ClinicalEvidence

Opioid dependence

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ABSTRACT

INTRODUCTION: Dependence on opioids is a multifactorial condition involving genetic and psychosocial factors. There are three stages to treating opioid dependence. Stabilisation is usually by opioid substitution treatments, and aims to ensure that the drug use becomes independent of mental state (such as craving and mood) and independent of circumstances (such as finance and physical location). The next stage is to withdraw (detox) from opioids. The final stage is relapse prevention. This treatment process contributes to recovery of the individual, which also includes improved overall health and wellbeing, as well as engagement in society. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for stabilisation (maintenance) in people with opioid dependence? What are the effects of drug treatments for withdrawal in people with opioid dependence? What are the effects of drug treatments for relapse prevention in people with opioid dependence? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 26 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: buprenorphine; clonidine; lofexidine; methadone; naltrexone; and ultra-rapid withdrawal regimens.

QUESTIONS

INTERVENTIONS

Key points

- Dependence on opioids is a multifactorial condition involving genetic and psychosocial factors.
- There are three stages to treating opioid dependence.

  Stabilisation is usually by opioid substitution treatments, and aims to ensure that the drug use becomes independent of mental state (such as craving and mood) and independent of circumstances (such as finance and physical location).

  The next stage is to withdraw (detox) from opioids.

  The final stage is relapse prevention.
- Methadone and buprenorphine help to stabilise opioid use, as they decrease heroin use and help to retain people in treatment programmes.

  Methadone and buprenorphine seem equally effective at stabilising opioid use.
- Methadone, buprenorphine, and alpha$_2$-adrenoceptor agonists (lofexidine, clonidine) can all help people to withdraw from dependence on illicit opioids.

Lofexidine and clonidine may be less effective than methadone and buprenorphine in withdrawal, although evidence is weak.

Ultra-rapid withdrawal can help in detoxification, although there are important safety risks in keeping people heavily sedated or under general anaesthesia for a day, or under general anaesthesia for a few hours, and outcomes are no better.

- Naltrexone can help to prevent relapse of heroin use if combined with psychosocial treatment.

DEFINITION

Opioids (opiates) are highly addictive, and opioid dependence is a chronic relapsing disorder. Heroin is the most commonly abused opioid; others include morphine, buprenorphine, codeine, and methadone. Dependence is a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance takes on a much higher priority for a given individual than other behaviours that once had a greater value. [1] **Diagnosis:** Diagnosis of dependence syndrome is usually made from a combination of history and examination including urinalysis to corroborate the history, looking for the presence of opioid metabolites (e.g., morphine) in the urine. A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some stage during the previous year: 1) a strong desire or compulsion to take opioids; 2) difficulties in controlling substance-taking behaviour in terms of its onset, termination, and levels of use; 3) a physiological withdrawal state; 4) evidence of tolerance; 5) progressive neglect of alternative pleasures or interests because of opioid use; and 6) persisting with substance use despite clear evidence of overtly harmful consequences. [1] [2] Physical examination can also provide evidence of acute intoxication, withdrawal, and chronic or physical consequences of drug administration, such as abscesses, malnutrition, poor dentition, and DVT. When commencing treatment, urinalysis should confirm the use of opioids, and some practitioners require a number of samples be taken several days apart to confirm ongoing use. However, regular urinalysis might not be necessary with continuing treatment because studies report that, in situations where there is no coercion, self-reports of drug users are sufficiently reliable and valid to provide descriptions of drug use, drug-related problems, and the natural history of drug use. [3] Random sampling is, however, still useful. **Population:** All patients reported in this review were 16 years and older.

INCIDENCE/ PREVALENCE

Opioid use/intravenous drug use rose substantially in the 1990s. New notifications to the Addicts Index (a register held by the UK Home Office) by physicians of people dependent on opioids increased over 30-fold, from approximately 600 in 1966 to >18,000 in 1996, and nearly tripled during the 1990s. [4] The UK drug strategy reported 100,000 to 200,000 problem drug users in the mid-1990s. [5] A pilot study of national estimation methods suggested that there were 143,000 to 266,000 problem drug users, with about 75,000 to 150,000 opioid users in England and Wales in 1996. [6] More recently, the number of people becoming dependent on opioids in 2000 ranged from 13,000 (0.06/100 adults aged 15–44 years) to >26,000 (0.13/100 adults aged 15–44 years). [7] A reduction in the supply of heroin in Australia has also led to a halving in the prevalence of opioid abuse and dependence between the late 1990s and the present. [8] In 2008/9; a report from the National Drug Evidence centre estimated 262,428 problematic opiate users in England, suggesting a rate of 7.69 per 1000 population aged 15 to 64 years. [9]

AETIOLOGY/ RISK FACTORS

Opioid dependence is a multifactorial condition involving genetic and psychosocial factors. Studies in twins report that both the genetic and shared environmental effects on risk for use and misuse are usually entirely non-specific in their effects. Environmental experiences unique to the person largely determine whether predisposed individuals will use or misuse opioids. [10]

PROGNOSIS

Addictive disorders are chronic relapsing conditions with no known "cure". [11] Naturalistic studies have demonstrated that over a 5-year period, approximately half of individuals recover from the dependence. [12]

AIMS OF INTERVENTION

The main aims of intervention can be broadly divided into three main stages: 1) **stabilisation (maintenance)** treatment of opioid dependence; 2) treatments for **withdrawal (detoxification)** from opioids; and 3) **relapse prevention**. Stabilisation (maintenance) treatment aims to ensure that the drug use becomes independent of mental state (such as craving and mood) and circumstances (such as finance and physical location). Substitution treatment assists in this, but is not always necessary before undertaking treatments for withdrawal. Stabilisation is appropriate when the person with opioid addiction is unprepared for a life of abstinence, and where successful withdrawal is unrealistic; it also has the benefit of reducing harm from opioid use (reduces injecting, stabilises drug use and lifestyle, reduces criminal behaviour by avoiding the need to obtain expensive drugs, and reduces mortality). Withdrawal is not a primary goal in itself, and there is much more to detoxification than purely the physical withdrawal. Developing 'recovery capital' including personal and life skills, beliefs and desires around recovery, and supports and engagement in family and community are all important. It is much harder to stay off than to get off drugs; therefore, relapse

prevention is an important component of opioid dependence treatment and is also considered here, together with withdrawal.

OUTCOMES

Mortality: from treatment failure. **Opioid misuse**: self-reported heroin use; relapse rates; proportion of drug-free days; proportion of drug metabolite-free urine samples; rates of injection-risk behaviours. **Retention in treatment**: retention in the trial; withdrawal rates; treatment completion. **Criminality**: rates of criminal activity; general criminality, rates of sexual risk-taking behaviours. **Adverse effects**: mortality from treatment; other adverse effects of treatment. *In addition, for the question on treatments for withdrawal:* **Severity of withdrawal symptoms**: severity and incidence of withdrawal symptoms.

METHODS

Clinical Evidence search and appraisal March 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2011, Embase 1980 to March 2011, and The Cochrane Database of Systematic Reviews, February 2011 [online] (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs, RCTs, and controlled clinical trials in any language, including open studies and containing >10 individuals of whom >70% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs, RCTs, and controlled clinical trials where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs).We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 42). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug treatments for stabilisation (maintenance) in people with opioid dependence?**

OPTION BUPRENORPHINE FOR STABILISATION

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Buprenorphine helps to stabilise opioid use, as it decreases heroin use and helps to retain people in treatment programmes.
- Buprenorphine and methadone seem equally effective at stabilising opioid use.

Benefits and harms

Buprenorphine versus placebo:

We found two systematic reviews (search dates 2006 [13] and 2005 [14]) comparing buprenorphine versus placebo for maintenance treatment of opioid dependence. The reviews reported on different outcomes and the first systematic review performed a meta-analysis, which we report below. [13] The second review included RCTs and systematic reviews, but did not pool data from the RCTs identified or provide data from the trials. [14] The second review did not perform a meta-analysis, but reported that the systematic reviews it identified found that buprenorphine was more effective at retaining people in treatment, and at reducing opiate use, compared with placebo or no drug treatment.

Mortality

No data from the following reference on this outcome. [13]

Opioid misuse

Compared with placebo High-dose buprenorphine (16 mg) is more effective than placebo at reducing opioid misuse (assessed by urinalysis) at 2 to 52 weeks. However, we don't know whether low-dose buprenorphine (2–5 mg) is more effective than placebo at reducing opioid misuse (assessed by urinalysis) at 2 to 52 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Opioid misuse					
[13] Systematic review	487 people 2 RCTs in this analysis	**Morphine-positive urine samples , 2 to 52 weeks** with low-dose buprenorphine (2–5 mg) with placebo Absolute results not reported	SMD +0.10 95% CI –0.80 to +1.01 P = 0.83	⟷	Not significant
[13] Systematic review	463 people 2 RCTs in this analysis	**Morphine-positive urine samples , 2 to 52 weeks** with medium-dose buprenorphine (6–12 mg) with placebo Absolute results not reported	SMD –0.28 95% CI –0.47 to –0.10 P = 0.0029	○○○	buprenorphine
[13] Systematic review	620 people 3 RCTs in this analysis	**Morphine-positive urine samples , 2 to 52 weeks** with high-dose buprenorphine (16 mg) with placebo Absolute results not reported	SMD –1.23 95% CI –1.95 to –0.51 P = 0.00081	○○○	buprenorphine

Retention in treatment

Compared with placebo Buprenorphine is more effective than placebo at increasing the proportion of people retained in treatment at 2 to 52 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[13] Systematic review	1131 people 5 RCTs in this analysis	**Proportion of people retained in treatment , 2 to 52 weeks** 340/564 (60%) with low-dose buprenorphine (2–4 mg) 224/567 (40%) with placebo	RR 1.50 95% CI 1.19 to 1.88 P = 0.00054	●○○	buprenorphine
[13] Systematic review	887 people 4 RCTs in this analysis	**Proportion of people retained in treatment , 2 to 52 weeks** 281/430 (65%) with medium-dose buprenorphine (6–12 mg) 172/457 (38%) with placebo	RR 1.74 95% CI 1.06 to 2.87 P = 0.030	●○○	buprenorphine
[13] Systematic review	728 people 4 RCTs in this analysis	**Proportion of people retained in treatment , 2 to 52 weeks** 227/362 (63%) with high-dose buprenorphine (16 mg)	RR 1.74 95% CI 1.02 to 2.96 P = 0.042	●○○	buprenorphine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		150/366 (41%) with placebo			

Criminality

No data from the following reference on this outcome. [13]

Adverse effects

No data from the following reference on this outcome. [13]

Frequency of buprenorphine:
We found one RCT. [15]

Mortality

No data from the following reference on this outcome. [15]

Opioid misuse

Different dose frequencies compared with each other We don't know whether buprenorphine taken three times weekly is more effective than buprenorphine taken daily at reducing the proportion of people with opioid-positive urine tests (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Opioid misuse					
[15] RCT	92 people	**Proportion of people with opioid-positive urine tests** 57% with daily buprenorphine (16 mg/70 kg) 58% with 3 times-weekly buprenorphine (34 mg/70 kg twice weekly plus 44 mg/70 kg once weekly) Absolute numbers not reported	P = 0.84	⟷	Not significant

Retention in treatment

Different dose frequencies compared with each other We don't know whether buprenorphine taken three times weekly is more effective than buprenorphine taken daily at increasing the average length of time retained in treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[15] RCT	92 people	**Average length of time of retention in treatment**	P = 0.64	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		11.2 weeks with daily buprenorphine (16 mg/70 kg) 11.0 weeks with 3 times-weekly buprenorphine (34 mg/70 kg twice weekly plus 44 mg/70 kg once weekly)			

Criminality

No data from the following reference on this outcome. [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	92 people	**Adverse effects** with daily buprenorphine (16 mg/70 kg) with 3 times-weekly buprenorphine (34 mg/70 kg twice weekly plus 44 mg/70 kg once weekly) The RCT reported that "there were no reports of serious adverse effects of buprenorphine among patients in either treatment group"		⟷	Not significant

Dose of buprenorphine:

We found one systematic review (search date 2005), which searched for systematic reviews and RCTs from 2001 to 2005, and identified 9 systematic reviews comparing different doses of buprenorphine versus each other. [14] The review did not perform a meta-analysis, but reported that the systematic reviews found that higher doses of buprenorphine were more effective than lower doses at increasing the proportion of people retained in treatment. [14]

Buprenorphine versus methadone:

See option on buprenorphine versus methadone for stabilisation, p 11 .

Further information on studies

[13] In this review the placebo group consisted of buprenorphine doses of either 0 mg or 1 mg.

Comment: One cohort study found that people were retained in treatment for significantly longer with buprenorphine (16 mg/day) than with placebo (106 people; mean days of participation: 42 days

with buprenorphine *v* 14 days with placebo; P <0.001). [16] It also found that self-reported heroin use decreased significantly more with buprenorphine than with placebo at 12 weeks (measured on a 0–10 visual analogue scale, where 0 = drug-free, 10 = daily heavy drug use: –3.21 with buprenorphine *v* +0.52 with placebo; P <0.001). Quality of life and life satisfaction also significantly improved with buprenorphine compared with placebo (quality of life: P <0.01; life satisfaction: P <0.05). The cohort study found that significantly fewer people had exanthema with buprenorphine than with placebo (P <0.05). [16] It also reported that "no serious adverse effects were observed".

We found one RCT that compared buprenorphine implant (80 mg per implant) versus placebo. [17] The study reported that the buprenorphine implant group had significantly more urine samples that were negative for illicit opioids during weeks 1 to 16 compared with the placebo group (P = 0.04). In this study, 71/108 (66%) people who received buprenorphine implants completed the study compared with 17/55 (31%) who received placebo implants (P <0.001). There was no statistically significant difference in treatment-emergent adverse events between the two groups. Minor implant site reactions were the most common adverse event. [17]

Clinical guide:
NICE recommends flexible dosing regimens of methadone and buprenorphine as part of a programme of supportive care. They advise that administration of the drug should be on a daily basis under supervision for at least the first 3 months, and when compliance is assured, daily administration can be relaxed. The UK 'Orange Guidelines' from the Department of Health state that the clinical need for supervision should be reviewed regularly, and may be relaxed following assessment of the patient's compliance and individual circumstances, and may be as little as 2 weeks in highly compliant patients. [18] The decision about which drug to use for maintenance therapy should be made on a case-by-case basis and, if both drugs are considered equally suitable, they recommend methadone as first choice. [19] However, some people might have a preference for one drug over the other, which can influence compliance and retention in treatment. For people at the lower range of dependence who are planning on becoming abstinent, buprenorphine can provide greater flexibility and enable earlier detoxification compared with methadone. It is an additional treatment option for people dependent on heroin, especially those who do not wish to start or continue with methadone, or for those who do not seem to benefit from adequate dosages of methadone (Praveen KT, Law F, Melichar J, O'Shea J, personal observation). Buprenorphine can be a good alternative to methadone in people with less chaotic lives, and in those who wish to stabilise for a short period before heading on to detoxification. Pharmacologically, buprenorphine differs from methadone. Buprenorphine is a partial opioid agonist, and has a high affinity for opioid receptors: this reduces the impact of additional illicit heroin/opioid use by preventing illicit opioids from occupying these receptors — the higher the buprenorphine dose used, the less of a subjective 'high' experienced from 'on-top' heroin use by the individual. Therefore, buprenorphine might be better suited to people who wish to stop using illicit heroin completely. Buprenorphine has a high affinity for opioid receptors and also has a prolonged duration of action at higher doses, which does not correlate with its plasma concentration. This permits alternate-day or even three times-weekly dispensing regimens with only minimal withdrawal symptoms on the intervening days at higher buprenorphine doses.

OPTION METHADONE FOR STABILISATION

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Methadone helps to stabilise opioid use, as it decreases heroin use and helps to retain people in treatment programmes.
- Methadone and buprenorphine seem equally effective at stabilising opioid use.

Benefits and harms

Methadone versus no opioid replacement therapy:

We found three systematic reviews [20] [14] [21] and one subsequent RCT [22] comparing methadone versus no opioid replacement therapy or placebo. The reviews reported on different outcomes and comparisons. The first systematic review (search date 2008, 11 RCTs, 1969 people) [20] performed a meta-analysis and is reported in full. The second review (search date 2005) [14] identified 12 systematic reviews. This review did not perform a meta-analysis, but reported that the systematic reviews found that methadone was more effective at increasing retention in treatment and at reducing self-reported opioid use compared with placebo or no drug treatment. The third systematic review (search date 2004, 8 RCTs) [21] has been superseded by the first review, [20] so will not be reported further here.

Mortality

Compared with no opioid replacement therapy We don't know whether methadone maintenance treatment is more effective than no methadone maintenance treatment at reducing mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[20] Systematic review	576 people 4 RCTs in this analysis	**Mortality** 3/287 (1%) with methadone maintenance treatment 8/289 (3%) with no methadone maintenance treatment	RR 0.48 95% CI 0.10 to 2.39 P = 0.37	⟷	Not significant

No data from the following reference on this outcome. [22]

Opioid misuse

Compared with no opioid replacement therapy Methadone is more effective than control at reducing opioid misuse (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Opioid misuse					
[20] Systematic review	1129 people 6 RCTs in this analysis	**Morphine-positive urine samples** 218/615 (35%) with methadone 342/514 (67%) with control	RR 0.66 95% CI 0.56 to 0.78 P <0.00001	●●○	methadone

No data from the following reference on this outcome. [22]

Retention in treatment

Compared with no opioid replacement therapy Methadone seems more effective than control at increasing the proportion of people retained in treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[20] Systematic review	505 people 3 RCTs in this analysis The RCTs included in this analysis predate the year 2000	**Proportion of people retained in treatment** 173/254 (68%) with methadone 63/251 (25%) with control Methadone dose slightly higher than used in some countries Control group consisted of placebo, withdrawal, or detoxification, drug-free rehabilitation treatment, and no treatment or waiting list controls The interventions in this study generally lasted from several weeks to 2 years	RR 3.05 95% CI 1.75 to 5.35 Significant heterogeneity was found between RCTs (P = 0.02)	●●○	methadone
[20] Systematic review	750 people 4 RCTs in this analysis The RCTs in this analysis were done after 2000	**Proportion of people retained in treatment** 318/433 (73%) with methadone 52/317 (16%) with control	RR 4.44 95% CI 3.26 to 6.04 P <0.00001	●●○	methadone

No data from the following reference on this outcome. [22]

Criminality

Compared with no opioid replacement therapy We don't know whether methadone is more effective than control at reducing criminality (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Criminality					
[20] Systematic review	363 people 3 RCTs in this analysis	**Criminal activity** 5/178 (3%) with methadone 18/185 (10%) with control	RR 0.39 95% CI 0.12 to 1.25 P = 0.11	⟷	Not significant
[22] RCT	319 people	**Mean number of arrests , 6 months** 0.20 with interim methadone 0.34 with control	P = 0.02	○○○	interim methadone
[22] RCT	319 people	**Mean number of arrests , 12 months** 0.33 with interim methadone 0.39 with control	P = 0.16	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [20] [22]

Higher- versus lower-dose methadone:

We found three systematic reviews (search dates 2001 [23] and 2005 [14] [24]). The first systematic review included 21 trials, 10 of which were prospective controlled trials, and 11 RCTs (2279 people); the RCT data are reported in full below. [23] The second systematic review identified 9 systematic reviews. [14] It did not perform a meta-analysis or report data from any identified studies, but reported that the systematic reviews found that higher doses of methadone increased the proportion of people retained in treatment and reduced heroin abstinence rates (self-reported heroin use and urine-confirmed opioid abstinence). The third review included 24 articles, of which 12 were randomised, controlled, or double-blind clinical trials. The review did not perform a meta-analysis but reported a consensus of methadone dosing in the range of 60 mg to 100 mg daily to improve the proportion of people retained in treatment. [24]

Mortality

No data from the following reference on this outcome. [23]

Opioid misuse

Higher-dose methadone compared with lower-dose methadone Higher-dose methadone (60–109 mg/day) may be more effective than lower-dose methadone (1–39 mg/day) at increasing heroin abstinence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heroin use					
[23] Systematic review	237 people 3 RCTs in this analysis	**Heroin abstinence (method of determining abstinence unclear) , time of assessment unclear** with higher-dose (60–109 mg/day) methadone with lower-dose (1–39 mg/day) methadone See further information on studies	RR 1.59 95% CI 1.16 to 2.18	●○○	higher-dose methadone

Retention in treatment

Higher-dose methadone compared with lower-dose methadone Higher-dose methadone (60–109 mg/day) may be more effective than lower-dose methadone (1–39 mg/day) at increasing the proportion of people retained in treatment at 3 to 26 weeks, but we don't know whether it is more effective at 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[23] Systematic review	496 people 5 RCTs in this analysis	**Treatment retention rates , 3 to 26 weeks** with higher-dose (60–109 mg/day) methadone with lower-dose (1–39 mg/day) methadone See further information on studies	RR 1.36 95% CI 1.13 to 1.63	●○○	higher-dose methadone
[23] Systematic review	75 people Data from 1 RCT	**Treatment retention rates , 52 weeks** with higher-dose (60–109 mg/day) methadone with lower-dose (1–39 mg/day) methadone See further information on studies	RR 1.62 95% CI 0.95 to 2.77	⟷	Not significant

Criminality

No data from the following reference on this outcome. [23]

Adverse effects

No data from the following reference on this outcome. [23]

Methadone versus buprenorphine:

See option on buprenorphine versus methadone for stabilisation, p 11 .

Further information on studies

[23] **Higher- versus lower-dose methadone:** Two RCTs included in the review reported that heroin use was lower by two uses weekly with higher-dose rather than lower-dose methadone (no further data reported). Retention rates ranged from 20% with lower-dose methadone to 71% with higher-dose methadone. The review found no significant difference in adverse effects between higher- and lower-dose methadone (1 RCT, 110 people; no further data or adverse effects reported).

Comment:

One large cohort study found that acquisitive crime was reduced by 23% of initial levels at 4 to 5 years of following a methadone maintenance programme. [25]

Adverse effects:

In general, most studies did not report on adverse effects. Instead, most looked at harm-reduction issues, such as the concurrent use of cocaine, and mortality. We found one RCT (164 people) comparing the safety and adverse-effect profiles of buprenorphine (84 people) and methadone (80 people) in the maintenance treatment of opioid dependence in an outpatient setting over 16 weeks. [26] Outcomes measured included liver function tests, vital signs (blood pressure, heart rate, temperature, or respiratory rate), and self-reported adverse effects. The RCT found that both buprenorphine and methadone had similar safety profiles, and found no significant difference in adverse effects between the two drugs (reported as not significant for liver function tests, vital signs, and self-reported adverse effects; data tabulated in original paper for all 3 outcomes). [26]

Clinical guide:

NICE recommends flexible dosing regimens of methadone and buprenorphine as part of a programme of supportive care. They advise that administration of the drug should be on a daily basis under supervision for at least the first 3 months, and when compliance is assured, daily administration can be relaxed (see comment on buprenorphine for stabilisation, p 3). The UK 'Orange Guidelines' from the Department of Health state that the clinical need for supervision should be reviewed regularly, and may be relaxed following assessment of the patient's compliance and individual circumstances, and may be as little as 2 weeks in highly compliant patients. [18] Because the half-life of methadone is on average 26 hours, daily dosing is necessary, and supervised consumption is recommended. The half-life of methadone does, however, depend on many factors, and may rarely be as short as 12 hours in some individuals ('rapid metabolisers') or as long as 36 hours or more. To find the optimum dosage for individuals, clinical judgement is required. Induction to methadone should be in a stepwise fashion, and people should be assessed regularly, along with urinalysis if indicated, for detection of continued opioid use. Methadone is a full opioid agonist, and therefore has potential to produce and/or maintain dependence. Patients typically experience withdrawal symptoms if they miss a dose, and detoxification can be a lengthy process by gradual reductions of 2 mg to 5 mg every 1 to 2 weeks. Rapid detoxification from methadone is now the preferred technique, because a slow detoxification is associated with an increased relapse rate. Rapid detoxification techniques include alpha$_2$-adrenergic agonists such as lofexidine and clonidine (see option on lofexidine/clonidine for withdrawal, p 26), or converting from lower-dose methadone (20–40 mg) to buprenorphine for the final 2 weeks or so of the detoxification. Although it is accepted by most clinicians that withdrawal severity is reduced using this technique, there has been minimal research in this area. Unlike buprenorphine, there is also no ceiling to the level of respiratory depression or sedation that methadone can induce, and methadone overdose is therefore potentially fatal. The inconvenience of daily dosing on patient lifestyle and the potential disruption to employment from attending a pharmacy daily should also be noted, along with the fact that take-away dosing results in the problem of diversion of the drug for illicit use by those not in treatment.

OPTION BUPRENORPHINE VERSUS METHADONE FOR STABILISATION

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Methadone and buprenorphine seem equally effective at stabilising opioid use.

Benefits and harms

Buprenorphine versus methadone for stabilisation:

We found three systematic reviews (search dates 2002, [27] 2005, [14] and 2006 [13]) and 4 subsequent RCTs [28] [29] [30] [31] comparing buprenorphine versus methadone. The first systematic review (14 RCTs, number of people not reported) [27] was also identified by the second systematic review. [14] The first review did not perform a meta-analysis but reported that "low-dose methadone (20 mg/day) is less effective than buprenorphine (2–8 mg/day), and

that higher doses of methadone (50–65 mg/day or more) are slightly more effective than buprenorphine (2–8 mg/day)". [27] As this review did not include a meta-analysis, we have not reported it further.

Mortality

Buprenorphine compared with methadone We don't know whether buprenorphine is more effective at reducing longitudinal mortality in heroin-dependent people (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[28] RCT	405 heroin-dependent people aged at least 18 years	**Mortality , 10 years** 16/200 (8%) with buprenorphine 14/205 (7%) with methadone This was a 10-year follow-up study	Mortality of 8.84 deaths per 1000 person-years of follow-up Reported as not significant	⟷	Not significant

No data from the following reference on this outcome. [13] [14] [29] [30] [31]

Opioid misuse

Buprenorphine compared with methadone Buprenorphine and methadone may be equally effective at reducing opioid misuse as measured by urinalysis or self-reported heroin use (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Morphine-positive urine samples					
[13] Systematic review	837 people 6 RCTs in this analysis	**Morphine-positive urine samples** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	SMD –0.12 95% CI –0.26 to +0.02 P = 0.083	⟷	Not significant
[13] Systematic review	59 people Data from 1 RCT	**Morphine-positive urine samples** with low-dose buprenorphine with low-dose methadone Absolute results not reported	SMD –0.35 95% CI –0.87 to +0.16 P = 0.18	⟷	Not significant
[13] Systematic review	57 people Data from 1 RCT	**Morphine-positive urine samples** with low-dose buprenorphine with medium-dose methadone Absolute results not reported	SMD 0.88 95% CI 0.33 to 1.42 P = 0.0016	○○○	medium-dose methadone
[13] Systematic review	317 people 3 RCTs in this analysis	**Morphine-positive urine samples** with medium-dose buprenorphine with low-dose methadone Absolute results not reported	SMD –0.23 95% CI –0.45 to –0.01 P = 0.04 Significant heterogeneity between trials: P = 0.04	○○○	medium-dose buprenorphine
[13] Systematic review	314 people 3 RCTs in this analysis	**Morphine-positive urine samples** with medium-dose buprenorphine with medium-dose methadone Absolute results not reported	SMD 0.27 95% CI 0.05 to 0.50 P = 0.017 Significant heterogeneity between trials: P = 0.01	○○○	medium-dose methadone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT	361 people	**Morphine-positive urine samples , 6 months** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	OR 2.13 95% CI 1.50 to 3.02 P = 0.000	●●○	flexible-dose buprenorphine
[30] RCT	140 people	**Morphine-positive urine samples , 6 months** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
Self-reported heroin use					
[13] Systematic review	420 people 3 RCTs in this analysis	**Self-reported heroin use** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	SMD –0.12 95% CI –0.31 to +0.07 P = 0.22	⟷	Not significant
[13] Systematic review	48 people Data from 1 RCT	**Self-reported heroin use** with low-dose buprenorphine with low-dose methadone Absolute results not reported	SMD –0.45 95% CI –0.12 to +1.03 P = 0.12	⟷	Not significant
[13] Systematic review	46 people Data from 1 RCT	**Self-reported heroin use** with low-dose buprenorphine with medium-dose methadone Absolute results not reported	SMD +0.10 95% CI –0.48 to +0.68 P = 0.73	⟷	Not significant
[13] Systematic review	40 people Data from 1 RCT	**Self-reported heroin use** with medium-dose buprenorphine with medium-dose methadone Absolute results not reported	SMD –0.27 95% CI –0.90 to +0.35 P = 0.39	⟷	Not significant
[31] RCT	116 people	**Mean days of self-reported heroin use , 3 months** 13.7 days with flexible-dose buprenorphine 14.4 days with flexible-dose methadone	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [14] [28]

Retention in treatment

Buprenorphine compared with methadone Methadone may be more effective at increasing the proportion of people retained in treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[13] Systematic review	253 people 3 RCTs in this analysis	**Retention in treatment** 54/142 (38%) with low-dose buprenorphine 62/111 (56%) with low-dose methadone	RR 0.67 95% CI 0.52 to 0.87 P = 0.0027	●○○	low-dose methadone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[13] Systematic review	305 people 3 RCTs in this analysis	**Retention in treatment** 75/169 (44%) with low-dose buprenorphine 96/136 (71%) with medium-dose methadone	RR 0.67 95% CI 0.55 to 0.81 P = 0.000027	●○○	medium-dose methadone
[13] Systematic review	1068 people 8 RCTs in this analysis	**Retention in treatment** 281/531 (53%) with flexible-dose buprenorphine 340/537 (63%) with flexible-dose methadone	RR 0.85 95% CI 0.73 to 0.98 P = 0.027 Significant heterogeneity between trials: P = 0.03	●○○	flexible-dose methadone
[14] Systematic review	976 opiate-dependent people 7 RCTs in this analysis	**Retention in treatment** 310/492 (63%) with flexible-dose methadone 255/484 (53%) with flexible-dose buprenorphine	RR 1.20 95% CI 1.07 to 1.33	●○○	flexible-dose methadone
[29] RCT	361 people	**Retention in treatment or detox , 6 months** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	OR 0.34 95% CI 0.20 to 0.59 P <0.001	●●○	flexible-dose methadone
[30] RCT	140 people	**Completed treatment , 6 months** 55% with flexible-dose buprenorphine 48% with flexible-dose methadone Absolute numbers not reported	P = 0.42	⟷	Not significant

No data from the following reference on this outcome. [28] [31]

Criminality

Buprenorphine compared with methadone Buprenorphine and methadone seem equally effective at reducing criminal activity (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Criminality					
[13] Systematic review	212 people Data from 1 RCT	**Self-reported criminal activity** with flexible-dose buprenorphine with flexible-dose methadone Absolute results not reported	SMD –0.14 95% CI –0.41 to +0.14	⟷	Not significant
[31] RCT	113 people	**Mean self-reported arrest , 3 months** 0.69 with flexible-dose buprenorphine 0.71 with flexible-dose methadone	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [14] [28] [29] [30]

Adverse effects

No data from the following reference on this outcome. [13] [14] [28] [29] [30] [31]

Further information on studies

[13] The review divided doses into treatment groups in the following way: in the case of methadone doses between 20 mg and 35 mg were classified as low dose, between 50 mg and 80 mg as medium dose, and 120 mg or more as high dose. In the case of buprenorphine studies where methadone was the comparator, doses of buprenorphine between 2 mg and 6 mg were classified as low dose, between 7 mg and 15 mg as medium dose, and 16 mg as high dose. For the comparison of high-dose buprenorphine versus low-dose methadone, the review reported significant heterogeneity between RCTs for retention data, so did not report a meta-analysis for this outcome.

[14] This review reported the same meta-analysis for morphine-positive samples as the first systematic review. [13] The review did not identify any additional RCTs for this comparison. [14]

Comment: See comments under buprenorphine, p 3 and methadone, p 7 for stabilisation.

Clinical guide:
NICE recommends flexible-dose regimens of methadone and buprenorphine as part of a programme of supportive care. They advise that administration of the drug should be on a daily basis under supervision for at least the first 3 months, and when compliance is assured, daily administration can be relaxed [19] (see comments on buprenorphine, p 3 and methadone, p 7 for stabilisation).

QUESTION What are the effects of drug treatments for withdrawal in people with opioid dependence?

OPTION BUPRENORPHINE FOR WITHDRAWAL

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Buprenorphine can help people to withdraw from dependence on illicit opioids.
- Lofexidine and clonidine may be less effective than buprenorphine in withdrawal, although evidence is weak.
- We found no direct information from RCTs about whether buprenorphine is better than no active treatment for people withdrawing from opioids.

Benefits and harms

Buprenorphine versus placebo:

We found no systematic review or RCTs.

Buprenorphine versus methadone:

We found two systematic reviews comparing buprenorphine versus methadone for the management of opioid withdrawal. [32] [33] The first review (search date 2006, 23 RCTs, 2112 people) [32] included slightly different evidence from the second review (search date 2008, 22 RCTs, 1736 people), [33] so both are reported here.

Mortality

No data from the following reference on this outcome. [32] [33]

Opioid misuse

No data from the following reference on this outcome. [32] [33]

Retention in treatment

Buprenorphine compared with methadone Buprenorphine and methadone are equally effective at increasing the proportion of people who complete treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people completing treatment					
[33] Systematic review	168 people 4 RCTs in this analysis	**Proportion completing treatment** 52/85 (61%) with buprenorphine 43/83 (52%) with methadone	RR 1.18 95% CI 0.93 to 1.49 P = 0.18	⟷	Not significant
[32] Systematic review	96 people 3 RCTs in this analysis	**Completion of treatment** 31/54 (57%) with buprenorphine 30/42 (71%) with methadone	OR 0.92 95% CI 0.03 to 29.30	⟷	Not significant

Criminality

No data from the following reference on this outcome. [32] [33]

Severity of withdrawal symptoms

Buprenorphine compared with methadone Buprenorphine is more effective at improving the mean peak score for severity of withdrawal (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal scores					
[33] Systematic review	432 people 4 RCTs in this analysis	**Mean peak withdrawal score** with buprenorphine with methadone	SMD –0.45 95% CI –0.64 to –0.25 P <0.00001	○○○	buprenorphine

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] Systematic review	3 RCTs in this analysis	**Adverse events** with buprenorphine with methadone 1 RCT in the review found "no severe adverse effects in either			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		buprenorphine or methadone groups". The other RCTs gave no information about adverse effects			

No data from the following reference on this outcome. [32]

Buprenorphine versus clonidine:

We found two systematic reviews comparing buprenorphine versus clonidine for the management of opioid withdrawal. [32] [33] The first review (search date 2006, 23 RCTs, 2112 people) [32] included slightly different evidence from the second review (search date 2008, 22 RCTs, 1736 people), [33] so both are reported here.

Mortality

No data from the following reference on this outcome. [32] [33]

Opioid misuse

No data from the following reference on this outcome. [32] [33]

Retention in treatment

Buprenorphine compared with clonidine Buprenorphine is more effective than clonidine at increasing the length of time people stay in outpatient treatment and at increasing the proportion of people who complete treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[33] Systematic review	725 people 6 RCTs in this analysis	**Proportion of people who completed outpatient treatment** 233/406 (57%) with buprenorphine 137/319 (43%) with clonidine	RR 1.45 95% CI 1.12 to 1.88 P = 0.005	●○○	buprenorphine
[33] Systematic review	481 people 5 RCTs in this analysis	**Proportion of people who completed inpatient treatment** 208/260 (80%) with buprenorphine 94/221 (43%) with clonidine	RR 1.93 95% CI 1.27 to 2.92 P = 0.002	●○○	buprenorphine
[32] Systematic review	829 people 8 RCTs in this analysis	**Proportion of people who completed treatment** 344/424 (81%) with buprenorphine 169/405 (42%) with clonidine	OR 2.22 95% CI 1.10 to 4.26	●●○	buprenorphine

Criminality

No data from the following reference on this outcome. [32] [33]

Severity of withdrawal symptoms

Buprenorphine compared with clonidine Buprenorphine seems more effective than clonidine at reducing withdrawal scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal scores					
[33] Systematic review	432 people 4 RCTs in this analysis	**Mean peak withdrawal scores** with buprenorphine with clonidine	SMD –0.45 95% CI –0.64 to –0.25 P <0.00001	○○○	buprenorphine
[33] Systematic review	425 people 2 RCTs in this analysis	**Mean overall withdrawal scores** with buprenorphine with clonidine	SMD –0.59 95% CI –0.79 to –0.39 P <0.00001	○○○	buprenorphine

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] Systematic review	113 people Data from 1 RCT	**Number of people with adverse effects as inpatients** 4/77 (5%) with buprenorphine 4/36 (11%) with clonidine	RR 0.47 95% CI 0.12 to 1.76 P = 0.26	⟷	Not significant
[33] Systematic review	345 people 2 RCTs in this analysis	**Number of people with an adverse effect as outpatients** 26/215 (12%) with buprenorphine 47/130 (36%) with clonidine	RR 1.20 95% CI 0.81 to 1.30 P = 0.86	⟷	Not significant

No data from the following reference on this outcome. [32]

Buprenorphine versus lofexidine:

See option on lofexidine/clonidine for withdrawal, p 26 .

Buprenorphine versus oxazepam:

We found one systematic review (search date 2008, 22 studies, 1736 people) comparing buprenorphine versus oxazepam for the management of opioid withdrawal. [33]

Mortality

No data from the following reference on this outcome. [33]

Opioid misuse

No data from the following reference on this outcome. [33]

Retention in treatment

Buprenorphine compared with oxazepam We don't know how buprenorphine and oxazepam compare at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people who completed treatment					
[33] Systematic review	27 people Data from 1 RCT	**Proportion of people who completed treatment** 11/15 (73%) with buprenorphine 7/12 (58%) with oxazepam	Reported as not significant P value not reported	⟷	Not significant

Criminality

No data from the following reference on this outcome. [33]

Severity of withdrawal symptoms

Buprenorphine compared with oxazepam Buprenorphine may be more effective than oxazepam at reducing withdrawal severity scores (timeframe unclear). However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal severity					
[33] Systematic review	Number of people unclear Data from 1 RCT	**Withdrawal severity (measured by Short Opiate Withdrawal Scale)** with buprenorphine with oxazepam	Reported as withdrawal severity significantly lower with buprenorphine compared with oxazepam No further data reported	○○○	buprenorphine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] Systematic review	Data from 1 RCT	**Adverse events** with buprenorphine with oxazepam Absolute results not reported 1 RCT in the review reported "no severe adverse effects in either group and no significant differences in blood pressure or heart rate"			

Different rates of buprenorphine dose reduction:

The systematic review reported three RCTs of different rates of buprenorphine dose reduction, but did not report a meta-analysis; see further information on studies. [33] We also identified one additional RCT (516 people), which compared the effects of a short (7-day) or long (28-day) taper schedule of buprenorphine withdrawal, after stabilisation. [34]

Opioid misuse

Compared with 28-day taper buprenorphine Seven-day taper buprenorphine is more effective at increasing the proportion of people with urine samples free of illicit opiates at the end of taper; however, 7-day and 28-day taper buprenorphine are equally effective at 1 and 3 months of follow-up (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Opioid misuse					
[34] RCT	516 people	**Urine sample free of illicit opiates , end of taper** 113/255 (44%) with 7-day taper buprenorphine 78/261 (30%) with 28-day taper buprenorphine	P = 0.0007	○○○	7-day taper buprenorphine
[34] RCT	516 people	**Urine sample free of illicit opiates , 1 month** 45/255 (17.6%) with 7-day taper buprenorphine 46/261 (17.6%) with 28-day taper buprenorphine	P = 0.99	⟷	Not significant
[34] RCT	516 people	**Urine sample free of illicit opiates , 3 months** 31/255 (12%) with 7-day taper buprenorphine 35/261 (13%) with 28-day taper buprenorphine	P = 0.67	⟷	Not significant

No data from the following reference on this outcome. [33]

Mortality

No data from the following reference on this outcome. [33] [34]

Retention in treatment

No data from the following reference on this outcome. [33] [34]

Criminality

No data from the following reference on this outcome. [33] [34]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [33] [34]

Adverse effects

No data from the following reference on this outcome. [33] [34]

Further information on studies

[33] **Different rates of buprenorphine dose reduction:** One RCT found that participant-rated withdrawal severity was significantly worse with rapid-tapered compared with gradual-tapered buprenorphine. Another RCT found that people stayed in withdrawal for a similar length of time with rapid-tapered and gradual-tapered buprenorphine. The review reported that one RCT gave no information about adverse effects, a second RCT reported no adverse effects associated with buprenorphine, and a third RCT found no significant difference in adverse effects between different doses of buprenorphine.

Comment:

Frequency of buprenorphine: We found one further crossover RCT, which gave 16 people single doses of buprenorphine, a double dose every 48 hours, or a triple dose every 72 hours, in random order. [35] It found no significant difference between groups in withdrawal effects at 24 hours, and it found no significant difference between double dose compared with triple dose after 48 hours (results and significance assessment between groups not reported). It reported no discontinuation in any treatment arm due to adverse effects of treatment.

Clinical guide:

The authors of the systematic review also concluded that even low doses of buprenorphine (1–2 mg/day) are more effective than clonidine in ameliorating the signs and symptoms of opioid withdrawal. [33] However, higher doses (6–8 mg/day) seem necessary at the outset of withdrawal to achieve patient comfort and to suppress illicit opioid use. The partial agonist buprenorphine has been shown to be an effective withdrawal medication in patients with opioid dependency. Research activity has primarily focused on the use of buprenorphine as a maintenance pharmacotherapy, but there is growing interest in the use of buprenorphine for short periods of time in managing withdrawal from opioids. This is because it has morphine-like effects, and so will reduce the symptoms of opioid withdrawal. Additionally, because it is a long-acting partial agonist, when it is itself withdrawn, it will produce limited withdrawal symptoms compared with full agonists, such as methadone and heroin. The lower level of withdrawal symptoms during buprenorphine detoxification has meant that buprenorphine has been favoured clinically in patients who are likely to be ready for detoxification in the near future. However, lower-dose methadone patients (20–40 mg) can also be converted to buprenorphine before the detoxification, and it is thought that such patients also get the advantage of lower levels of withdrawal symptoms, although this has yet to be confirmed through research.

OPTION METHADONE FOR WITHDRAWAL

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Methadone can help people to withdraw from dependence on illicit opioids.
- Lofexidine and clonidine may be less effective than methadone in withdrawal, although evidence is weak.

Benefits and harms

Methadone versus placebo:

We found one systematic review (search date 2007, 20 RCTs, 1907 people). [36] The RCTs were conducted over 3 to 30 days, and the mean starting dose of methadone was 29 mg daily.

Mortality

No data from the following reference on this outcome. [36]

Opioid misuse

No data from the following reference on this outcome. [36]

Retention in treatment

Compared with placebo Methadone at tapered doses may be more effective than placebo at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Completed treatment					
[36] Systematic review	38 people 2 RCTs in this analysis	**Completion of treatment** 18/19 (95%) with tapered methadone 9/19 (47%) with placebo	RR 1.95 95% CI 1.21 to 3.13 P = 0.0058 Significant heterogeneity: P = 0.04	●○○	methadone

Criminality

No data from the following reference on this outcome. [36]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [36]

Adverse effects

No data from the following reference on this outcome. [36]

Methadone versus buprenorphine:

See option on buprenorphine for withdrawal, p 15 .

Methadone versus any other drug treatment:

We found one systematic review (search date 2007, 20 RCTs, 1907 people). [36] The RCTs were conducted over 3 to 30 days, and the mean starting dose of methadone was 29 mg daily.

Mortality

No data from the following reference on this outcome. [36]

Opioid misuse

Methadone compared with any other drug treatment We don't know whether tapered methadone is more effective than any other pharmacological treatment (results of all combined in analysis) at reducing the number of people abstinent at follow-up (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
People abstinent at follow-up					
[36] Systematic review	97 people 2 RCTs in this analysis	**Abstinent at follow-up** 21/50 (42%) with tapered methadone 17/47 (36%) with other drug treatment	RR 1.17 95% CI 0.72 to 1.92	⟷	Not significant

Retention in treatment

Methadone compared with any other drug treatment Tapered methadone seems as effective as any other pharmacological treatment (results of all combined in analysis) at increasing the proportion of people who complete treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people completing treatment					
[36] Systematic review	890 people 14 RCTs in this analysis	**Proportion of people completing treatment** 244/393 (62%) with tapered methadone 283/497 (57%) with other drug treatment	RR 1.08 95% CI 0.95 to 1.24 P = 0.26 Significant heterogeneity: P = 0.02	⟷	Not significant

Criminality

No data from the following reference on this outcome. [36]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [36]

Adverse effects

No data from the following reference on this outcome. [36]

Methadone versus adrenoceptor agonists:

See option on lofexidine/clonidine for withdrawal, p 26 .

Methadone versus other opioid agonists:

We found one systematic review (search date 2007, 20 RCTs, 1907 people). [36] The RCTs were conducted over 3 to 30 days, and the mean starting dose of methadone was 29 mg daily.

Mortality

No data from the following reference on this outcome. [36]

Opioid misuse

No data from the following reference on this outcome. [36]

Retention in treatment

Methadone compared with other opioid agonists We don't know how tapered methadone and other opioid agonists (results for all combined in analysis) compare at increasing the proportion of people who complete treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people completing treatment					
[36] Systematic review	204 people 5 RCTs in this analysis	**Proportion of people completing treatment** 50/102 (49%) with tapered methadone 44/102 (43%) with other opioid agonists	RR 1.06 95% CI 0.66 to 1.69 P = 0.81	⟷	Not significant
[36] Systematic review	72 people Data from 1 RCT	**Proportion of people completing treatment** 25/36 (69%) with tapered methadone 15/36 (42%) with propoxyphene	RR 1.67 95% CI 1.07 to 2.60	●○○	methadone

Criminality

No data from the following reference on this outcome. [36]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular adverse effects					
[36] Systematic review	Number of people unclear Data from 1 RCT	**Blood pressure** with tapered methadone with other opioid agonists 1 RCT in the review reported that significantly fewer people had lowered blood pressure with methadone compared with buprenorphine (no further data reported)			

Methadone versus chlordiazepoxide:

We found one systematic review (search date 2007, 20 RCTs, 1907 people). [36] The RCTs were conducted over 3 to 30 days, and the mean starting dose of methadone was 29 mg daily.

Mortality

No data from the following reference on this outcome. [36]

Opioid misuse

No data from the following reference on this outcome. [36]

Retention in treatment

Methadone compared with chlordiazepoxide We don't know how tapered methadone and chlordiazepoxide compare at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people completing treatment					
[36] Systematic review	24 people Data from 1 RCT	**Proportion of people completing treatment** 5/13 (38%) with tapered methadone 4/11 (36%) with chlordiazepoxide	RR 1.06 95% CI 0.37 to 3.00	⟷	Not significant

Criminality

No data from the following reference on this outcome. [36]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [36]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiovascular adverse effects					
[36] Systematic review	Number of people unclear Data from 1 RCT	**Bradycardia , 4 and 7 days** with tapered methadone with chlordiazepoxide 1 RCT in the review found significantly more bradycardia with methadone compared with chlordiazepoxide at 4 and 7 days (no further data reported)			

Further information on studies

[36] The review also pooled data from two RCTs (47 people), which compared the effects of methadone versus anxiolytics (chlordiazepoxide and buspirone) on the proportion of people who completed treatment (RR 0.63, 95% CI 0.18 to 2.24; P = 0.48).

[36] The RCT comparing methadone versus placebo, and the RCT comparing methadone versus chlordiazepoxide, were small and might have been underpowered.

Comment:

Clinical guide:
Many people return to regular heroin use shortly after detoxification, and it seems that a brief, inexpensive intervention is unlikely to alter the course of a chronic relapsing disorder such as heroin addiction. Whether people relapse into heroin use has a lot to do with the degree of preparation for detoxification and a life of abstinence, the robustness of the 'aftercare plan', and the extent of the 'recovery capital', which includes personal and life skills, beliefs and desires around recovery, and supports and engagement in family and community. For people who are not fully ready for abstinence, the investment into addiction treatment could be more justified if more modest goals were being achieved, such as temporary reduction of daily heroin dosage, with its consequent reduction in dependence and illegally obtained income, and the possibility of reaching drug-dependent people who would otherwise not have accessed treatment. Managed withdrawal or detoxification is not in itself a treatment for dependence, but can serve two useful functions in the recovery journey. First, detoxification can be a brief transitional stage between a dependent state and an abstinent state, which may itself involve longer-term treatment, and is likely to be particularly applicable in patients who are well prepared for a life of abstinence or those entering therapy in a protective environment such as a residential drug rehabilitation centre. Second, detoxification may be used as a 'learning experience' in order to help patients decide whether they are ready for a lifestyle of abstinence or need to work on their recovery capital during a period of stabilisation or maintenance on a prescribed opioid. In both groups it is particularly important that the patient is fully aware of the risks of detoxification (e.g., opioid overdose), and that steps are put in place to mitigate these risks — including rapid access back into opioid substitution treatment if required.

OPTION LOFEXIDINE/CLONIDINE FOR WITHDRAWAL

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Alpha$_2$-adrenoceptor agonists (lofexidine, clonidine) can help people to withdraw from dependence on illicit opioids.
- Lofexidine and clonidine may be less effective than methadone and buprenorphine in withdrawal, although evidence is weak.

- Lofexidine and clonidine are better than no active treatment in people withdrawing from opioids.

Benefits and harms

Alpha$_2$-adrenoceptor agonists versus placebo:

We found one systematic review (search date 2008, 24 studies, 21 RCTs, 1631 people) comparing alpha$_2$-adrenoceptor agonists versus tapering doses of methadone. [37]

Mortality

No data from the following reference on this outcome. [37]

Opioid misuse

No data from the following reference on this outcome. [37]

Retention in treatment

Compared with placebo Alpha$_2$-adrenoceptor agonists seem more effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Completion of treatment					
[37] Systematic review	149 people 3 RCTs in this analysis	**Proportion of people who completed treatment** 41/76 (54%) with alpha$_2$-adrenoceptor agonists 21/73 (29%) with placebo	RR 1.90 95% CI 1.28 to 2.81 P = 0.0014	●○○	alpha$_2$-adrenoceptor agonists

Criminality

No data from the following reference on this outcome. [37]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [37]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	149 people 3 RCTs in this analysis	**Adverse effects** with alpha$_2$-adrenoceptor agonists with placebo	The review reported that alpha$_2$-adrenoceptor agonists seemed to be associated with more adverse effects than placebo		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			

Alpha$_2$-adrenoceptor agonists versus methadone:

We found three systematic reviews (search date 2008, 24 studies, 21 RCTs, 1637 people; [37] search date 2007, 20 RCTs, 1907 people; [36] and search date 2006, 23 RCTs, 2112 people [32]) comparing alpha$_2$-adrenoceptor agonists versus tapering doses of methadone. All the reviews included slightly difference evidence, so all are reported here; however, the third review [32] did not report any outcomes of interest for this review, for this comparison.

Mortality

No data from the following reference on this outcome. [37] [36] [32]

Opioid misuse

Alpha$_2$-adrenoceptor agonists compared with methadone We don't know how alpha$_2$-adrenoceptor agonists and tapered methadone compare at increasing the proportion of people who complete withdrawal from opioids (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rates of withdrawal from opioids					
[37] Systematic review	690 people 10 RCTs in this analysis	**Proportion of people who completed withdrawal** 210/386 (54.4%) with alpha$_2$-adrenoceptor agonists 164/304 (53.9%) with tapered methadone	RR 0.95 95% CI 0.81 to 1.12 P = 0.56 Meta-analysis limited by diversity in study design and in assessment and reporting of outcomes	⟷	Not significant

No data from the following reference on this outcome. [36] [32]

Retention in treatment

Alpha$_2$-adrenoceptor agonists compared with methadone Alpha$_2$-adrenoceptor agonists may be less effective than tapered methadone at increasing time in treatment, but we don't know whether they are more or less effective at increasing the proportion of people retained in treatment or at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[37] Systematic review	311 people 3 RCTs in this analysis	**Length of time in treatment** with alpha$_2$-adrenoceptor agonist with tapered methadone Absolute results not reported	SMD –1.07 95% CI –1.31 to –0.83 Meta-analysis limited by diversity in study design and in assessment and reporting of outcomes	○○○	methadone
[37] Systematic review	399 people 5 RCTs in this analysis	**Proportion retained in treatment** 104/192 (54%) with alpha$_2$-adrenoceptor agonists 135/207 (65%) with tapered methadone	RR 0.81 95% CI 0.64 to 1.04 Meta-analysis limited by diversity in study design and in assessment and reporting of outcomes Heterogeneity: P = 0.03	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[36] Systematic review	577 people 7 RCTs in this analysis	**Proportion of people completing treatment** 168/251 (67%) with tapered methadone 192/326 (59%) with alpha$_2$-adrenoceptor agonists	RR 1.10 95% CI 0.90 to 1.32 P = 0.34 Significant heterogeneity: P = 0.01	⟷	Not significant

No data from the following reference on this outcome. [32]

Criminality

No data from the following reference on this outcome. [37] [36] [32]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [37] [36] [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	525 people 7 RCTs in this analysis	**Adverse effects** 41/315 (13%) with alpha$_2$-adrenoceptor agonists 15/210 (7%) with methadone	RR 2.13 95% CI 1.30 to 3.48 P = 0.0026	●●○	methadone
[36] Systematic review	1907 people	**Blood pressure** with clonidine with methadone The review reported that 5 of the included RCTs reported higher mean blood pressure (less hypotension) with methadone compared with alpha$_2$-adrenoceptor agonists, but 2 RCTs reported no significant difference between groups			

No data from the following reference on this outcome. [32]

Lofexidine versus clonidine:

We found two systematic reviews (search date 2008, 24 studies, 21 RCTs, 1631 people; [37] and search date 2007, 23 RCTs, 2112 people) [32] comparing lofexidine versus clonidine.

Mortality

No data from the following reference on this outcome. [37] [32]

Opioid misuse

Lofexidine compared with clonidine Lofexidine and clonidine seem equally effective at increasing the proportion of people who complete withdrawal at 4 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rates of withdrawal from opioids					
[38] RCT	50 people In review [37]	**Proportion of people completing withdrawal , 4 weeks** 17/26 (65%) with lofexidine 12/24 (50%) with clonidine	P = 0.20	⟷	Not significant

No data from the following reference on this outcome. [32]

Retention in treatment

Lofexidine compared with clonidine We don't know whether lofexidine is more effective at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Completion of treatment					
[32] Systematic review	90 people 3 RCTs in this analysis	**Completion of treatment** with lofexidine with clonidine Absolute results not reported	OR 1.50 95% CI 0.53 to 4.11	⟷	Not significant

No data from the following reference on this outcome. [37]

Criminality

No data from the following reference on this outcome. [37] [32]

Severity of withdrawal symptoms

Lofexidine compared with clonidine We don't know how lofexidine and clonidine compare at reducing opioid withdrawal symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of withdrawal symptoms					
[39] RCT	80 people In review [37]	**Opioid withdrawal symptoms (measured by the Abstinence Symptoms Rating Scale)** with lofexidine with clonidine	Reported similar scores with both groups (further data not reported)	⟷	Not significant

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	1709 people	**Hypotension** with lofexidine with clonidine More hypotension reported with lofexidine than with clonidine in the included RCTs			
[38] RCT	In review [37]	**Adverse effects** with lofexidine with clonidine	P <0.05 Data not clear	○○○	lofexidine
[37] Systematic review	Number of people not reported Data from 1 RCT	**Doses omitted due to low blood pressure** 4% with lofexidine 9% with clonidine	P <0.001	○○○	lofexidine

No data from the following reference on this outcome. [32]

Lofexidine versus buprenorphine:

We found one systematic review (2006, 23 RCTs, 2112 people). [32]

Mortality

No data from the following reference on this outcome. [32]

Opioid misuse

No data from the following reference on this outcome. [32]

Retention in treatment

Lofexidine compared with buprenorphine We don't know how lofexidine and buprenorphine compare at increasing the proportion of people who complete treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Completion of treatment					
[32] Systematic review	210 people Data from 1 RCT	**Proportion of people who completed treatment** 47/103 (46%) with lofexidine 70/107 (65%) with buprenorphine	OR 1.40 95% CI 0.009 to 193.3	⟷	Not significant

Criminality

No data from the following reference on this outcome. [32]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [32]

Adverse effects

No data from the following reference on this outcome. [32]

Clonidine versus buprenorphine:
See option on buprenorphine for withdrawal, p 15 .

Further information on studies

Comment:

Clinical guide:
The use of alpha$_2$-adrenoceptor agonists, such as clonidine (doses of 50–100 micrograms 3 times daily increased to a maximum of 400 micrograms 2 times daily) and lofexidine (doses of 200 micrograms once daily increasing to a maximum of 600 micrograms once daily), in the treatment of opioid withdrawal has developed since the late 1970s and 1980s. Opioids inhibit noradrenaline release, and discontinuing them causes a rebound release of noradrenaline. Alpha$_2$-adrenoceptor agonists help to reduce the noradrenergic storm that occurs when opioids are discontinued. The clinical objective is to ensure that the peak dose of the alpha$_2$-adrenoceptor agonist coincides with the period of peak opiate withdrawal symptoms, so the dose needs to be titrated against the anticipated or actual level of withdrawal symptoms. In addition, dose levels need to be increased gradually over a few days because of the risk of hypotension and sedation, and reduced gradually on termination because rapid reductions of the alpha$_2$-adrenoceptor agonist dose produce opiate-like withdrawal symptoms. Patients need to be monitored for hypotension, sedation, and the small risk of bradycardia, particularly while dose levels are increasing. Most studies of alpha$_2$-adrenoceptor agonists have reported on the adverse-effect profiles, especially the problems associated with blood pressure changes, which are smaller for lofexidine than clonidine. If blood pressure changes are identified, these typically resolve rapidly even when staying on the same dose level — at least with lofexidine. Both lofexidine and clonidine have been shown to be effective treatments in helping to reduce physical withdrawal symptoms. These withdrawal symptoms include: tachycardia, sweating, restlessness, pupil dilation, bone and joint pains, rhinorrhoea, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin. Alpha$_2$-adrenoceptor agonists do not eliminate most withdrawal symptoms, so adjunctive medications such as analgesics and hypnotics are often needed, and sometimes also smooth muscle relaxants for stomach cramps, antiemetics, antidiarrhoeal agents, and anxiolytics. For people who are well prepared for withdrawal and seeking earlier resolution of withdrawal symptoms, alpha$_2$-adrenoceptor agonist treatment might be preferred. Alpha$_2$-adrenoceptor agonists are also used in all situations where opiate withdrawal symptoms occur, and where it is considered important to avoid the use of an opioid substitute. Clonidine and

lofexidine seem equally effective for inpatient settings, but the lower incidence of hypotension and sedation makes lofexidine more suited for use in outpatient settings.

OPTION ULTRA-RAPID WITHDRAWAL

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Ultra-rapid withdrawal can help in detoxification, although there are important safety risks in keeping people heavily sedated or under general anaesthesia for a few hours, and outcomes are no better.
- Serious adverse effects may occur in people undergoing detoxification under anaesthesia.

Benefits and harms

Ultra-rapid withdrawal versus standard withdrawal:

We found two systematic reviews (search date 1997, 9 studies [2 of which were RCTs], 424 people; [40] and search date 2009, 9 studies, 1109 people [41]) comparing withdrawal with heavy sedation versus standard withdrawal. The first review did not perform a meta-analysis because of the short duration and the differing methods of ultra-rapid opioid detoxification; therefore, we have not reported data from this review. [40] However, overall, it concluded that the existing literature on rapid detoxification and ultra-rapid detoxification is limited, in terms of the number of people evaluated, the variation in protocols studied, the lack of randomised design and use of control groups, and the short-term nature of the outcomes reported. Further research is needed, using more rigorous research methods, longer-term outcomes, and comparisons with other methods of treatment for opioid dependence. [40] The second review did perform meta-analysis and is reported in full. [41]

Mortality

No data from the following reference on this outcome. [41]

Opioid misuse

Compared with conventional withdrawal Antagonist-induced withdrawal seems as effective at increasing the proportion of people who are retained in naltrexone maintenance or abstinent at 12 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retained in naltrexone maintenance or abstinent					
[41] Systematic review	30 people Data from 1 RCT	**Retained in naltrexone maintenance or abstinent , 12 weeks** 10/15 (67%) with antagonist-induced withdrawal 5/15 (33%) with tapered methadone	RR 2.00 95 % CI 0.90 to 4.45 P = 0.09	⟷	Not significant
[41] Systematic review	240 people 3 RCTs in this analysis	**Retained in naltrexone maintenance or abstinent , 12 weeks** 26/122 (21%) with antagonist-induced withdrawal 9/118 (8%) with clonidine	RR 2.77 95% CI 1.37 to 5.61 P = 0.004	●●○	antagonist-induced withdrawal
[41] Systematic review	72 people Data from 1 RCT	**Retained in naltrexone maintenance or abstinent , 12 weeks** 7/35 (20%) with antagonist-induced withdrawal 9/37 (24%) with buprenorphine	RR 0.82 95% CI 0.34 to 1.97 P = 0.66	⟷	Not significant

Retention in treatment

Compared with standard conventional withdrawal We don't know whether antagonist-induced withdrawal is more effective at increasing the proportion of people who complete detoxification treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[41] Systematic review	30 people Data from 1 RCT	**Completion of detoxification** 15/15 (100%) with antagonist-induced withdrawal 8/15 (53%) with tapered methadone	RR 1.82 95% CI 1.14 to 2.91 P = 0.012	●○○	antagonist-induced withdrawal
[41] Systematic review	70 people Data from 1 RCT	**Completion of detoxification** 28/36 (78%) with antagonist-induced withdrawal 21/34 (62%) with clonidine	RR 1.26 95% CI 0.92 to 1.73 P = 0.15	⟷	Not significant

Criminality

No data from the following reference on this outcome. [41]

Severity of withdrawal symptoms

No data from the following reference on this outcome. [41]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] Systematic review	Number of people unclear Data from 1 RCT	**Adverse effects** with antagonist-induced withdrawal with conventional withdrawal	1 RCT included in the review reported 3 potentially life-threatening adverse events: 1 person with a possible previous history of sleep apnoea developed severe pulmonary oedema and aspiration pneumonia; the second person, who had a history of bipolar affective disorder, developed a mixed bipolar state; and the third person, who had insulin-dependent diabetes, developed ketoacidosis		

Further information on studies

Comment: NICE states that ultra-rapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death.

Clinical guide:
When detoxification is given to people with opioid dependence, other approaches, such as clonidine, methadone, or buprenorphine, are likely to be at least as effective as anaesthesia-assisted detoxification, and are also safer and far less costly. Because medical detoxification addresses only the very first steps of treatment, and many programmes, being privately provided, do not provide ongoing treatment beyond detoxification, this approach can be fundamentally flawed for most people, especially those with chronic relapsing opioid dependence. Most data on this treatment are in the form of case series and non-randomised studies. Safety concerns have also been raised. Along with the risks inherent in general anaesthesia, complications such as pulmonary and cardiac problems have been reported. However, despite the lack of evidence and important safety concerns, this form of treatment is still available. [40] However, the effectiveness and safety of anaesthesia-assisted detoxification have been called into question. The additional risk, which should not be underestimated, is that the patient can see this as a "magic bullet", with no need to make any meaningful life changes.

QUESTION **What are the effects of drug treatments for relapse prevention in people with opioid dependence?**

OPTION **NALTREXONE FOR RELAPSE PREVENTION**

- For GRADE evaluation of interventions for Opioid dependence, see table, p 42 .
- Naltrexone can help to prevent relapse of heroin use if combined with psychosocial treatment.

Benefits and harms

Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial treatment):
We found two systematic reviews (search date 2010, 13 RCTs, 696 people; [42] and search date 2007, 7 RCTs [43]) and one additional RCT, [44] which assessed the effectiveness of naltrexone versus other interventions in opioid dependence.

Mortality

No data from the following reference on this outcome. [42] [43] [44]

Opioid misuse

Compared with placebo (with or without psychological treatment) Naltrexone (with or without psychological treatment) may be more effective at reducing opioid misuse at up to 6 months of follow-up (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Opioid use					
[42] Systematic review	143 people 4 RCTs in this analysis	**Abstinence** 41/94 (44%) with naltrexone 19/49 (39%) with placebo	RR 1.39 95% CI 0.61 to 3.17 P = 0.44 Significant heterogeneity: P = 0.05	●○○	naltrexone
[42] Systematic review	116 people 3 RCTs in this analysis	**Abstinence at follow-up** 27/63 (43%) with naltrexone 18/53 (34%) with placebo	RR 1.28 95% CI 0.80 to 2.05 P = 0.31	⟷	Not significant
[44] RCT	56 abstinence-oriented people who completed inpatient treatment for opioid dependence Open-label RCT	**Self-reported opioid use , 180 days** with naltrexone implant with control Absolute results not reported	SMD 60.2 days 95% CI 20.9 days to 99.5 days	○○○	naltrexone

No data from the following reference on this outcome. [43]

Retention in treatment

Compared with placebo We don't know whether naltrexone is more effective at increasing the proportion of people who are retained in treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[42] Systematic review	203 people 2 RCTs in this analysis	**Proportion of people retained in treatment** 26/50 (52%) with naltrexone 15/33 (45%) with placebo	RR 1.18 95% CI 0.72 to 1.91 P = 0.51	⟷	Not significant
[43] Systematic review	40 people Data from 1 RCT	**Proportion of people retained in treatment** 15/22 (68%) with high-dose naltrexone 7/18 (39%) with placebo	RR 1.75 95% CI 0.92 to 3.34 P = 0.88	⟷	Not significant
[43] Systematic review	38 people Data from 1 RCT	**Proportion of people retained in treatment** 12/20 (60%) with low-dose naltrexone 7/18 (39%) with placebo	RR 1.54 95% CI 0.78 to 3.05	⟷	Not significant

No data from the following reference on this outcome. [44]

Criminality

Compared with placebo Naltrexone seems to reduce the proportion of people who are re-incarcerated (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Re-incarceration					
[42] Systematic review	86 people 2 RCTs in this analysis	**Re-incarceration** 13/54 (24%) with naltrexone 16/32 (50%) with placebo	RR 0.47 95% CI 0.26 to 0.48 P = 0.01	●●○	naltrexone

No data from the following reference on this outcome. [43] [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] Systematic review	159 people 4 RCTs in this analysis	**Proportion of people with at least 1 adverse effect (not described)** 43/96 (45%) with naltrexone 17/63 (27%) with placebo	RR 1.29 95% CI 0.54 to 3.11 P = 0.57	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] Systematic review	40 people Data from 1 RCT	**Proportion of people with at least 1 adverse effect (not described)** 15/22 (68%) with high-dose naltrexone 9/18 (50%) with placebo	RR 1.36 95% CI 0.79 to 2.35 P = 0.42	⟷	Not significant
[43] Systematic review	38 people Data from 1 RCT	**Proportion of people with at least 1 adverse effect (not described)** 13/20 (65%) with low-dose naltrexone 9/18 (50%) with placebo	RR 1.30 95% CI 0.74 to 2.28 P = 0.36	⟷	Not significant

No data from the following reference on this outcome. [44]

Different doses of naltrexone:

We found one systematic review (search date 2007, 7 RCTs) [43] and one additional RCT. [45]

Mortality

No data from the following reference on this outcome. [43] [45]

Opioid misuse

Different doses of naltrexone compared with each other We don't know whether any one dose of naltrexone is more effective than any other dose of naltrexone at reducing opioid misuse as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Heroin use					
[46] RCT	60 people, all of whom had detoxification and oral naltrexone for 3 days pre-randomisation In review [43] Data from 1 RCT	**Proportion of urine samples negative for heroin (missing samples were not considered positive)** 73.5% with depot naltrexone 192 mg given at 1 and 5 weeks after detoxification 79.4% with depot naltrexone 384 mg given at 1 and 5 weeks after detoxification 74.2% with depot placebo given at 1 and 5 weeks after detoxification Absolute numbers not reported	P = 0.85 for difference among groups	⟷	Not significant
[45] RCT	66 people, all of whom had detoxification and naltrexone 50 mg daily for 1 week pre-randomisation Data from 1 RCT	**Heroin use over 6 months** with oral naltrexone 0.05 mg with oral naltrexone 0.5 mg with oral naltrexone 50 mg	P = 0.156	⟷	Not significant

Retention in treatment

Different doses of naltrexone compared with each other We don't know whether any one dose of naltrexone is more effective than any other dose of naltrexone at increasing the proportion of people retained in treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention in treatment					
[45] RCT	66 people, all of whom had detoxification and naltrexone 50 mg daily for 1 week pre-randomisation Data from 1 RCT	**Mean number of days retained in treatment** 47.8 days with oral naltrexone 0.05 mg 46.6 days with oral naltrexone 0.5 mg 58.9 days with oral naltrexone 50 mg	P = 0.93 for difference among groups	⟷	Not significant
[43] Systematic review	42 people Data from 1 RCT	**Proportion of people retained in treatment** 15/22 (68%) with high-dose naltrexone 12/20 (60%) with low-dose naltrexone	RR 1.14 95% CI 0.72 to 1.80 P = 0.58	⟷	Not significant

Criminality

No data from the following reference on this outcome. [43] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT	66 people, all of whom had detoxification and naltrexone 50 mg daily for 1 week pre-randomisation Data from 1 RCT	**Ratings of adverse effects (depression, increased erections, increased thirst, low energy, and tiredness)** with oral naltrexone 0.05 mg with oral naltrexone 0.5 mg with oral naltrexone 50 mg Absolute results reported graphically	P = 0.98 for difference among groups	⟷	Not significant
[43] Systematic review	42 people Data from 1 RCT	**Adverse effects** 15/22 (68%) with high-dose naltrexone 13/20 (65%) with low-dose naltrexone	RR 1.05 95% CI 0.68 to 1.16 P = 0.83	⟷	Not significant

Further information on studies

Comment:

Harms alert:
The FDA issued a drug safety alert on the increased risk of injection-site reactions, including cellulitis, induration, haematoma, abscess, sterile abscess, and necrosis associated with extended-release naltrexone injection (http://www.fda.gov).

The authors of the review discussed here [42] concluded that the available studies included in their review did not provide an objective evaluation of naltrexone treatment in the field of opioid dependence, and felt that the conclusions were limited owing to the heterogeneity of the trials, both in the interventions and in the assessment of outcomes. Naltrexone is a pure mu-opioid receptor antagonist, is non-addictive, and produces no euphoric effects. From a pharmacological perspective, naltrexone works to block opioid use. However, in clinical practice, medication compliance and retention rates are poor.

Clinical guide:
Naltrexone is an effective treatment for relapse prevention in opioid addiction, but only for a limited group of people, because few seem able to continue taking it for extended periods of time. It appears, therefore, to be most successful in highly motivated people with a vested interest in remaining opioid-free. Doses of 50 mg daily seem most accepted and successful. The development of newer, longer-acting preparations might provide an alternative to the delivery of this form of treatment, and might improve compliance. Naltrexone might be an efficacious adjuvant therapy, especially in people who fear severe consequences if they relapse back to taking illicit opioids. This target group includes healthcare professionals, who could lose their jobs, or parolees, who risk re-incarceration. NICE recommends naltrexone as a detoxification treatment in people who are highly motivated. They recommend administration under adequate supervision, and people should be fully informed of its adverse effects. Effectiveness should be reviewed regularly and, if there is evidence of misuse, treatment with naltrexone should be discontinued. [47]

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Ultra-rapid opioid detoxification A relatively new approach for treating opioid dependence is ultra-rapid opioid detoxification, induced with an opioid antagonist while the person is under anaesthesia or heavy sedation. This approach offers the possibility of a rapid and painless withdrawal under anaesthesia, after which the person awakens in a non-opioid-dependent state, thereby, at least in theory, avoiding the discomfort of physical withdrawal. It is designed to limit withdrawal-related discomfort by rendering the person unconscious during withdrawal.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Buprenorphine for stabilisation One systematic review updated. [13] Categorisation unchanged (Beneficial).

Buprenorphine for withdrawal One systematic review updated. [33] New evidence added. [32] [34] Categorisation unchanged (Beneficial).

Buprenorphine versus methadone for stabilisation One systematic review updated. [13] New evidence added. [28] [29] [30] [31] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the effects of buprenorphine versus methadone for stabilisation.

Lofexidine/clonidine for withdrawal One systematic review updated. [37] Categorisation unchanged (Likely to be beneficial).

Methadone for stabilisation One systematic review updated. [20] New evidence added. [22] [24] Categorisation unchanged (Beneficial).

Methadone for withdrawal One systematic review updated. [36] Categorisation unchanged (Beneficial).

Naltrexone for relapse prevention One systematic review updated. [42] New evidence added. [43] [44] Categorisation unchanged (Likely to be beneficial).

Ultra-rapid withdrawal (antagonist-assisted [naltrexone and naloxone only]) New evidence added. [41] Categorisation unchanged (Unknown effectiveness), as there remains insufficient good-quality evidence to assess the effects of withdrawal under heavy sedation.

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Disclaimer

GRADE **Evaluation of interventions for Opioid dependence.**

Important outcomes		Criminality, Mortality, Opioid misuse, Retention in treatment, Severity of withdrawal symptoms							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of drug treatments for stabilisation (maintenance) in people with opioid dependence?									
at least 4 RCTs (at least 620) [13]	Opioid misuse	Buprenorphine versus placebo	4	0	0	0	0	High	
at least 5 (at least 1131) [13]	Retention in treatment	Buprenorphine versus placebo	4	0	0	0	0	High	
1 (92) [15]	Opioid misuse	Frequency of buprenorphine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (92) [15]	Retention in treatment	Frequency of buprenorphine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (576) [20]	Mortality	Methadone versus no opioid replacement therapy	4	0	0	–1	0	Moderate	Directness point deducted for small number of events (11 in total)
6 (1129) [20]	Opioid misuse	Methadone versus no opioid replacement therapy	4	0	0	0	0	High	
at least 6 RCTs (at least 1013) [20]	Retention in treatment	Methadone versus no opioid replacement therapy	4	0	–1	–1	+1	Moderate	Consistency point deducted for heterogeneity between RCTs. Directness point deducted for diverse population in control group. Effect-size point added for RR >2
4 (682) [20] [22]	Criminality	Methadone versus no opioid replacement therapy	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for diverse population in control group
3 (237) [23]	Opioid misuse	Higher- versus lower-dose methadone	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for unclear outcome measurement (heroin abstinence) and wide range of dosages used in each group
at least 5 (at least 496) [23]	Retention in treatment	Higher- versus lower-dose methadone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for wide range of dosages in each group
1 (405) [28]	Mortality	Buprenorphine versus methadone for stabilisation	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 8 (at least 1338) [13] [29] [30] [31]	Opioid misuse	Buprenorphine versus methadone for stabilisation	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of data and heterogeneity between trials
at least 13 (at least 1822) [13] [14] [29] [30]	Retention in treatment	Buprenorphine versus methadone for stabilisation	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of data and heterogeneity between trials.

Important outcomes		Criminality, Mortality, Opioid misuse, Retention in treatment, Severity of withdrawal symptoms							
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (325) [13] [31]	Criminality	Buprenorphine versus methadone for stabilisation	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data
What are the effects of drug treatments for withdrawal in people with opioid dependence?									
5 (264) [33] [32]	Retention in treatment	Buprenorphine versus methadone	4	0	0	0	0	High	
4 (432) [33]	Severity of withdrawal symptoms	Buprenorphine versus methadone	4	0	0	0	0	High	
11 (1206) [33] [32]	Retention in treatment	Buprenorphine versus clonidine	4	0	0	0	0	High	
5 (776) [33]	Severity of withdrawal symptoms	Buprenorphine versus clonidine	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (27) [33]	Retention in treatment	Buprenorphine versus oxazepam	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (unclear) [33]	Severity of withdrawal symptoms	Buprenorphine versus oxazepam	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for unclear outcome assessment (timing and application of measuring tool) and unclear clinical relevance
1 (516) [34]	Opioid misuse	Different rates of buprenorphine dose reduction	4	0	0	0	0	High	
2 (38) [36]	Retention in treatment	Methadone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and heterogeneity between trials
2 (97) [36]	Opioid misuse	Methadone versus any other drug treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for broad comparison group (including any other pharmacological treatment)
14 (890) [36]	Retention in treatment	Methadone versus any other drug treatment	4	0	0	–1	0	Moderate	Directness point deducted for broad comparison group including any other pharmacological treatment
5 (204) [36]	Retention in treatment	Methadone versus other opioid agonists	4	0	0	–1	0	Moderate	Directness point deducted for broad comparison group (including all other opioid agonists)
1 (24) [36]	Retention in treatment	Methadone versus chlordiazepoxide	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events (9 in total)
149 (3) [37]	Retention in treatment	Alpha$_2$-adrenoceptor agonists versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
10 (690) [37]	Opioid misuse	Alpha$_2$-adrenoceptor agonists versus methadone	4	0	0	–2	0	Low	Directness points deducted for diverse study designs and assessment and reporting of outcomes
at least 7 (at least 577) [37] [36]	Retention in treatment	Alpha$_2$-adrenoceptor agonists versus methadone	4	0	0	–2	0	Low	Directness points deducted for diverse study designs and assessment and reporting of outcomes

Important outcomes		Criminality, Mortality, Opioid misuse, Retention in treatment, Severity of withdrawal symptoms							
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (50) [37]	Opioid misuse	Lofexidine versus clonidine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (90) [32]	Retention in treatment	Lofexidine versus clonidine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (80) [39]	Severity of withdrawal symptoms	Lofexidine versus clonidine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting. Directness point deducted for no statistical analysis between groups
1 (210) [32]	Retention in treatment	Lofexidine versus buprenorphine	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and sparse data
5 (342) [41]	Opioid misuse	Ultra-rapid withdrawal versus standard withdrawal	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (100) [41]	Retention in treatment	Ultra-rapid withdrawal versus standard withdrawal	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
What are the effects of drug treatments for relapse prevention in people with opioid dependence?									
8 at most (315 at most) [42] [44]	Opioid misuse	Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial treatment)	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
4 at most (281 at most) [42] [43]	Retention in treatment	Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial treatment)	4	0	0	–2	0	Low	Directness points deducted for unclear comparison group (with or without psychological treatment) and use of co-intervention (psychological treatment)
2 (86) [42]	Criminality	Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial treatment)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (126) [43] [45]	Opioid misuse	Different doses of naltrexone	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and unclear analysis (missing samples not considered positive)
2 (108) [43] [45]	Retention in treatment	Different doses of naltrexone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for no direct comparison between groups in 1 RCT

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.