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Opioid dependence

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ABSTRACT

INTRODUCTION: Dependence on opioids is a multifactorial condition involving genetic and psychosocial factors. There are three approaches 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 aim is relapse prevention. 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 May 2008 (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 23 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 regimes.

QUESTIONS

What are the effects of drug treatments for stabilisation (maintenance) in people with opioid dependence? . . . 3

What are the effects of drug treatments for withdrawal in people with opioid dependence? . . . 8

What are the effects of drug treatments for relapse prevention in people with opioid dependence? . . . 13

INTERVENTIONS

DRUG TREATMENTS FOR STABILISATION (MAINTENANCE)

Beneficial

Buprenorphine for stabilisation . . . 3

Methadone for stabilisation . . . 5

Unknown effectiveness

Buprenorphine versus methadone for stabilisation (both beneficial and seem as effective as each other) . . . 7

DRUG TREATMENTS FOR WITHDRAWAL

Beneficial

Buprenorphine for withdrawal . . . 8

Methadone for withdrawal . . . 10

Likely to be beneficial

Lofexidine/clonidine for withdrawal . . . 11

Unknown effectiveness

Ultra-rapid withdrawal (antagonist-assisted [naltrexone and naloxone only]) . . . 12

DRUG TREATMENTS FOR RELAPSE PREVENTION

Likely to be beneficial

Naltrexone for relapse prevention . . . 13

To be covered in future updates

Adjunctive psychosocial interventions

Benzodiazepines

Treatments in pregnant women

Treatments in young people under 16 years of age

Key points

- Dependence on opioids is a multifactorial condition involving genetic and psychosocial factors.
- There are three approaches 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 aim is relapse prevention.
- Methadone and buprenorphine help to stabilise opioid use, as they decrease heroin use and help 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 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, and outcomes are no better.

- Naltrexone can help 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 urinalysis, 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, DVT, etc. When commencing treatment, urinalysis should confirm the use of opioids, and a number of samples should 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] **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 more than 18,000 in 1996, and nearly tripled during the 1990s. [4] The UK drug strategy reported 100,000–200,000 problem drug users in the mid-1990s. [5] A pilot study of national estimation methods suggested that there were 143,000–266,000 problem drug users, with about 75,000–150,000 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 over 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]

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. [9]

PROGNOSIS

Addictive disorders are chronic relapsing conditions with no known “cure”. [10]

AIMS OF INTERVENTION

The main aims of intervention can be broadly divided into three main approaches: 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 prior to 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. 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; proportion of drug-free days; proportion of drug metabolite-free urine samples; retention in the trial; withdrawal symptoms; withdrawal rates; relapse rates; rates of criminal activity; rates of sexual risk-taking behaviours; rates of injection-risk behaviours; harm-reduction models (overall assessment of health in terms of reduction in mortality, criminality, injecting

risk, and cost effectiveness); mortality from treatment;other adverse effects of treatment; self-reported heroin use; quality of life.

METHODS

Clinical Evidence search and appraisal May 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2008, Embase 1980 to May 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 1. An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for 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 pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs and controlled clinical trials in any language, including open studies. The minimum number of individuals in each trial was 10. There is no minimum length of follow-up. The size of follow-up is at least 70%. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (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, p 18).

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

OPTION BUPRENORPHINE FOR STABILISATION

Retention in treatment

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

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 proportion of people retained in treatment (low-quality evidence).

Compared with methadone Buprenorphine and methadone seem to be equally effective at increasing the proportion of people retained in treatment (moderate-quality evidence).

Opioid misuse

Compared with placebo High-dose buprenorphine (at least 8 mg) is more effective at reducing opioid misuse as assessed by urinalysis at 16 weeks. However, low-dose buprenorphine (2–4 mg) is no more effective at reducing opioid misuse as assessed by urinalysis at 2–16 weeks (high-quality evidence).

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 opioid misuse as assessed by urinalysis (low-quality evidence).

Compared with methadone Buprenorphine and methadone seem to be equally effective at reducing opioid misuse as assessed by self-reported heroin use and urinalysis (moderate-quality evidence).

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits:

Buprenorphine versus placebo:

We found two systematic reviews (search dates 2001 and 2005) [11] [12] 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, and are therefore reported separately.

The first systematic review (search date 2001, 13 RCTs, 2544 people), [11] which was also identified by the second systematic review, [12] compared different doses of buprenorphine versus placebo. The review found no significant difference between low-dose buprenorphine (2–4 mg) and placebo for 2–16 weeks in morphine-positive urine samples (2 RCTs, 487 people; SMD +0.10, 95% CI –0.80 to +1.01). However, significantly more people were retained in treatment with low-dose buprenorphine than with placebo (2 RCTs, 487 people; 141/242 [58%] with buprenorphine *v* 114/245 [47%] with placebo; RR 1.24, 95% CI 1.06 to 1.45). It also found significantly fewer morphine-positive urine samples, and that significantly more people were retained in treatment with high-

dose buprenorphine (8 mg) than with placebo for 2–16 weeks (morphine-positive urine samples: 2 RCTs, 463 people; SMD –0.28, 95% CI –0.47 to –0.10; retention: 119/218 [55%] with buprenorphine *v* 114/245 [47%] with placebo; RR 1.21, 95% CI 1.02 to 1.44). Furthermore, it found significantly fewer morphine-positive urine samples, and that significantly more people were retained in treatment with high-dose buprenorphine (16 mg) than with placebo for 16 weeks (morphine-positive urine samples: 1 RCT, 366 people; SMD –0.65, 95% CI –0.86 to –0.44; retention: 1 RCT, 366 people; 110/181 [61%] with buprenorphine *v* 74/185 [40%] with placebo; RR 1.52, 95% CI 1.23 to 1.88). [11]

The second systematic review which is also the most recent review (search date 2005) [12] searched for systematic reviews and RCTs from 2001 to 2005. The review did not pool data from the RCTs identified by this additional search. The review included narrative reviews, reviews of non-RCT evidence, and reviews of any type of drug abuse rather than specifically opioid dependence. The systematic review reported considerable overlap between reviews in terms of the RCTs identified. Therefore, we only report RCTs and systematic reviews included in the review and also identified by our search that meet our inclusion criteria for reporting. The review identified four systematic reviews (including the review reported above [11]) comparing buprenorphine versus placebo. The 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. [12]

Frequency of buprenorphine:
One crossover RCT gave 16 people single doses of buprenorphine, a double dose every 48 hours, or a triple dose every 72 hours, in random order. [13] 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). A second RCT (92 people) compared daily buprenorphine (16 mg/70 kg) versus three times weekly buprenorphine (34 mg/70 kg twice weekly plus 44 mg/70 kg once weekly). [14] It found no significant difference between treatments in the proportion of opioid-positive urine tests (57% with daily *v* 58% with 3 times weekly; P = 0.84, absolute numbers not reported). It also found no significant difference between treatments in the average length of time people were retained in treatment (11.2 weeks with daily *v* 11.0 weeks with 3 times weekly; P = 0.64).

Dose of buprenorphine:
The second systematic review (search date 2005) [12] identified nine systematic reviews comparing different doses of buprenorphine versus each other (for further description of the review, see the comparison buprenorphine versus placebo above). The review did not perform a meta-analysis, but reported that the systematic reviews found higher doses of buprenorphine were more effective than lower doses at increasing the proportion of people retained in treatment. [12]

We found one additional RCT comparing three doses of buprenorphine (1, 3, and 8 mg/day). [15] The RCT only reported completion rates of the study at 18 weeks. It found that completion of the trial increased with higher doses of buprenorphine (29% with 1 mg/day *v* 46% with 3 mg/day *v* 68% with 8 mg/day; between-group comparison not reported).

Buprenorphine versus methadone:
See benefits of buprenorphine versus methadone for stabilisation, p 7 .

Harms:

Buprenorphine versus placebo:
Neither of the reviews gave information on adverse effects. [11] [12]

Frequency of buprenorphine:
The first RCT reported no discontinuation in any treatment arm owing to adverse effects of treatment. [13] The second RCT found “there were no reports of serious adverse effects of buprenorphine among patients in either treatment group”. [14]

Dose of buprenorphine:
The review and the additional RCT gave no information on adverse effects. [12] [15]

Buprenorphine versus methadone:
See harms of buprenorphine versus methadone for stabilisation, p 7 .

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 exanthaema with buprenorphine than with placebo (P < 0.05). [16] It also reported that "no serious adverse effects were observed".

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 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. [17] 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 (O'Shea J, Law F, Melichar 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. 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 produces minimal withdrawal syndrome and potentially enables alternate day and 3 times weekly dispensing regimens.

OPTION METHADONE FOR STABILISATION

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

Compared with buprenorphine Methadone and buprenorphine seem to be equally effective at increasing the proportion of people retained in treatment (moderate-quality evidence).

Higher doses compared with lower doses 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 3–26 weeks but not at 1 year (low-quality evidence).

Opioid misuse
Compared with no opioid replacement therapy Methadone is more effective at reducing opioid misuse as assessed by self-reported heroin use (moderate-quality evidence).

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

Compared with buprenorphine Buprenorphine and methadone seem to be equally effective at reducing opioid misuse as assessed by self-reported heroin use and urinalysis (moderate-quality evidence).

Mortality
Compared with no opioid replacement therapy Methadone seems to be no more effective at reducing mortality (moderate-quality evidence).

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits:

Methadone versus no opioid replacement therapy:
We found three systematic reviews (search dates 2001, [18] 2004, [19] and 2005 [12]) comparing methadone versus no opioid replacement therapy or placebo. The reviews reported on different outcomes and comparisons, and are therefore reported separately.

The systematic review with a more recent search date (search date 2005) [12] identified 12 systematic reviews (including the first systematic review [18]) comparing methadone versus placebo or no treatment (for further description of the review, see benefits of buprenorphine for stabilisation, p 3). The review did not perform a meta-analysis, but reported that the systematic reviews found methadone was more effective at increasing retention in treatment and at reducing self-reported opioid use compared with placebo or no drug treatment.

One systematic review (search date 2001, 6 RCTs, 954 people) found no significant difference in mortality between methadone maintenance treatment compared with no methadone maintenance treatment (3 RCTs, 435 people; 3/216 [1%] with methadone *v* 7/219 [3%] with control; RR 0.49, 95% CI 0.06 to 4.23). [18] However, the review found that significantly more people were retained in treatment with methadone (20–100 mg/day; slightly higher than routinely used in clinical practice in some parts of the world) than with no opioid replacement (placebo, withdrawal, or detoxification; drug-free rehabilitation treatment; and no treatment or waiting list controls) (3 RCTs, 505 people; 173/254 [68%] with methadone *v* 63/251 [25%] with control; RR 3.05, 95% CI 1.75 to 5.35). The interventions in this study generally lasted from several weeks to 2 years. The review found no significant difference between groups in criminal activity (3 RCTs, 363 people; 5/178 [3%] with methadone *v* 18/185 [10%] with control; RR 0.39, 95% CI 0.12 to 1.25). It found that methadone significantly decreased self-reported heroin use more than treatments with no opioid replacement (3 RCTs, 230 people; 28/108 [26%] with methadone *v* 110/126 [87%] with control; RR 0.32, 95% CI 0.23 to 0.44).

The other systematic review (search date 2004, 8 RCTs, 6 of which were identified by the first systematic review, [18] 1511 people) [19] included two additional RCTs, but performed a weak meta-analysis. It found that methadone significantly increased retention in treatment (6 RCTs, 1013 people; SMD 0.90, 95% CI 0.53 to 1.27), opioid abuse (7 RCTs, 1046 people; SMD 0.61, 95% CI 0.38 to 0.83), and criminality (5 RCTs, 707 people; SMD 0.35, 95% CI 0.01 to 0.69) compared with non-active controls (detoxification, placebo, or untreated, non-active controls). The review found significant statistical heterogeneity among RCTs included in the meta-analysis because of differences in study design ($P < 0.01$; review set statistical heterogeneity as significant if $P < 0.05$). [19]

Higher- versus lower-dose methadone:
We found two systematic reviews (search dates 2001 [20] and 2005 [12]).

The systematic review with the more recent search date (search date 2005) [12] identified nine systematic reviews (including the first systematic review [18]) comparing different doses of methadone versus each other (for further description of the review, see benefits of buprenorphine for stabilisation, p 3). The review did not perform a meta-analysis, 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). [12]

The other systematic review (11 RCTs, 2279 people) found that heroin abstinence was significantly higher with higher-dose (60–109 mg/day) compared with lower-dose (1–39 mg/day) methadone (3 RCTs, 237 people; RR 1.59, 95% CI 1.16 to 2.18; time and measure of heroin abstinence unclear). [20] 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). It also found that higher-dose methadone had significantly higher retention rates in the trials compared with lower-dose methadone in the short term, but found no significant difference in the longer term (3–26 weeks: 5 RCTs, 496 people; RR 1.36, 95% CI 1.13 to 1.63; 52 weeks: 1 RCT, 75 people; RR 1.62, 95% CI 0.95 to 2.77). Retention rates ranged from 20% with lower-dose methadone to 71% with higher-dose methadone.

Methadone versus buprenorphine:
See benefits of buprenorphine versus methadone for stabilisation, p 7 .

Harms:

In general, most studies did not report on harmful effects. Instead, most looked at harm-reduction issues, such as the concurrent use of cocaine, and mortality rates. 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. 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 no significant differences 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). [21]

Methadone versus no opioid replacement therapy:
The reviews gave no information on adverse effects. [12] [18] [19]

Higher- versus lower-dose methadone:
The first 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). [20] The second review gave no information on adverse effects. [12]

Methadone versus buprenorphine:
See harms of buprenorphine versus methadone for stabilisation, p 7 .

Comment: One large cohort study found that acquisitive crime was reduced by 23% of initial levels at 4–5 years of following a methadone maintenance programme. [22]

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 clinical guide of buprenorphine for stabilisation, p 3). Because the half-life of methadone is 24–36 hours, daily dosing is necessary, and supervised consumption is recommended. 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 experience withdrawal symptoms if they miss a dose, and detoxification is a lengthy process if attempted. 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 limit to employment 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

Retention in treatment
Compared with methadone Buprenorphine and methadone seem to be equally effective at increasing the proportion of people retained in treatment (moderate-quality evidence).

Opioid misuse
Compared with methadone Buprenorphine and methadone seem to be equally effective at reducing opioid misuse as assessed by self-reported heroin use and by urinalysis (moderate-quality evidence).

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits: We found three systematic reviews (search dates 2001, [11] 2004, [23] and 2005 [12]) comparing buprenorphine versus methadone.

The first systematic review (search date 2001, 13 RCTs, 2544 people) [11] found no significant difference between flexible-dose buprenorphine and flexible-dose methadone in heroin use (by urinalysis or self-reported heroin use) (urinalysis: 6 RCTs, 837 people; SMD –0.12, 95% CI –0.26 to +0.02; self-reported: 2 RCTs, 326 people; SMD –0.10, 95% CI –0.32 to +0.12). The review found no significant difference between flexible-dose buprenorphine and flexible-dose methadone in criminal activity (1 RCT, 212 people; SMD –0.14, 95% CI –0.41 to +0.14). It found no significant difference between low-dose buprenorphine and low-dose methadone in morphine-positive urine samples, retention in treatment, or self-reported heroin use (morphine-positive urine samples: 1 RCT, 59 people; SMD –0.35, 95% CI –0.87 to +0.16; retention: 2 RCTs, 121 people; 24/57 [42%] with buprenorphine *v* 37/64 [58%] with methadone; RR 0.74, 95% CI 0.52 to 1.06; self-reported heroin: 1 RCT, 44 people; SMD –0.28, 95% CI –0.35 to +0.90). It found significantly more morphine-positive urine samples with low-dose buprenorphine than with high-dose methadone (1 RCT, 57 people; SMD 0.88, 95% CI 0.33 to 1.42). However, there was no significant difference between low-dose buprenorphine and high-dose methadone in retention in treatment or self-reported heroin use (retention: 2 RCTs, 120 people; 24/57 [42%] with buprenorphine *v* 39/63 [62%] with methadone; RR 0.69, 95% CI 0.45 to 1.06; self-reported heroin use: 1 RCT, 38 people; SMD –0.06, 95% CI –0.70 to +0.58). It found significantly fewer morphine-positive urine samples with high-dose buprenorphine than with low-dose methadone (3 RCTs, 317 people; SMD –0.23, 95% CI –0.45 to –0.01). The review reported significant heterogeneity between RCTs for retention data, so did not report a meta-analysis. However, one RCT found that fewer people were retained in treatment with high-dose buprenorphine than with low-dose methadone, and two RCTs found no significant difference between groups. The review also found no significant difference between these groups in self-reported heroin use (1 RCT, 37 people; SMD +0.64, 95% CI –0.06 to +1.33). It found significantly more morphine-positive urine samples with high-dose buprenorphine than with high-dose methadone (3 RCTs, 314 people; SMD 0.27, 95% CI 0.05 to 0.50). However, it found no significant difference between groups for retention in treatment or self-reported heroin use (retention: 5 RCTs, 449 people; 92/223 [41%] with buprenorphine *v* 117/226 [52%] with methadone; RR 0.79, 95% CI 0.62 to 1.01; self-reported heroin use: 2 RCTs, 74 people; SMD –0.02, 95% CI –0.48 to +0.45). [11]

The second systematic review (search date 2002, 14 RCTs, 9 of which were included in the first review; [11] number of people not reported) [23] was also identified by the third systematic review. [12] The 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)". [23]

The third systematic review (search date 2005) [12] identified 12 systematic reviews including the second systematic review [23] comparing buprenorphine versus methadone (for further description of the review, see benefits of buprenorphine for stabilisation, p 3). The review presented a meta-analysis of seven RCTs comparing flexible-dose methadone versus flexible-dose buprenorphine (6 RCTs were also identified by the first systematic review) [11] for retention in treatment and morphine-positive urinalysis. The review found that flexible-dose methadone significantly increased retention in treatment compared with flexible-dose buprenorphine (7 RCTs, 976 opiate-dependent people; 310/492 [63%] with methadone *v* 255/484 [53%] with buprenorphine; RR 1.20, 95% CI 1.07 to 1.33). The review reported the same meta-analysis for morphine-positive urine samples as the first systematic review. The review did not identify additional RCTs for this comparison.

We found one additional RCT (164 people) comparing methadone (30 mg/day) and three doses of buprenorphine (1, 3, and 8 mg/day). [15] The RCT only reported on completion rates of the study at 18 weeks. It found that significantly more people completed treatment with methadone than with buprenorphine 1 mg daily (82 people; 61.0% with methadone *v* 29.3% with buprenorphine 1 mg/day; P = 0.004). However, it found no significant difference in completion rates between methadone compared with 3 mg daily and 8 mg daily buprenorphine (123 people; 61% with methadone *v* 46% with buprenorphine 3 mg/day; P = 0.18; 61% with methadone *v* 68% with buprenorphine 8 mg/day; P = 0.49).

Harms: The systematic reviews gave no information on adverse effects. [11] [12] [23]

Comment: See comments under buprenorphine, p 3 and methadone, p 5 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 [17] (see clinical guides of buprenorphine, p 3 and methadone, p 5 for stabilisation).

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

OPTION BUPRENORPHINE FOR WITHDRAWAL

Withdrawal rates
Compared with methadone Buprenorphine and methadone seem to be equally effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with clonidine Buprenorphine seems to be more effective at lowering withdrawal scores and at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with lofexidine We don't know whether buprenorphine is more effective at increasing the proportion of people who complete detoxification or who abstain from heroin at 1 month (low-quality evidence).

Compared with oxazepam Buprenorphine and oxazepam seem to be equally effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Note
We found no direct information from RCTs about whether buprenorphine is better than no active treatment for people withdrawing from opioids.

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits: We found one systematic review (search date 2005, 18 studies [14 RCTs; 1 partially randomised trial; 3 non-randomised trials], 1356 people) comparing buprenorphine for the management of opioid withdrawal. [24]

Buprenorphine versus methadone:
The systematic review found no significant difference between buprenorphine and methadone in the proportion of people who completed treatment, although completion of withdrawal seemed

more likely with buprenorphine (3 RCTs, 156 people; 42/75 [56%] with buprenorphine *v* 33/81 [41%] with methadone; RR 1.30, 95% CI 0.97 to 1.73; P = 0.08). [24]

Buprenorphine versus clonidine:
The systematic review found that withdrawal scores were significantly lower with buprenorphine than with clonidine (3 RCTs, 266 people; SMD –0.61, 95% CI –0.86 to –0.36; P < 0.001). [24] The review also found that people stayed in outpatient treatment for significantly longer with buprenorphine compared with clonidine (number of RCTs and people not clear; SMD 0.82, 95% CI 0.57 to 1.06; P < 0.001). The review found that significantly more people completed treatment with buprenorphine than with clonidine (8 RCTs, 760 people; 268/441 [61%] with buprenorphine *v* 127/319 [40%] with clonidine; RR 1.73, 95% CI 1.21 to 2.47; P = 0.003).

Buprenorphine versus lofexidine:
See benefits of lofexidine/clonidine for withdrawal, p 11 .

Buprenorphine versus oxazepam:
The systematic review found that withdrawal severity (Short Opiate Withdrawal Scale) was significantly lower with buprenorphine than with oxazepam (1 RCT; no further data reported). [24] However, it found no significant difference between buprenorphine and oxazepam in the proportion of people who completed treatment (11/15 [73%] with buprenorphine *v* 7/12 [58%] with oxazepam; P value not reported, reported as not significant).

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. [24] 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.

Harms:

Buprenorphine versus methadone:
The review reported that one RCT found “no severe adverse effects in either buprenorphine or methadone groups”. [24] The other RCTs gave no information on adverse effects.

Buprenorphine versus clonidine:
The review found no significant difference between buprenorphine and clonidine in either the number of people experiencing adverse effects or the number of people who withdrew because of adverse effects (number of people with adverse effects: 3 RCTs, 458 people; RR 0.97, 95% CI 0.76 to 1.23; number of people who withdrew: 3 RCTs, 134 people; RR 0.20, 95% CI 0.04 to 1.09). [24]

Buprenorphine versus lofexidine:
See harms of lofexidine/clonidine for withdrawal, p 11 .

Buprenorphine versus oxazepam:
The review reported that one RCT “reported no severe adverse effects in either group and no significant differences in blood pressure or heart rate”. [24]

Different rates of buprenorphine dose reduction:
The review reported that one RCT gave no information on 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. [24]

Comment:

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. However, higher doses (6–8 mg/day) appear necessary at the outset of withdrawal to achieve patient comfort and to suppress illicit opioid use. [24] 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-acting agonists, such as methadone and heroin.

OPTION METHADONE FOR WITHDRAWAL

Withdrawal rates

Compared with placebo Methadone at tapered doses seems more effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with buprenorphine Methadone and buprenorphine seem to be equally effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with any other pharmacological treatments Tapered methadone seems as effective as other pharmacological treatments at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with adrenoceptor agonists Methadone seems to be more effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with other opioid agonists We don't know whether tapered methadone is more effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

Compared with chlordiazepoxide Tapered methadone and chlordiazepoxide seem to be equally effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits:

We found one systematic review (search date 2004, 16 RCTs, 1187 people). [25] The RCTs were conducted over 3–30 days, and the mean starting dose of methadone was 29 mg daily.

Methadone versus placebo:
The systematic review found that significantly more people completed treatment with tapered methadone than with placebo, although the RCT was small and might have been underpowered (1 RCT, 22 people; 10/11 [91%] with methadone *v* 3/11 [27%] with placebo; RR 3.33, 95% CI 1.25 to 8.91). [25]

Methadone versus buprenorphine:
See benefits of buprenorphine for withdrawal, p 8 .

Methadone versus any other pharmacological treatments:
The systematic review found no significant difference between tapered methadone and any other pharmacological treatment for withdrawal in either the proportion of people completing treatment or the number of people abstinent at follow-up (completing treatment: 11 RCTs, 748 people; 21/50 [42%] with methadone *v* 17/47 [36%] with other treatments; RR 1.12, 95% CI 0.94 to 1.34; abstinent at follow-up: 2 RCTs, 97 people; RR 1.17, 95% CI 0.72 to 1.92). [25]

Methadone versus adrenoceptor agonists:
See benefits of lofexidine/clonidine for withdrawal, p 11 .

Methadone versus other opioid agonists:
The systematic review found no significant difference between tapered methadone and other opioid agonists in the proportion of people completing treatment (4 RCTs, 165 people; 44/81 [54%] with methadone *v* 35/84 [42%] with other opioid agonists; RR 1.25, 95% CI 0.80 to 1.93). [25] However, it found that significantly more people completed treatment with methadone than with propoxyphene (1 RCT, 72 people; 25/36 [69%] with methadone *v* 15/36 [42%] with other treatments; RR 1.67, 95% CI 1.07 to 2.60).

Methadone versus chlordiazepoxide:
The systematic review found no significant difference between tapered methadone and chlordiazepoxide in the proportion of people completing treatment, although the RCT was small and might have been underpowered (1 RCT, 24 people; 5/13 [38%] with methadone *v* 4/11 [36%] with other treatments; RR 1.06, 95% CI 0.37 to 3.00). [25]

Harms:

Methadone versus placebo:
The review gave no information on adverse effects. [25]

Methadone versus buprenorphine:
See harms of buprenorphine for withdrawal, p 8 .

Methadone versus any other pharmacological treatments:
The review reported adverse effects in variable ways, preventing quantitative analysis. [25]

Methadone versus adrenoceptor agonists:
See harms of lofexidine/clonidine for withdrawal, p 11 .

Methadone versus other opioid agonists:
The review found one RCT that reported significantly fewer people with lowered blood pressure with methadone compared with buprenorphine (no further data reported). [25]

Methadone versus chlordiazepoxide:
The review reported one RCT that found significantly more bradycardia with methadone compared with chlordiazepoxide at 4 and 7 days (no further data reported). [25]

Comment:

Clinical guide:
Many people return to regular heroin use shortly after detoxification, and it appears 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 no bearing on the success or otherwise of a reported detoxification procedure. Therefore, the investment into methadone 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, in illegally obtained income, and the possibility of reaching drug addicts who would otherwise not have accessed treatment. Managed withdrawal or detoxification is not in itself a treatment for dependence, but detoxification remains a required first step for many forms of longer-term treatments. Methadone was first used to treat heroin dependence as a tapering agent after the Second World War, and was introduced in the treatment of opioid dependence for maintenance purposes rather than detoxification until the 1960s. Despite the numerous reports of high relapse rates following detoxification, methadone is a common treatment used in opioid detoxification, notwithstanding its prolonged withdrawal syndrome compared with other treatments.

OPTION LOFEXIDINE/CLONIDINE FOR WITHDRAWAL

Withdrawal rates
Alpha$_2$-adrenoceptor agonists compared with methadone Alpha$_2$-adrenoceptor agonists seem to be less effective at increasing the proportion of people who complete treatment (moderate-quality evidence).

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

Lofexidine compared with buprenorphine We don't know whether lofexidine is more effective at increasing the proportion of people who complete detoxification treatment or who abstain from heroin at 1 month (low-quality evidence).

Clonidine compared with buprenorphine Clonidine seems to be less effective at lowering withdrawal scores and at increasing the proportion of people who complete treatment (moderate-quality evidence).

Note
We found no direct information from RCTs about whether alpha$_2$-adrenoceptor agonists are better than no active treatment in people withdrawing from opioids.

For GRADE evaluation of interventions for opioid dependence, **see table, p 18 .**

Benefits:

Alpha$_2$-adrenoceptor agonists versus methadone:
We found two systematic reviews (search date 2003, 18 RCTs, 4 CCTs, 1709 people; [26] search date 2004; 16 RCTs, 1187 people) comparing alpha$_2$-adrenoceptor agonists versus tapering doses of methadone. [25]

The first systematic review found that people stayed in treatment for significantly less time with alpha$_2$-adrenoceptor agonists than with methadone (3 RCTs, 311 people; SMD –1.07, 95% CI –1.31 to –0.83). Also, significantly fewer people were retained in treatment with alpha$_2$-adrenoceptor agonists than with methadone (3 RCTs, 210 people; 69/103 [67%] with adrenoceptor agonists *v* 96/107 [90%] with methadone; RR 0.73, 95% CI 0.54 to 0.99). There was no significant difference between groups in the number of people who completed withdrawal (9 RCTs, 612 people; 156/324 [48%] with adrenoceptor agonists *v* 153/288 [53%] with methadone; RR 0.89, 95% CI 0.77 to 1.03). Meta-analysis was limited by diversity in study design, and assessment and reporting of outcomes. [26]

The second systematic review found no significant difference between tapered methadone and adrenoceptor agonists in the proportion of people completing treatments (7 RCTs, 577 people; 168/251 [67%] with methadone *v* 192/326 [59%] with adrenoceptor agonists; RR 1.09, 95% CI 0.90 to 1.32). [25]

Lofexidine versus clonidine:
We found one systematic review (search date 2003, 3 RCTs, 158 people). [26] It found no significant difference in the number of people completing withdrawal at 4 weeks (1 RCT, 50 people; 17/26 [65%] with lofexidine *v* 12/24 [50%] with clonidine; P = 0.20). [27] It also found that opioid withdrawal symptoms, as measured by the Abstinence Symptoms Rating Scale, were similar with lofexidine and clonidine (data not reported). [28]

Lofexidine versus buprenorphine:
One RCT (210 people) found that fewer people were abstinent from heroin at 1 month with lofexidine than with buprenorphine (35.7% with lofexidine *v* 45.9% with buprenorphine; significance assessment not performed; measurement of abstinence not clear). [29] The RCT also found that fewer people completed detoxification with lofexidine than with buprenorphine (46% with lofexidine *v* 65% with buprenorphine; significance assessment not performed).

Clonidine versus buprenorphine:
See benefits of buprenorphine for withdrawal, p 8 .

Harms:

Alpha$_2$-adrenoceptor agonists versus methadone:
The first review did not provide a meta-analysis of adverse effects because of the variability of the RCTs. [26] It reported that the main adverse effect of clonidine was orthostatic hypotension. Other adverse effects associated with clonidine included sedation, vomiting, headache, dysphagia, and feeling of a swollen tongue. Most RCTs reported more adverse effects associated with clonidine compared with methadone. The second review reported five RCTs, which found higher mean blood pressure (less hypotension) in people taking methadone compared with taking alpha$_2$-adrenoceptor agonists, but reported two RCTs that found no significant difference. [25]

Lofexidine versus clonidine:
The review did not provide a meta-analysis of adverse effects because of the variability of the RCTs. [26] It reported more hypotension in people with lofexidine than with clonidine in the RCTs it included. One RCT included in the review found significantly fewer adverse effects with lofexidine than with clonidine (data not clear; P < 0.05). [27] Another RCT included in the review found that significantly fewer doses of lofexidine had to be omitted because of low blood pressure compared with clonidine (4% of total doses with lofexidine *v* 9% of total doses with clonidine; P < 0.001).

Lofexidine versus buprenorphine:
The RCT did not report on adverse effects. [29]

Clonidine versus buprenorphine:
See harms of buprenorphine for withdrawal, p 8 .

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 1.2 mg daily), in the treatment of opioid withdrawal has developed since the late 1970s and 1980s. Pharmacologically, alpha$_2$-adrenoceptor agonists help to reduce the noradrenergic storm that follows on from discontinuing opioids. Opioids inhibit noradrenaline release, and discontinuing them causes a rebound release of noradrenaline. If the overproduction ceases quickly, then the alpha$_2$-adrenoceptor agonists will change this balance excessively, and therefore produce hypotensive effects. Therefore, the adverse effect most frequently reported is that of expected hypotension. Most studies in this area have reported on the difference in adverse-effect profiles, especially the problems associated with blood pressure changes following the administration of alpha$_2$-adrenoceptor agonists. Both lofexidine and clonidine have been shown to be effective treatments in helping to reduce the biological withdrawal symptoms. These withdrawal symptoms include: tachycardia, sweating, restlessness, pupil dilatation, bone and joint pains, rhinorrhoea, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin. For those well prepared for withdrawal and seeking earlier resolution of withdrawal symptoms, alpha$_2$-adrenoceptor agonist treatment might be preferred. Clonidine and lofexidine appear to be equally effective for inpatient settings, but the lower incidence of hypotension makes lofexidine more suited to use in outpatient settings.

OPTION ULTRA-RAPID WITHDRAWAL

Withdrawal rates
Compared with standard inpatient withdrawal Ultra-rapid detoxification programmes (precipitated withdrawal, 1-day withdrawal) seem to be more effective at increasing the proportion of people retaining in treatment at 3 months (moderate-quality evidence).

Opioid misuse

Compared with standard inpatient withdrawal Ultra-rapid detoxification programmes (precipitated withdrawal, 1-day withdrawal) may be more effective at reducing heroin misuse as assessed by self-reported use and by analysis of hair samples at 12 months (low-quality evidence).

Adverse effects
Serious adverse effects may occur in people undergoing detoxification under anaesthesia.

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits: We found one systematic review (search date 1997, 9 studies [2 of which were RCTs], 424 people). [30] It provided no meta-analysis because of the short duration, and differing methods of ultra-rapid opioid detoxification. 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.

We found one subsequent RCT comparing 1-day precipitated withdrawal with naloxone under anaesthetic with standard inpatient withdrawal (clonidine plus symptomatic medication), followed by 9 months of naltrexone (50 mg/day) and counselling after withdrawal. [31] It found that significantly more people started naltrexone maintenance with precipitated withdrawal than with standard inpatient withdrawal (40/51 [78%] with precipitated withdrawal *v* 14/50 [28%] with standard inpatient withdrawal; $P < 0.001$). It also found that significantly more people were retained in treatment at 3 months with 1-day withdrawal than with standard inpatient withdrawal (8/51 [16%] with precipitated withdrawal *v* 1/50 [2%] with standard inpatient withdrawal; $P < 0.05$). Overall, there was a significant reduction in self-reported heroin use over the 12-month period (results presented graphically; $P < 0.001$). There was also an overall reduction in morphine concentration in hair over the study period (results presented graphically; $P < 0.05$).

Harms: The review and subsequent RCT did not report on adverse effects. [30] [31] One further RCT found serious adverse effects in three people in the anaesthesia-assisted group. [32] One person with a possible previous history of sleep apnoea developed severe pulmonary oedema and aspiration pneumonia. The second, who had a history of bipolar affective disorder, developed a mixed bipolar state, and the third, who was an insulin-dependent diabetic, developed ketoacidosis.

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).

Comment: **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. [30] 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

Relapse rates
Naltrexone alone or combined with psychosocial treatment compared with placebo alone or combined with psychosocial treatment Naltrexone alone or combined with psychosocial treatment seems to be no more effective at reducing the proportion of people who relapse (moderate-quality evidence).

Opioid misuse

Naltrexone alone or combined with psychosocial treatment compared with placebo alone or combined with psychosocial treatment Naltrexone alone seems less effective at reducing heroin misuse as assessed by urinalysis, but is more effective when combined with psychosocial treatment (moderate-quality evidence).

For GRADE evaluation of interventions for opioid dependence, see table, p 18 .

Benefits:

We found one systematic review (search date 2005, 10 RCTs, 696 people who depended on heroin, or former heroin addicts dependent on methadone) [33] and two additional RCTs. [34] [35]

Naltrexone (alone) versus placebo (alone):
The systematic review found no significant difference between naltrexone alone and placebo alone in the use of heroin (assessed by urinalysis over 1–10 months), in the proportion of people who relapsed at follow-up, or in the proportion of people retained in treatment (use of heroin: 3 RCTs, 134 people; 42/81 [52%] with naltrexone *v* 30/53 [57%] with placebo; RR 0.79, 95% CI 0.59 to 1.06; relapse: 1 RCT, 50 people; 19/28 [68%] with naltrexone *v* 14/22 [64%] with placebo; RR 1.07, 95% CI 0.71 to 1.60; retention: 2 RCTs, 88 people; 6/47 [13%] with naltrexone *v* 10/41 [24%] with placebo; RR 0.50, 95% CI 0.20 to 1.24). [33]

Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial) treatment:
The systematic review found that naltrexone (with or without psychosocial treatment) compared with placebo (with or without psychosocial treatment) significantly reduced the use of heroin (assessed by urinalysis over 1–10 months) (6 RCTs, 249 people; 68/139 [49%] with naltrexone *v* 69/110 [63%] with placebo; RR 0.72, 95% CI 0.58 to 0.90). [33] However, it found no significant difference in the proportion of people who relapsed at follow-up, or in the number of people retained in treatment (relapse: 2 RCTs, 81 people; 26/43 [60%] with naltrexone *v* 24/38 [63%] with placebo; RR 0.94, 95% CI 0.67 to 1.34; retention: 5 RCTs, 203 people; 35/105 [33%] with naltrexone *v* 31/98 [32%] with placebo; RR 1.08, 95% CI 0.74 to 1.57).

Naltrexone (with psychosocial treatment) versus placebo (with psychosocial treatment):
The systematic review found that naltrexone (with psychosocial treatment) compared with placebo (with psychosocial treatment) significantly reduced the use of heroin (assessed by urinalysis over 1–10 months) (2 RCTs, 115 people; 26/58 [45%] with naltrexone *v* 39/57 [68%] with placebo; RR 0.66, 95% CI 0.47 to 0.92). [33] However, it found no significant difference in the proportion of people who relapsed at follow-up, or in the proportion of people retained in treatment (relapse: 1 RCT, 35 people; 8/20 [40%] with naltrexone *v* 4/15 [27%] with placebo; RR 1.50, 95% CI 0.55 to 4.06; retention: 1 RCT, 51 people; 18/34 [53%] with naltrexone *v* 6/17 [32%] with placebo; RR 1.50, 95% CI 0.73 to 3.07).

Different doses of naltrexone:
The first additional RCT (66 people) compared oral naltrexone 0.05, 0.5, and 50 mg daily (after detoxification and naltrexone 50 mg/day for 1 week). [34] The RCT found no significant difference between all three doses in heroin use over 6 months (P = 0.156). It also found no significant difference in the mean number of days retained in treatment (47.8 days with 0.05 mg *v* 46.6 days with 0.5 mg *v* 58.9 days with 50 mg; P = 0.93 between groups). The second additional RCT (60 people) compared depot naltrexone 192 and 384 mg, and depot placebo given at 1 and 5 weeks (after detoxification and oral naltrexone for 3 days). [35] It found that the proportion of people retained in treatments at 8 weeks was 12/20 (60%) with naltrexone 192 mg, 15/22 (68%) with naltrexone 384 mg, and 7/18 (39%) with placebo (significance assessment not performed). It also found no significant difference in the proportion of negative urine samples (when missing samples were not considered positive) (73.5% with 192 mg *v* 79.4% with 384 mg *v* 74.2% with placebo; P = 0.85 between groups).

Harms:

Naltrexone (alone) versus placebo (alone):
The review found no significant difference between groups in the proportion of people with at least one adverse effect (not described) (2 RCTs, 87 people; RR 0.96, 95% CI 0.65 to 1.42). [33]

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).

Naltrexone (with or without psychosocial treatment) versus placebo (with or without psychosocial treatment):
The review found no significant difference between groups in the proportion of people with at least one adverse effect (not described) (3 RCTs, 139 people; RR 1.21, 95% CI 0.81 to 1.81). [33]

Naltrexone (with psychosocial treatment) versus placebo (with psychosocial treatment):
The review found no significant difference between groups in the number of people with at least one adverse effect (not described) (1 RCT, 52 people; RR 2.47, 95% CI 0.74 to 8.28). [33]

Different doses of naltrexone:
The first additional RCT found no significant difference between naltrexone 0.05, 0.5, and 50 mg/day in ratings of adverse effects (depression, increased erections, increased thirst, low energy, and tiredness) (data presented graphically; P = 0.98). [34] The second additional RCT reported that 6/20 (30%) people had adverse effects with naltrexone 192 mg , 3/22 (14%) with naltrexone 384 mg , and 2/19 (11%) with placebo (adverse effects reported as fatigue, injection-site induration, and injection-site pain; significance assessment not performed). [35]

Comment:

The authors of the review discussed here [33] 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 per day 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 affect compliance. Naltrexone might be an efficacious adjuvant therapy, especially in people who fear severe consequences if they do not stop taking 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. [36]

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 they awaken 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.

SUBSTANTIVE CHANGES

Buprenorphine for stabilisation: One systematic review that searched for systematic reviews and RCTs added. [12] The systematic review found no new evidence that met our reporting criteria. The systematic review did not perform a meta-analysis for buprenorphine versus placebo but reported that the reviews found buprenorphine was more effective at retaining people in treatment (with higher doses being more effective than lower doses) and at reducing opiate use compared with placebo or no drug treatment. Categorisation of Buprenorphine versus placebo unchanged (Beneficial). The systematic review carried out a meta-analysis for buprenorphine versus methadone and found that flexible dosing regimens of buprenorphine were less effective at increasing retention in treatment compared with flexible dosing regimens of methadone. However, previous data reporting similar rates of opioid use with both buprenorphine and methadone were unchanged so still insufficient data to assess which drug is more effective. Categorisation of Buprenorphine versus methadone unchanged (Unknown effectiveness; both beneficial and seem as effective as each other).
Methadone for stabilisation: Two systematic reviews added. [12] [19] One systematic review [12] searched for systematic reviews and RCTs and found no new evidence that met our reporting criteria. The systematic review did not perform a meta-analysis for methadone versus placebo. It reported that the reviews found methadone was more effective at increasing retention in treatment and at reducing opioid misuse as assessed by self-reported heroin compared with placebo or no drug treatment. It also found higher doses of methadone were more effective than lower doses at increasing the proportion of people retained in treatment, and at reducing heroin abstinence rates (self-reported heroin use and urine-confirmed opioid abstinence). Categorisation of Methadone versus placebo unchanged (Beneficial). The systematic review carried out a meta-analysis for methadone versus buprenorphine and

found that flexible dosing regimens of methadone were more effective at increasing retention in treatment compared with flexible dosing regimens of buprenorphine. [12] The other systematic review found that methadone increased the proportion of people retained in treatment compared with placebo, control, and buprenorphine. [19] However, previous data reporting similar rates of opioid use with both methadone and buprenorphine unchanged so still insufficient data to assess which drug is more effective. Categorisation of Buprenorphine versus methadone unchanged (Unknown effectiveness; both beneficial and seem as effective as each other).

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Disclaimer

TABLE **GRADE evaluation of interventions for opioid dependence.**

Important outcomes	Retention in treatment, opioid misuse, withdrawal rates, relapse rates, mortality, and adverse effects								
Number of 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?									
2 (at least 487) [11] [12]	Retention in treatment	Buprenorphine *v* placebo	4	0	+1	0	0	High	Consistency point added for positive dose response
2 (at least 487) [11] [12]	Opioid misuse	Buprenorphine *v* placebo	4	0	+1	0	0	High	Consistency point added for positive dose response
1 (92) [14]	Retention in treatment	Different frequencies of buprenorphine compared with each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (92) [14]	Opioid misuse	Different frequencies of buprenorphine compared with each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 6 RCTs (at least 1013) [11] [19]	Retention in treatment	Methadone *v* no opioid-replacement therapy	4	0	0	–1	0	Moderate	Directness point deducted for large variation in study duration and design
At least 7 RCTs (at least 1013) [11] [19]	Opioid misuse	Methadone *v* no opioid-replacement therapy	4	0	0	–1	0	Moderate	Directness point deducted for large variation in study duration and design
3 (435) [18]	Mortality	Methadone *v* no opioid-replacement therapy	4	0	0	–1	0	Moderate	Directness point deducted for large variation in study duration and design
3 (237) [20]	Opioid misuse	High-dose methadone *v* lower-dose methadone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about timing and method of measuring abstinence
7 (at least 976) [11] [12]	Retention in treatment	Buprenorphine *v* methadone	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity among RCTs
6 (at least 837) [11] [12]	Opioid misuse	Buprenorphine *v* methadone	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity among RCTs
What are the effects of drug treatments for withdrawal in people with opioid dependence?									
3 (156) [24]	Withdrawal rates	Buprenorphine *v* methadone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
8 (760) [24]	Withdrawal rates	Buprenorphine *v* clonidine	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (17) [24]	Withdrawal rates	Buprenorphine *v* oxazepam	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (22) [25]	Withdrawal rates	Methadone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
11 (748) [25]	Withdrawal rates	Methadone *v* any other pharmacological treatments	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about comparators
5 (237) [25]	Withdrawal rates	Methadone *v* other opioid agonists	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (24) [25]	Withdrawal rates	Methadone *v* chlordiazepoxide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Retention in treatment, opioid misuse, withdrawal rates, relapse rates, mortality, and adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 9 RCTs (at least 612) [25]	Withdrawal rates	Alpha$_2$-adrenoceptor agonists *v* methadone	4	0	0	–1	0	Moderate	Directness point deducted for diverse study designs, assessment and reporting of outcomes
1 (50) [27]	Withdrawal rates	Lofexidine *v* clonidine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 RCT (210) [29]	Withdrawal rates	Lofexidine *v* buprenorphine	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear measurement of outcomes
1 (101) [31]	Withdrawal rates	Ultra-rapid withdrawal *v* standard withdrawal	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (101) [31]	Opioid misuse	Ultra-rapid withdrawal *v* standard withdrawal	4	–2	0	0	0	Low	Quality points deducted for sparse data and for incomplete reporting of results
What are the effects of drug treatments for relapse prevention in people with opioid dependence?									
1 (50) [33]	Relapse rates	Naltrexone alone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (134) [33]	Opioid misuse	Naltrexone alone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (35) [33]	Relapse rates	Naltrexone (with psychosocial treatment) *v* placebo (with psychosocial treatment)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (115) [33]	Opioid misuse	Naltrexone (with psychosocial treatment) *v* placebo (with psychosocial treatment)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational;
Consistency: similarity of results across studies;
Directness: generalisability of population or outcomes.