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Dihydrocodeine for detoxification and maintenance treatment in illicit opiate-dependent individuals (Protocol)

Carney T, Van Hout MC, Norman I, Dada S, Parry CDH

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[Intervention Protocol]

Dihydrocodeine for detoxification and maintenance treatment in illicit opiate-dependent individuals

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To investigate the effects of dihydrocodeine (DHC) in comparison to other pharmaceutical opioids and placebos in the detoxification of opiate-dependent individuals, as well as in maintenance substitution therapy.

BACKGROUND

Description of the condition

According to the World Drug Report (2014), between 162 million and 324 million people (3.5 per cent and 7.0 per cent of the world population aged 15 to 64 years) in 2012 had used an illicit drug at least once in the previous year, with an estimated 183,000 (range: 95,000 to 226,000) drug-related deaths (UNODC 2014). This corresponds to a mortality rate of 40.0 (range: 20.8 to 49.3) deaths per million among the population in this age range. Problem drug use remained stable at between 16 and 39 million individuals in this reporting period. Injecting drug use is estimated by the United Nations Office on Drugs and Crime (UNODC), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Bank and the World Health Organization (WHO), as ranging between 8.9 million and 22.4 million, and with an estimated prevalence rate of 0.27 per cent (range: 0.19 to 0.48 per cent) of the population aged 15 to 64 years (UNODC 2014). In addition to related social, economic and law enforcement costs, injecting risk behaviours contribute to HIV and hepatitis C vulnerability and transmission. Harm reduction services act as a major component in global tactics and responses to the spread of HIV, and include needle and syringe programmes, opioid substitution therapy, HIV testing and counselling, and antiretroviral therapy (UNODC 2014). According to the World Health Bulletin in 2011, governments of countries in which injecting drug use and HIV epidemics represent a public health problem are increasingly preoccupied with alternative opioid substitution therapy modalities, within integrated HIV prevention and treatment

programmes (Kermode 2011).

There are an estimated 15.5 to 15.6 (WHO) million people worldwide aged 15 and older who are dependent on illicit opiates (Degenhardt 2014; WHO 2009), which is an estimated prevalence of 0.14% for males and 0.30% for females. In 2007 it was estimated that 7 million of these individuals use heroin (UNODC 2007). In terms of illicit opiates and opioids, recent global trends indicate displacement between pharmaceutical and/or prescription opioids and heroin, dependent on pricing, availability and access in illicit drug markets (UNODC 2014). Opioid dependence is estimated to account for 9.2 million disability-adjusted life years lost (DALYs) worldwide in 2010, which is 0.37% of the total DALYs lost worldwide (Degenhardt 2014). The burden increased 73% in 10 years (from 1990 to 2010). Seven million of these DALYs were lost due to disability (YLD), which accounts for almost half (43.7%) of YLDs that are attributed to illicit drug use disorders in total and 0.94% of all YLDs worldwide. In addition, 2 million years of life lost are estimated to be due to opioid dependence (Degenhardt 2014). In 2010 alone, a total of 43,000 deaths were attributed to illicit opiate dependence (Degenhardt 2014).

Opiate dependence develops following the regular use of opioids, and is defined as a chronic, relapsing disorder and permanent metabolic deficiency (Dole 1965) and contributes to compulsive drug-seeking behaviours, difficulties in controlling consumption, a withdrawal state upon reduction or cessation, and evidence of tolerance, despite destructive physical and psychosocial consequences for the user (WHO 2009). Opiate dependence is characterised by three or more of the following features occurring together in the previous year of use:

- a strong desire or sense of compulsion to take opioids,
- difficulties in controlling opioid use,
- a physiological withdrawal state,
- tolerance,
- progressive neglect of alternative pleasures or interests because of opioid use, and
- persisting with opioid use despite clear evidence of overtly harmful consequences (WHO 2007).

Opiate dependence incurs health, social, law enforcement and economic costs. In terms of health, illicit opioid use is a major causal factor in mortality from both intoxication (overdose, driving accidents), and transmission of blood-borne disease via injecting risk behaviours (Degenhardt 2011). The primary cause of death for opiate users is overdose (UNODC 2013). Although data are limited, it is estimated that 70,000 to 100,000 people die from opioid overdose every year (UNODC WHO 2013). Other causes of death include trauma (including violence and homicide, injuries and accidents), suicide, and liver- and respiratory-related disease (Darke 2002; Darke 2012; Degenhardt 2011; Vlahov 2004). Illicit opiate users often inject their drugs, which is strongly related to HIV transmission. An estimated 5% to 10% of HIV transmissions are estimated to be due to injecting drug use, often of an opiate such as heroin. In some parts of the world, this is as high as 40% (Mathers 2010). A recent systematic review also found that AIDS-related mortality was 1.88 per 100 person years across studies conducted in Asia, Europe (central and western), North America and Australasia (Degenhardt 2011). Unsafe injecting practices associated with illicit opiate use have also been associated with hepatitis C transmission, with an estimated 3 to 4 million people newly infected every year and 90% of these new infections attributable to unsafe injection practices (Hellard 2009).

In addition, opiate dependence can cause harm beyond the individual who uses opiates. The use of illicit opiates such as heroin and morphine among opiate-using pregnant women can have serious effects for their unborn babies including spontaneous abortion and infant mortality. Opiates are also transferrable to the foetus and change the placental function, making preterm delivery a strong possibility. Babies can be born with congential issues, and experience withdrawal from opiates (Malek 2012). Neonatal abstinence syndrome (NAS), which is the withdrawal from opioids of a newborn baby, is a well-established phenomenon (Finnegan 1975). It may last up to 10 weeks after delivery and require that the affected child-to-be is placed in the intensive care unit, because if they are untreated this can lead to increased risk of infant mortality (Jansson 2009; Malek 2012). This may have significant costs for healthcare services (Patrick 2012).

Description of the intervention

Evidence has shown that opioid substitution therapy programmes are effective in reducing illicit opiate use, HIV-related risk behaviours, fatal overdose and criminal activity, and associated family, community and financial stress. They also enhance access to and continued use of medical and social services in both adolescents (Minozzi 2014) and adults (Ferri 2011; Gowing 2011; Lawrinson 2008; Mattick 2014; Weber 2009), including pregnant women (Minozzi 2013). Despite this evidence of effectiveness, it is estimated globally that only 8% of injecting drug users receive opioid substitution therapy, with lower figures in developing countries (Mathers 2010).

Opiate users often present to community and specialist services requesting detoxification (Oldham 2004). Approaches to assist and support individuals who are dependent on opiates include detoxification, relapse prevention programmes, outpatient counselling, therapeutic communities and long-term opiate substitution (Amato 2005; Amato 2011). Treatment and detoxification using various therapeutic agents is vital in the management of patients dependent on opiates. Agents include oral administration of full or partial opioid agonists (i.e. methadone, buprenorphine, levomethadyl acetate (LAAM), codeine or oral morphine) (Amato 2005; Gowing 2011; Riksheim 2014). Methadone maintenance treatment is the most frequently prescribed treatment worldwide. One exception is in France where greater proportions of patients are prescribed buprenorphine (Auriacombe 2004).

Methadone maintenance treatment has been extensively studied, showing strong evidence for its effectiveness in recent Cochrane reviews (Mattick 2009; Mattick 2014). Calls to scale up availability of methadone maintenance treatment have been evident in recent years (Mathers 2010; Mattick 2009). Low threshold methadone maintenance treatment is increasingly popular and designed to: attract a wider range of patients; reduce barriers to admission; improve retention of patients in treatment; and reduce heroin use, injecting risk behaviours, criminal activity and mortality rates (Strike 2013). Retention in treatment outcomes are related to appropriate and higher doses of methadone and individualisation of doses (Amato 2005; Bao 2009). However, methadone maintenance treatment remain controversial due to its indefinite and often long-term provision of dependence-producing medication (Amato 2005; Sees 2000).

Buprenorphine is also effective as a maintenance treatment agent, with comparisons to methadone in a Cochrane review concluding that both are effective in the maintenance treatment of heroin dependence, retention of patients in treatment at any dose above 2 mg, and suppression of illicit opioid use at doses of 16 mg or higher (Mattick 2014). However, this Cochrane review suggests that compared to methadone, buprenorphine results in poorer patient retention in treatment when doses are flexible or at low fixed doses. On the other hand, Maas 2013 advises the provision of buprenorphine as appropriate if the primary outcomes of treatment are stopping opiate use, as well as maintaining abstinence. Buprenorphine may cause fewer fatal intoxications than methadone (Soyka 2015). Comparisons between buprenorphine and methadone at fixed medium or high doses show that effectiveness relating to treatment retention and suppression of illicit opioid use appear similar (Mattick 2009). Of note is that flexible doses of these agents are more cost effective and applicable to patient care (Connock 2007), and that methadone is superior in retaining patients in treatment (Mattick 2014). Costs of methadone provision are also lower than those for buprenorphine (Maas 2013).

Recent studies have underscored the effects of varied aspects of these substitution programmes and the interplay of individual patient factors (Arora 2013; Riksheim 2014; Strike 2013). Other concerns centre on the safety and effectiveness of methadone and buprenorphine in specific patient subgroups (Connock 2007). Of note is that the presence of adjunct psycho-social support and treatment do not incur additional benefits to treatment outcomes, and highlight the need for employing varied criteria in assessment of treatment outcomes as they relate to individual, interpersonal, vocational, health and emotional functioning, and subsequent recommendations (Amato 2011; Davoli 2015). Alternatives include heroin substitution treatment, with Cochrane reviews suggesting the prescribing of heroin alongside flexible doses of methadone is a feasible option for long-term treatment-refractory opioid users who have a history of failed maintenance treatment (Ferri 2011). Use of slow release oral morphine (SROM) has also been assessed in several small trials but there is not sufficient evidence to show that it is effective, and there have also been reports of adverse events (Ferri 2013).

A Cochrane review comparing treatments for opiate withdrawals found no significant differences between methadone and buprenorphine in treatment completion, but faster reduction of withdrawal symptoms with buprenorphine, and with buprenorphine more effective than clonidine in the management of opioid withdrawal (Gowing 2009). Given positive retention rates of methadone maintenance treatment in comparison to detoxification programmes, studies have reported low support for diverting resources from methadone maintenance towards long-term detoxification (Sees 2000). Methadone has a long half-life and when tapering employs incremental dose reductions over a course of 7 to 21 days. However patients report unpleasant withdrawals in later stages of detoxification, giving rise to the increased use of alternatives such as clonidine, lofexidine and dihydrocodeine (DHC) to assist. Clonidine and lofexidine are more effective than placebo in withdrawal management (Gowing 2014). Complications caused by clonidine's hypotensive and sedative effect and lofexidine's limited capacity to manage withdrawals have reduced their popularity in primary and community care settings (Seivewright 2000). Slow tapering with temporary substitution of long-acting opioids can reduce severity of withdrawals (Amato 2013). Antagonist-induced withdrawal under heavy sedation or anaesthesia as a detoxification option lacks value due to cost, the potential for adverse life-threatening events, and required intensive care resources (Gowing 2010).

Not much is known about how DHC works in comparison to other pharmacological interventions that are commonly used. It is suggested, however, that DHC is a short-acting opioid (Banbery 2000), and therefore will need to be administered more frequently, up to a few times a day (Banbery 2000; Hall 2007). DHC has been proposed as a substitute for long-acting opioids such as methadone in order to assist with withdrawal symptoms (Banbery 2000). It is also proposed that switching from long-acting opioids such as methadone to DHC after detoxification can be used during the detoxification process (Day 2003).

How the intervention might work

DHC is a semi-synthetic opioid analogue of codeine (Klepstad 2005) and a short-acting drug which offers an alternative substitution treatment and detoxification support to individuals with less severe dependence on opiates, and to stabilise methadone patients (Banbery 2000; Krausz 1995; Krausz 1998). DHC is well tolerated orally and has a half-life of about 4 hours (Banbery 2000). In addition to its viable uses as an alternative to methadone treatment (Banbery 2000; Hall 2007; Krausz 1995; Krausz 1998), it is also commonly prescribed as an antitussive, anti-diarrhoeal agent and analgesic drug in the treatment of moderate pain (Leppert 2010; Moore 2000; Webb 2001).

DHC maintenance treatment is typically low threshold, less bureaucratic, increases patient choice and retention in treatment, and may be prescribed by general practitioners in the form of capsules and juice for dispensing at pharmacies (Krausz 1998). Banbery 2000 reports that DHC may have advantages in detoxifying methadone-maintained patients in a rapid two-week outpatient detoxification programme by successfully using DHC to cross-over from a methadone dose (30 mg). They report that, on consecutive use, a "steady-state" condition for DHC is achieved and weaning can be accomplished successfully with minimal complications within a few days.

However, in contrast to methadone and buprenorphine, DHC may be compromised by its short-acting properties, necessitating frequent dosing and risk of patients oscillating between sedation and withdrawals (Backmund 2001; Banbery 2000; Seymour 2001; Strang 2005). Prescribed DHC is often inadequate in relieving acute opiate withdrawals (Tompkins 2007). The importance of reducing periods of relative withdrawal between doses is thus emphasised (Mitchell 2003), along with the need for experienced prescribing practitioners in detoxification using DHC (similar to methadone) (Bao 2009).

Why it is important to do this review

The most recent World Drug Report (UNODC 2014) has highlighted gaps in service provision for problem drug users receiving access to drug dependence treatment, both in the community and in more specialised settings such as prisons. DHC's efficacy and effectiveness as substitution therapy and its use for detoxification is controversial (Banbery 2000; Ulmer 1997; Zamaprutti 2010) and debate centres on its potential for use as treatment and detoxification for specific individuals with less severe dependence on opiates and for stabilised methadone patients (Luty 2004). Dissatisfaction with the long half-life of methadone has stimulated patient interest in alternative forms of short-term detoxification, such as the use of short-acting drugs like DHC (Oldham 2004). If DHC is shown to be effective as a short-term detoxification treatment in community and special settings, it may well be a more cost-effective option for governments than the long-term use of methadone.

There have not been many studies on the possibility of using DHC as an alternative to other pharmacological interventions. There is some evidence on the usefulness of DHC in managing opiate withdrawals for individuals in police custody (Pearson 2000), and on its safety, flexibility, potential retention of patients in treatment and its capacity to reach wider groups of stabilised or low-threshold drug users who use opiates (Krausz 1998; MacLeod 1998; Robertson 1990; Swadi 1990). However, these studies are dated and there is a need for a more systematic review of the evidence. Given the potential for use in treating such wider groups of drug users, particularly those with lower severity of opiate dependence, accessing community care and general health settings, and as an alternative for use in developed and developing countries, DHC could present a useful alternative for short-term detoxification of individuals in the community or be provided as an alternative within specific settings such as prisons. A systematic review of the evidence also indicates the need for experienced prescribing practitioners in detoxification using DHC (Arora 2013), where there are no existing guidelines on standard use, as well as studies to establish whether it is feasible for maintenance therapy.

OBJECTIVES

To investigate the effects of dihydrocodeine (DHC) in comparison to other pharmaceutical opioids and placebos in the detoxification of opiate-dependent individuals, as well as in maintenance substitution therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Pre- and post-test studies and qualitative studies will be excluded from this review.

Types of participants

Participants are adolescent (aged 16 years and older) and adult individuals who are currently dependent on illicit opiates (heroin, opium and illegally-sourced opiates such as morphine and codeine), diagnosed according to the DSM (III, IV or V) criteria. Participants who have pre-existing conditions (psychiatric conditions, pregnancy) will be excluded. Individuals who have contraindications to DHC or the comparison pharmacological intervention will also be excluded.

Types of interventions

Experimental intervention:

DHC as dispensed to participants primarily for detoxification from opioid-agonist treatments, and secondarily for maintenance purposes. Since DHC is a short-acting opioid, treatment may initially need to be provided every four hours (Hall 2007). In addition, because there are no regulations for the provision of DHC as substitution therapy, there may be marked differences in the dispensing of DHC (NICE 2007; Strang 2005). However, it is expected that detoxification will last up to 15 days, and maintenance

for a minimum of 30 days, based on previous studies of opiate-substitution therapy.

Control intervention:
The control could either be treatment as usual, placebo or other types of pharmacological intervention. These include full (methadone, levomethadyl acetate or LAAM, oral morphine) or partial opioid antagonists (buprenorphine), as well as other medication such as Alpha 2 adrenergic agonists (clonidine and lofexidine) and antagonist medication (naltrexone).

Types of outcome measures

Primary outcomes

1. Treatment retention at the end of treatment and at follow-up appointments (since dropout is a major problem in the treatment of illegal opioids).
2. Abstinence from illicit opiate use after detoxification therapy following the detoxification process at follow-up appointments, either through self-report or urinalysis, measured as the number of subjects abstinent at the end of treatment and at follow up.
3. Abstinence from illicit opiate use after substitution/maintenance therapy at follow-up periods, either through self-report or urinalysis, measured as the number of subjects abstinent at the end of treatment and at follow up.
4. Number of participants who experienced serious adverse events. According to the guidelines, serious events include events that result in death, are life-threatening, require hospitalisation or an extension of existing hospitalisation, result in persistent or significant disability or incapacity, result in congenital problems or any other event that may put the participant's health in jeopardy and may require medical or surgical intervention to prevent this (OHRP 2007). This includes the development of drug abuse or dependency on DHC.
5. Number of participants who experienced adverse events. Including any unfavourable medical occurrences that participants experience at least partly due to their participation in the study. This includes both physical and psychological events (OHRP 2007).

Secondary outcomes

1. Use of other substances of abuse (both legal and illegal).
2. Engagement in crime.
3. Physical health consequences (typically related to substance use such as appetite, levels of energy, nausea).
4. Drug overdose (symptoms of overdose and not limited to death due to overdose).
5. Diversion (selling of drugs, use of prescribed opiates for illegal use).
6. Education or employment status.

Search methods for identification of studies

Electronic searches

We will undertake a comprehensive search of the following databases:

- Cochrane Drugs and Alcohol Group (CDAG) Specialised Register (most recent);
- Cochrane Central Register of Controlled Trials (CENTRAL) (most recent);
- MEDLINE (PubMed) (January 1966 to present);
- EMBASE (Elsevier, EMBASE.com) (January 1974 to present);
- Web of Science (Thomson Reuters) (January 1990 to present).

A detailed search strategy will be developed in CENTRAL and will then be revised accordingly for each database that will be searched to take into account differences in controlled vocabulary and syntax rules. The search strategy will combine the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials, as referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
The subject search will utilise a combination of controlled vocabulary and free-text terms based on the search strategy for searching CENTRAL (see Appendix 1).

Searching other resources

We will also contact authors and search reference lists in all relevant journal articles to obtain information on potential additional RCTs. In addition, the authors will also search for other unpublished studies and assess relevant conference proceedings for additional references. The following websites will also be searched:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
- Trialsjournal.cm.

All studies with an English abstract, whether or not the full article is in a foreign language, will be included in the search. If, after reading the abstract, the article appears to possibly meet the inclusion criteria, it will be obtained and translated into English.

Data collection and analysis

Selection of studies

Two authors (TC, IN) will independently inspect the titles and abstracts that are found in the searches. Potentially-relevant articles will be obtained in full text and further assessed for eligibility by the same two review authors. Where there is any disagreement between these two authors that cannot be resolved following their independent review of the full text, another author (MCVH) will read the studies in order to assist with making a decision on whether to include or exclude the article.

Data extraction and management

Two of the review authors (TC and MCVH) will independently extract data from the included studies using a data extraction form that will be adapted from a standard extraction form used by CDAG. These data will then be entered into the Cochrane Collaboration software (ReviewManager 5.3) for data analysis. The following data will be extracted: number of participants treated, route of administration of DHC and comparison, dosage of DHC and comparison, study design, study duration and length of follow-up, results related to the primary and secondary outcomes, funding source and conflict of interest of study authors.

When there is information missing from the original studies on outcomes or other important information, we will contact the corresponding author via e-mail in order to request additional data.

Assessment of risk of bias in included studies

The 'Risk of bias' assessment of RCTs in this review will be performed using the criteria recommended in the *Cochrane Handbook* (Higgins 2011). The recommended approach for assessing risk of bias in studies included in a Cochrane Review is a two-part tool that addresses seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias) blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments we will use the criteria indicated in the*Cochrane Handbook,* adapted to the addiction field. See Table 1 for details.

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

Blinding of participants, personnel and outcome assessors (avoidance of performance bias and detection bias) will be considered separately for objective outcomes (e.g. drop out, use of substance of abuse measured by urinalysis, subjects relapsed at the end of follow up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance, side effects, social functioning as integration at school or at work or in family relationships).

Incomplete outcome data (avoidance of attrition bias) will be considered for all outcomes except for treatment drop out, which is very often the primary outcome measure in trials on addiction.

Grading of evidence

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

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

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

Grading is decreased for the following reasons:

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

Grading is increased for the following reasons:

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

Only the primary outcomes will be included and graded in the 'Summary of findings' table (retention in treatment, abstinence

from illicit opiates following detoxification, abstinence from illicit opiates following maintenance or substitution therapy or serious adverse events) for DHC compared to methadone, buprenorphine, LAAM or morphine.

Measures of treatment effect

The outcomes of the experimental and control groups will be compared at follow-up appointments. For dichotomous data, risk ratios (with 95% confidence intervals (CIs)) will be calculated. For continuous data, the mean difference (MD) will be calculated, with 95% CIs. In the case of continuous data, the standardised mean difference (SMD) will be the treatment measure used, again with 95% CIs if the outcomes are measured with different tools (Higgins 2011). This is only expected to be a possibility for self-reported primary outcomes (abstinence) and any optional secondary outcomes (such as measures of physical health that may be linked to substance use e.g. dental problems, gastro-intestinal problems and tremors or shakes, engagement in illegal activity).

Unit of analysis issues

If included studies have more than one intervention group, simply entering each comparison in a meta-analysis may lead to the error of double counting (Higgins 2011). In this case, we will either combine groups to allow single comparisons, set up separate analyses or perform subgroup analyses (if possible) and deselect the calculation of overall totals to count the participants that were randomised and not the number of treatment attempts provided.

Dealing with missing data

We will contact the original investigators of research studies to request any missing data (including outcomes, summary data, individuals and study-level characteristics) by email. If we are not able to obtain missing data from the original investigators, we will need to decide whether the data are missing at random (not related to the actual data) or not missing at random (related to the actual data such as due to participant drop out). When study data are assumed to be missing at random, only the available data will be analysed. Where there seems to be a significant amount of missing data, the possible effects of this on the review's findings will be addressed in the Discussion section. If data are not missing at random, it will be assumed that the participants that dropped out at follow-up are continuing to use illicit opiates. However, this assumption will be tested with a sensitivity analysis, which will be monitored by one of the authors who has a background in statistical analysis.

Assessment of heterogeneity

If more than one study is found and included in the review, we will check for heterogeneity across the studies. Chi² (X^2) and I^2 statistical tests will be used to assess if observed differences in study results occur by chance alone or if these differences are estimates beyond chance. If the P value for the Chi² test is 0.10 or lower, and the I^2 is 50% or more, this indicates a potential problem with heterogeneity (Higgins 2011).

Assessment of reporting biases

If there are more than 10 included studies in the meta-analysis, we will consider the risk of publication bias by examining the symmetry of funnel plots. If any funnel plots are asymmetrical, these will be further explored, but this is not always indicative of publication biases (Higgins 2011).
In addition, when there seems to be selective outcome reporting, we will contact the authors of the relevant studies to request additional information.

Data synthesis

We will first summarise the main findings of the included studies, before we decide whether studies are appropriate for meta-analysis, namely if there two or more individual trials with comparable intervention methods and outcomes.
Given the heterogeneity of drug-using populations, as well as the fact that often intervention types are very different, we will use the random-effects model for analysis. If there is more than one follow-up period for single studies, separate analyses will be performed on the different follow-up periods. This will be short-term (one month or less), medium-term (two to six months) and long-term (seven months or more) follow-up, Where meta-analysis is not possible, we will report the findings narratively in the body of the review.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will only be possible if there are enough included studies that have large-enough sample sizes. These analyses may include:

- Age (16 to 17 year olds versus 18 years and over).
- Treatment history (first treatment attempt versus previous treatment attempts for opiates).
- Mode of illicit opiate use (injection versus other).

Sensitivity analysis

We will explore the effects of risk of selection bias by conducting the meta-analysis twice if possible, with the second meta-analysis excluding studies rated as high risk of allocation concealment and sequence generation. This will only take place if there are enough studies to conduct a meta-analysis, and only for the primary outcome (treatment retention, abstinence, serious adverse events).

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Criteria for 'Risk of bias' assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation

Table 1. Criteria for 'Risk of bias' assessment (*Continued*)

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

Table 1. Criteria for 'Risk of bias' assessment (*Continued*)

	unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
6. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically-relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically-relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to

Table 1. Criteria for 'Risk of bias' assessment (*Continued*)

		induce clinically-relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group)
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk

APPENDICES

Appendix 1. CENTRAL search strategy

ID	Search
#1	(dihydrocodeine or Codhydrin or codhydrine or codicontin or cohydrin or dehacodin or df118 or "dh codeine" or "di-hydrin" or didrate or dihydrin or dihydroneopine or drocode or hydrocodeine or hydrocodin or nadein or nadeine or napacodin or novicodin or paracodein or paracodin or parzone or rapacodin or remedacen or "tiamon mono"):ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Opioid-Related Disorders] explode all trees

(*Continued*)

#3	MeSH descriptor: [Substance Abuse, Intravenous] explode all trees
#4	MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees
#5	((opiate* or opioid* or narcot* or heroin* or drug or substance) and (abstin* or abstinen* or abus* or addict* or depend* or detoxify* or desintoxi* or disintoxi* or disintossi* or overdos* or intoxicat* or withdraw* or relaps*)):ti,ab
#6	#2 or #3 or #4 or #5
#7	#1 and #6

CONTRIBUTIONS OF AUTHORS

The protocol was drafted by TC and MCVH. All authors commented on and approved the final version of the protocol.

DECLARATIONS OF INTEREST

Tara Carney: None known

Marie Claire Van Hout: None known

Ian Norman: None known

Siphokazi Dada: None known

Charles DH Parry: None known

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