical opioids was not possible, though it was confirmed that there were participants that used a combination of heroin and pharmaceutical opioids
Liebschutz 2013	Too few participants (< 10) were using only pharmaceutical opioid, precluding meaningful comparisons
Ling 1996	Participants were primarily using heroin
Ling 1998	Participants were primarily using heroin
Ling 2010	Data not available to perform analyses on only those participants who were dependent on pharmaceutical opioids
Longshore 2005	Participants were primarily using heroin
Maremmani 1999	Unable to confirm if study met inclusion criteria from information available

(*Continued*)

McKenzie 2012	Participants were primarily using heroin
Montoya 2004	Participants were primarily using heroin
Petitjean 2001	Full text described sample in terms of their heroin use, unable to confirm with authors if any participants were primarily pharmaceutical opioid dependent people
Piralishvili 2015	Unclear if participants were dependent only on pharmaceutical opioids
Reimer 2011	Participants were primarily using heroin
Robertson 2006	Published paper did not indicate the primary opioid used by study participants, unable to confirm with study authors
Rosenthal 2013	Data not available to perform analyses on only those participants who were dependent on pharmaceutical opioids
Sees 2000	Participants were described as primarily using heroin. Unable to confirm with study authors if there were any pharmaceutical opioid dependent participants recruited
Sigmon 2013	Study was not of maintenance opioid treatment (all participants received different duration taper)
Stitzer 1983	All participants received detoxification, no maintenance comparison
Strain 1996	Participants were primarily using heroin
Strang 2000	Participants were primarily using heroin
Tennant 1982	Study design was not a randomised controlled trial
Uehlinger 1998	Unable to confirm if any participants were dependent on pharmaceutical opioids
Weiss 2011	All participants received buprenorphine (no non-buprenorphine control group). Participants were randomised to receive enhanced counselling versus standard care

DATA AND ANALYSES

Comparison 1. Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Days of unsanctioned opioid use	1	129	Mean Difference (IV, Random, 95% CI)	-1.41 [-3.37, 0.55]
2 Opioid positive urine drug screen at treatment completion	2	196	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.56, 1.18]
3 Self reported substance use (end of treatment)	2	155	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.08, 1.63]
4 Retention	3	360	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.39, 1.22]
5 Pain	2	153	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.22, 0.43]
6 Risk behaviours	1	170	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.02, 12.64]
7 Adverse effects	2	196	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.64, 1.91]
8 Physical health	1	127	Mean Difference (IV, Random, 95% CI)	1.28 [-3.83, 6.39]
9 Psychological health	1	127	Mean Difference (IV, Random, 95% CI)	-2.13 [-10.06, 5.80]

Comparison 2. Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

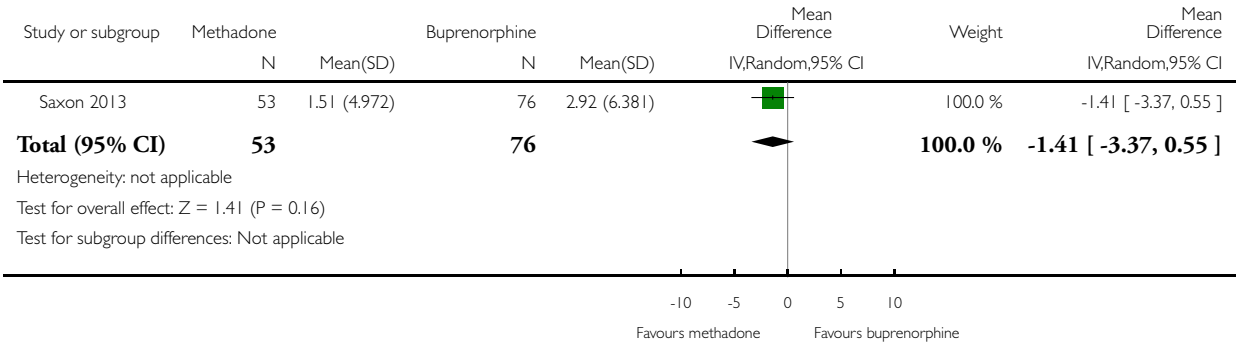
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Days of unsanctioned opioid use	2	133	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.66, 0.04]
2 Opioid positive (per urine drug screen, last week of treatment maintenance)	3	206	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.91]
3 Self reported opioid use at treatment completion (past 30 days)	3	204	Risk Ratio (IV, Random, 95% CI)	0.54 [0.31, 0.93]
4 Retention	3	247	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.23, 0.47]
5 Pain (some to extreme pain or discomfort)	1	36	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 1.01]
6 Risk behaviours	2	117	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.04, 3.67]
7 Adverse events	2	166	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.57]
8 Physical health	1	36	Mean Difference (IV, Random, 95% CI)	31.08 [12.40, 49.76]
9 Psychological health (moderate to extremely anxious or depressed)	1	36	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.53, 1.50]

Analysis 1.1. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 1 Days of unsanctioned opioid use.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 1 Days of unsanctioned opioid use

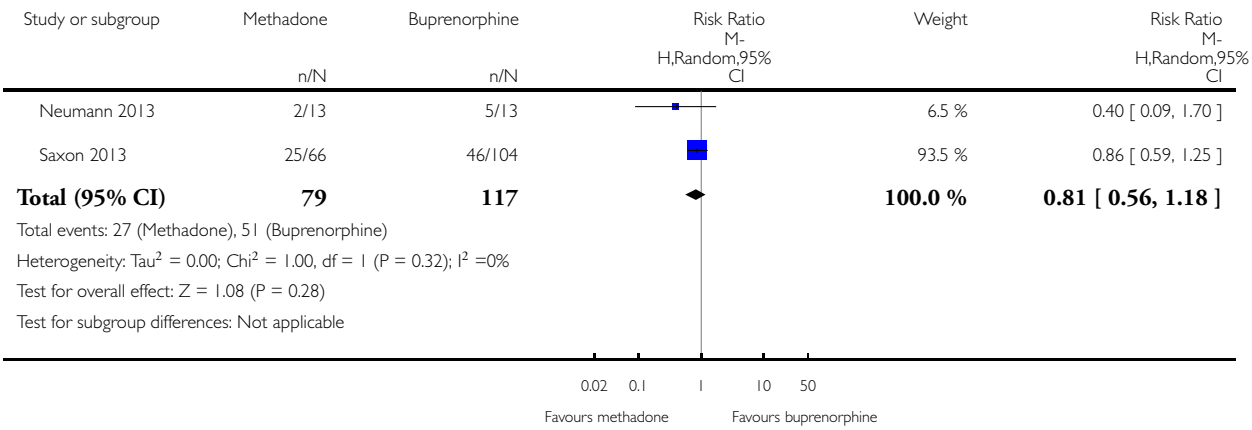


Analysis 1.2. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 2 Opioid positive urine drug screen at treatment completion.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 2 Opioid positive urine drug screen at treatment completion



Analysis 1.3. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 3 Self reported substance use (end of treatment).

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 3 Self reported substance use (end of treatment)

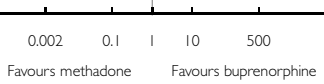
Study or subgroup	Methadone n/N	Buprenorphine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Neumann 2013	0/13	5/13		21.4 %	0.09 [0.01, 1.49]
Saxon 2013	11/53	29/76		78.6 %	0.54 [0.30, 0.99]
Total (95% CI)	**66**	**89**		**100.0 %**	**0.37 [0.08, 1.63]**

Total events: 11 (Methadone), 34 (Buprenorphine)

Heterogeneity: $Tau^2 = 0.63$; $Chi^2 = 1.59$, df = 1 (P = 0.21); $I^2 = 37\%$

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 4 Retention.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 4 Retention

Study or subgroup	Methadone n/N	Buprenorphine n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
Ahmadi 2003	57/68	40/68		31.1 %	0.39 [0.21, 0.72]
Neumann 2013	13/28	13/26		34.7 %	1.07 [0.64, 1.80]
Saxon 2013	51/66	72/104		34.2 %	0.74 [0.43, 1.26]
Total (95% CI)	**162**	**198**		**100.0 %**	**0.69 [0.39, 1.22]**

Total events: 121 (Methadone), 125 (Buprenorphine)

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 6.32$, df = 2 (P = 0.04); $I^2 = 68\%$

Test for overall effect: Z = 1.28 (P = 0.20)

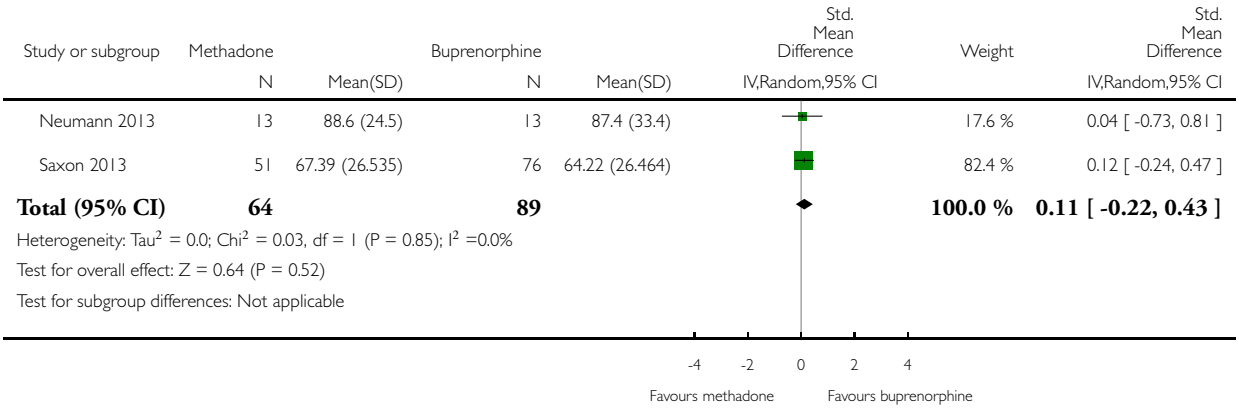
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 5 Pain.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 5 Pain

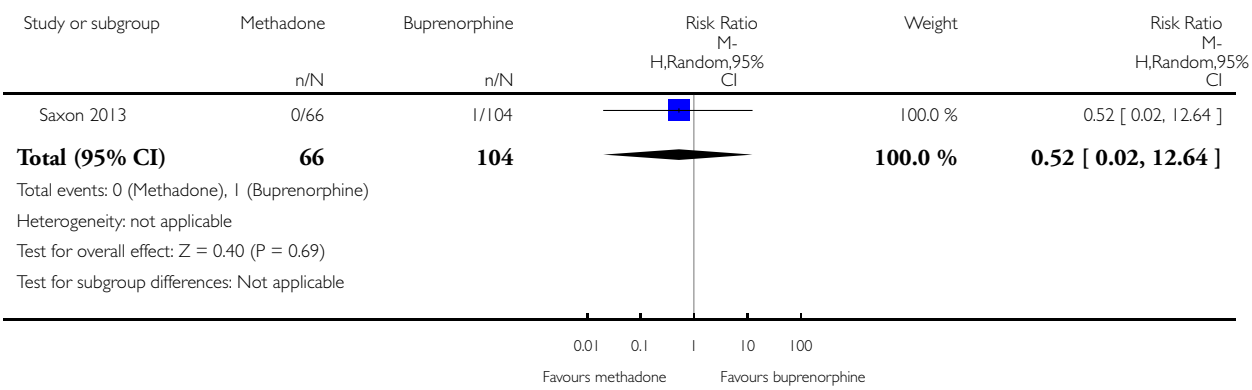


Analysis 1.6. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 6 Risk behaviours.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 6 Risk behaviours

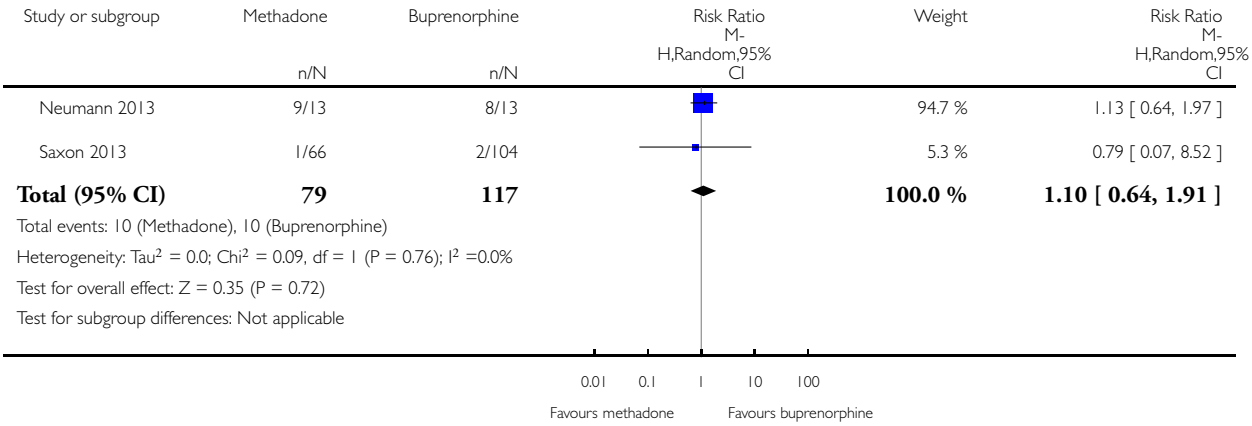


Analysis 1.7. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 7 Adverse effects.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 7 Adverse effects

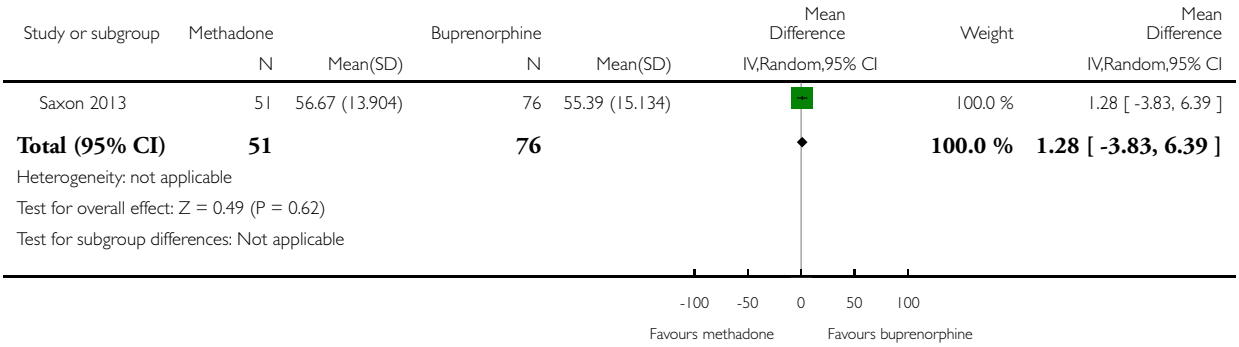


Analysis 1.8. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 8 Physical health.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 8 Physical health

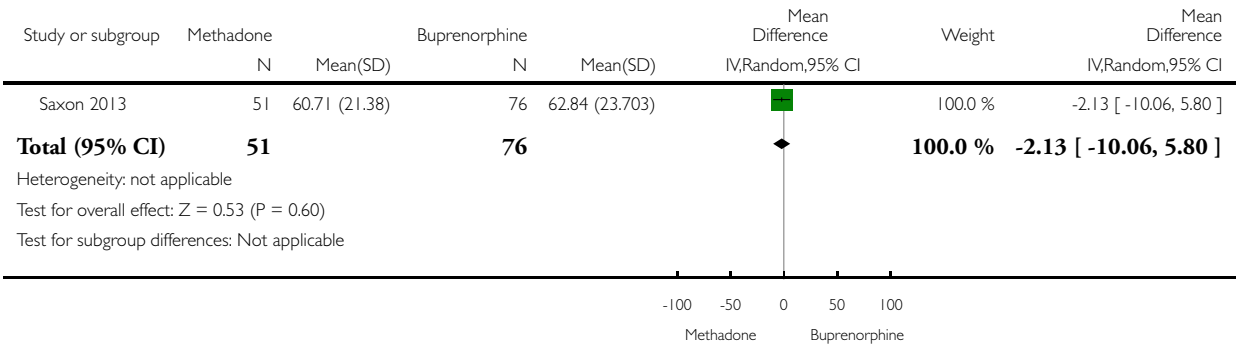


Analysis 1.9. Comparison 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists, Outcome 9 Psychological health.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 1 Full opioid agonists versus different full opioid agonists or partial opioid agonists

Outcome: 9 Psychological health



Analysis 2.1. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 1 Days of unsanctioned opioid use.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 1 Days of unsanctioned opioid use

Study or subgroup	BPN maintenance N	Mean(SD)	Taper/TAU N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
D'Onofrio 2015	26	0.5 (1.2379)	38	1.25 (2.1982)		48.5 %	-0.40 [-0.90, 0.11]
Fiellin 2014	43	2.05 (4.84)	26	3.32 (6.34)		51.5 %	-0.23 [-0.72, 0.26]
Total (95% CI)	**69**		**64**			**100.0 %**	**-0.31 [-0.66, 0.04]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 1.74 (P = 0.083)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 2 Opioid positive (per urine drug screen, last week of treatment maintenance).

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 2 Opioid positive (per urine drug screen, last week of treatment maintenance)

Study or subgroup	BPN maintenance n/N	Taper/TAU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
D'Onofrio 2015	5/22	10/34		14.3 %	0.77 [0.30, 1.96]
Fiellin 2014	31/56	47/57		75.4 %	0.67 [0.52, 0.87]
Woody 2008	3/19	10/18		10.3 %	0.28 [0.09, 0.87]
Total (95% CI)	**97**	**109**		**100.0 %**	**0.63 [0.43, 0.91]**
Total events: 39 (BPN maintenance), 67 (Taper/TAU)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.42, df = 2 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 2.44 (P = 0.015)					
Test for subgroup differences: Not applicable					

Analysis 2.3. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 3 Self reported opioid use at treatment completion (past 30 days).

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 3 Self reported opioid use at treatment completion (past 30 days)

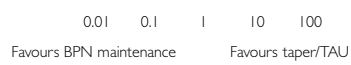
Study or subgroup	BPN maintenance n/N	Taper/TAU n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
D'Onofrio 2015	6/26	12/38		25.1 %	0.73 [0.31, 1.70]
Fiellin 2014	27/56	42/57		51.5 %	0.65 [0.48, 0.89]
Woody 2008	4/18	8/9		23.4 %	0.25 [0.10, 0.61]
Total (95% CI)	**100**	**104**		**100.0 %**	**0.54 [0.31, 0.93]**

Total events: 37 (BPN maintenance), 62 (Taper/TAU)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 4.18$, df = 2 (P = 0.12); $I^2 = 52\%$

Test for overall effect: Z = 2.22 (P = 0.026)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 4 Retention.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 4 Retention

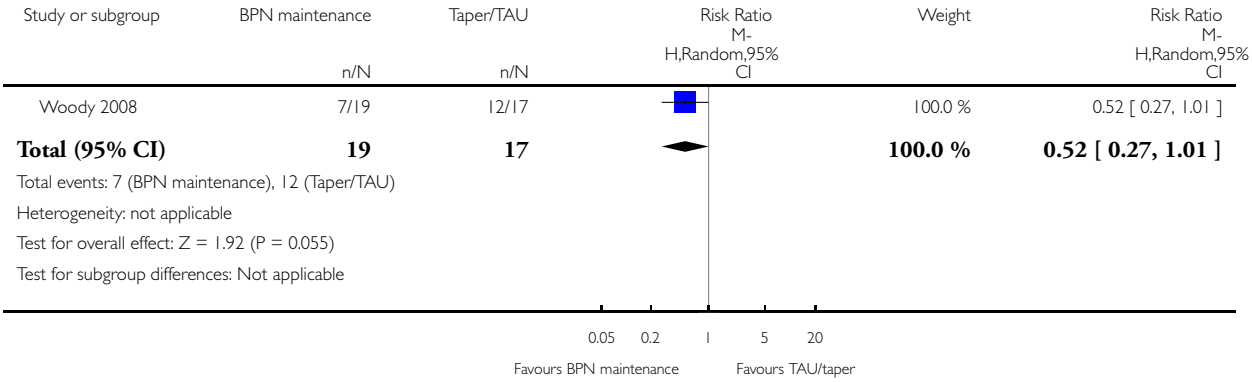
Study or subgroup	BPN maintanence n/N	Taper/TAU n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
D'Onofrio 2015	23/27	24/54		14.4 %	0.27 [0.10, 0.68]
Fiellin 2014	37/56	6/57		71.0 %	0.38 [0.26, 0.55]
Woody 2008	23/27	6/26		14.6 %	0.19 [0.08, 0.49]
Total (95% CI)	**110**	**137**		**100.0 %**	**0.33 [0.23, 0.47]**
Total events: 83 (BPN maintanence), 36 (Taper/TAU)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.17$, df = 2 (P = 0.34); $I^2 = 8\%$					
Test for overall effect: Z = 6.03 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 2.5. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 5 Pain (some to extreme pain or discomfort).

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 5 Pain (some to extreme pain or discomfort)

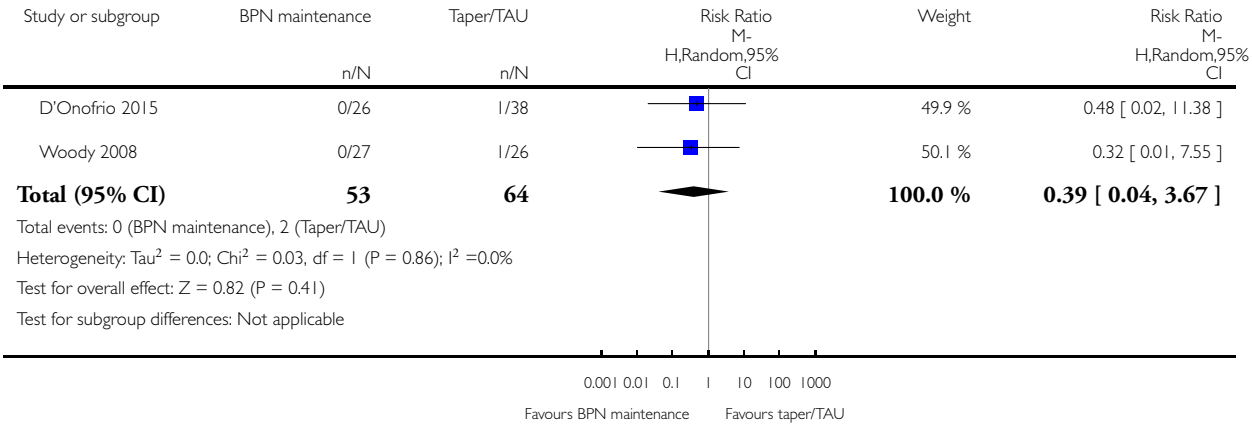


Analysis 2.6. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 6 Risk behaviours.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 6 Risk behaviours



Analysis 2.7. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 7 Adverse events.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 7 Adverse events

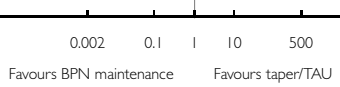
Study or subgroup	BPN maintenance n/N	Taper/TAU n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fiellin 2014	3/56	16/57		86.6 %	0.19 [0.06, 0.62]
Woody 2008	0/27	2/26		13.4 %	0.19 [0.01, 3.84]
Total (95% CI)	**83**	**83**		**100.0 %**	**0.19 [0.06, 0.57]**

Total events: 3 (BPN maintenance), 18 (Taper/TAU)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 2.96 (P = 0.0031)

Test for subgroup differences: Not applicable

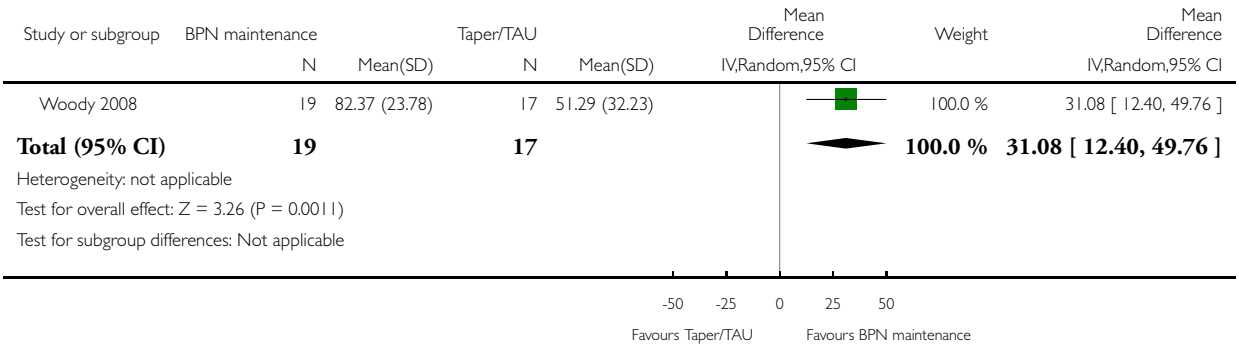


Analysis 2.8. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 8 Physical health.

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 8 Physical health

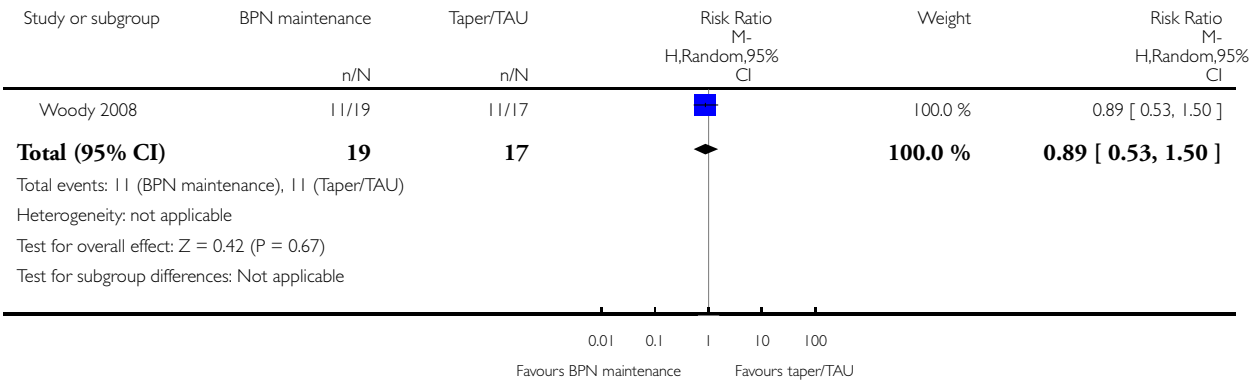


Analysis 2.9. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 9 Psychological health (moderate to extremely anxious or depressed).

Review: Opioid agonist treatment for pharmaceutical opioid dependent people

Comparison: 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment

Outcome: 9 Psychological health (moderate to extremely anxious or depressed)



APPENDICES

Appendix 1. Search strategies 2015

Cochrane Drugs and Alcohol Group (CDAG) Specialised Register of Trials

1 (((prescript* OR prescrib* OR pharmaceutical) NEAR (opioid* OR opiate*))) AND (INREGISTER)
2 (((opiate* OR opioid* OR morphin* OR morfin* OR narcot*) NEAR (abuse* OR abusing OR addict* OR misus* OR depend* OR disorder*)):TI:AB) AND (INREGISTER)
3 ((opiate* OR opioid*):XDI) AND (INREGISTER)
4 #2 AND #3
5 #1 AND #4
6 ((prescript* OR prescrib* OR pharmaceutical):XDI) AND (INREGISTER)
7 #5 OR #6

Cochrane Central Register of Controlled Trials (CENTRAL)

1. MESH DESCRIPTOR Opioid-Related Disorders EXPLODE ALL TREES
2. (((opiate* OR opioid* OR morphin* OR morfin* OR narcot*) NEAR (abuse* OR abusing OR addict* OR misus* OR depend* OR disorder*))):TI,AB,KY
3. #1 OR #2
4. (((opioid* OR opiat*) NEAR analges*)):TI,AB,KY
5. ((prescript* OR prescrib* OR pharmaceutical) NEAR (opioid* OR opiate*)):TI,AB,KY
6. MESH DESCRIPTOR Prescription Drugs EXPLODE ALL TREES
7. MESH DESCRIPTOR Narcotics
8. MESH DESCRIPTOR Analgesics, Opioid EXPLODE ALL TREES
9. #4 OR #5 OR #6 OR #7 OR
10. #3 AND #9

PubMed

1. "Opioid-Related Disorders"[MeSH]
2. ((opiate*[tiab] OR opioid*[tiab] OR morphin*[tiab] OR morfin*[tiab] OR narcot*[tiab]) AND (abuse*[tiab] OR abusing[tiab] OR addict*[tiab] OR misus*[tiab] OR depend*[tiab] OR disorder*[tiab]))
3. #1 OR #2
4. "Analgesics, Opioid"[MeSH]
5. "Narcotics"[MeSH]
6. ((opioid*[tiab] OR opiat*[tiab]) AND analges*[tiab])
7. "Prescription Drugs"[MeSH]
8. ((prescript*[tiab] OR prescrib*[tiab] OR pharmaceutical[tiab]) AND (opioid*[tiab] OR opiate*[tiab]))
9. #4 OR #5 OR #6 OR #7 OR #8
10. randomized controlled trial [pt]
11. controlled clinical trial [pt]
12. randomized [tiab]
13. placebo [tiab]
14. drug therapy [sh]
15. randomly [tiab]
16. trial [tiab]
17. groups [tiab]
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19. animals [mh] NOT humans [mh]
20. #18 NOT #19
21. #3 AND #9 AND #20

EMBASE

opiate addiction'/exp OR ((opiate* OR opioid* OR morphin* OR morfin* OR narcot*) NEAR/3 (abuse* OR abusing OR addict* OR misus* OR depend* OR disorder*)):ab,ti AND ('narcotic analgesic agent'/exp OR 'narcotic agent'/exp OR (analges* NEAR/6 (opioid* OR opiat*)):ab,ti OR 'prescription drug'/exp OR ((prescript* OR prescrib* OR pharmaceutical) NEAR/6 (opioid* OR opiate*)):ab,ti) AND ('crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'controlled clinical trial' OR

'clinical trial'/exp OR placebo:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR (cross:ab,ti AND over:ab,ti) OR 'randomized controlled trial'/exp)

CINAHL

S19 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18 TI placebo* or AB placebo*
S17 TI random* allocat* or AB random* allocat*
S16 MH "Random Assignment"
S15 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S14 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S13 TI clinic* N1 trial* or AB clinic* N1 trial*
S12 PT Clinical trial
S11 MH "Clinical Trials+"
S10 S3 AND S9
S9 S4 OR S5 OR S6 OR S7 OR S8
S8 TX (prescript* or prescrib* or pharmaceutical) N6 (opioid* or opiate*)
S7 (MH "Drugs, Prescription")
S6 TX (analges* N6 (opioid* or opiate*))
S5 MH "Analgesics, Opioid+"
S4 (MH "Narcotics+")
S3 S1 OR S2
S2 TX (opiate* or opioid* or morphin* or morfin* or narcot*) N6 (abuse* or abusing or addict* or misus* or depend* or disorder*)
S1 (MH "Substance Use Disorders+")

ISI Web of Science

7. #6 AND #2 AND #1
6. #5 OR #4 OR #3
5. TOPIC: ("prescription drugs")
4. TS=((prescript* or prescrib* or pharmaceutical) NEAR/3 (opioid* or opiate*))
3. TS=((opioid* or opiat*) near/2 analges*)
2. TS=(((opiate* or opioid* or morphin* or morfin* or narcot*) NEAR/6 (abuse* or abusing or addict* or misus* or depend*)))
1. TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

PsycINFO

1. exp Drug Dependency/ or exp Drug Abuse/ or exp Drug Withdrawal/ or exp Drug Addiction/
2. addiction/
3.((narcotic$ or opiate$ or opioid$ or morphin$) adj3 (misuse or abuse$ or addict$ or depend$)).ti,ab.
4. 1 or 2 or 3
5. ((opioid* or opiat*) adj3 analges*).ti,ab.
6. narcotic agonists/ or narcotic drugs/ or apomorphine/ or meperidine/ or methadone/ or tramadol/ or analgesic drugs/
7. exp Morphine/ or exp Analgesia/ or exp Analgesic Drugs/
8. prescription drugs/
9. ((prescript* or prescrib* or pharmaceutical) adj3 (opioid* or opiate*)).ti,ab.
10. or/5-9
11. 4 and 10
12. animals/ not (animals/ and human$.mp.)
13. (animal/ or animals/) not ((animal/ and human/) or (animals/ and humans/))
14 .(animal not (animal and human)).po.
15. random$.mp.
16. trial.mp.
17. groups.mp.
18. placebo.mp.
19. exp Clinical Trials/
20. or/15-19
21. 20 not (12 or 13 or 14)

22. 11 and 21

Appendix 2. Criteria for risk of bias assessment

Item	Judgement	Description
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding

(*Continued*)

	Unclear risk	Insufficient information to permit judgement of low or high risk
Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
Incomplete outcome data (attrition bias) For all outcomes except retention	Low risk	No missing outcome data Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough

(*Continued*)

		to have a clinically relevant impact on observed effect size Missing data have been imputed using appropriate methods All randomised participants are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop-out not reported for each group)
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported One or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not pre-specified One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk

CONTRIBUTIONS OF AUTHORS

Draft the protocol	SN, LD, NL, LG
Develop and run the search strategy	SN, BL, LD, CK
Obtain copies of studies	CK, BL, SN
Select which studies to include (2 people)	SN, BL
Extract data from studies (2 people)	SN, BL
Enter data into RevMan	SN
Carry out the analysis	SN
Interpret the analysis	SN, LD, NL, LG
Draft the final review	SN, LD, NL, LG
Update the review	SN, BL, LD, NL, LG

DECLARATIONS OF INTEREST

Suzanne Nielsen, Louisa Degenhardt, Briony Larance, and Nicholas Lintzeris have previously been investigators on research projects funded by untied educational grants from Reckitt Benckiser. That company has no role in the conception of, or decision to submit, this review. Suzanne Nielsen, Briony Larance, and Louisa Degenhardt are funded by National Health and Medical Research Council (NHMRC) fellowships. The NHMRC has no interest in the outcome of the review that could lead to a real or perceived conflict of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had originally intended to include any studies with pharmaceutical opioid dependent people in analyses if they could provide data for only those participants that were dependent on pharmaceutical opioids. On contacting authors, we became aware that some studies had only recruited very small numbers (e.g. two or three participants) of people who were dependent on pharmaceutical opioids, preventing meaningful analyses. For this reason, we added the criteria that at least 10 people must have been recruited who were dependent on pharmaceutical opioids to warrant re-analyses of the data for those people.

We did not produce funnel plots to examine risk of bias because of the small number of studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Prescription Drug Misuse; Analgesics, Opioid [therapeutic use]; Buprenorphine [*therapeutic use]; Methadone [*therapeutic use]; Narcotics [*therapeutic use]; Opiate Substitution Treatment [*methods]; Opioid-Related Disorders [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans