Carney, T, Van Hout, MC, Norman, I, Dada, S, Siegfried, N and Parry, CD

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Carney T, Van Hout MC, Norman I, Dada S, Siegfried N, Parry CDH.
Dihydrocodeine for detoxification and maintenance treatment in individuals with opiate use disorders.
Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD012254.
DOI: 10.1002/14651858.CD012254.pub2.

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[Intervention Review]

Dihydrocodeine for detoxification and maintenance treatment in individuals with opiate use disorders

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Editorial group: Cochrane Drugs and Alcohol Group
Publication status and date: New, published in Issue 2, 2020.

Citation: Carney T, Van Hout MC, Norman I, Dada S, Siegfried N, Parry CDH. Dihydrocodeine for detoxification and maintenance treatment in individuals with opiate use disorders. *Cochrane Database of Systematic Reviews* 2020, Issue 2. Art. No.: CD012254. DOI: 10.1002/14651858.CD012254.pub2.

ABSTRACT

Background

Medical treatment and detoxification from opiate disorders includes oral administration of opioid agonists. Dihydrocodeine (DHC) substitution treatment is typically low threshold and therefore has the capacity to reach wider groups of opiate users. Decisions to prescribe DHC to patients with less severe opiate disorders centre on its perceived safety, reduced toxicity, shorter half-life and more rapid onset of action, and potential retention of patients. This review set out to investigate the effects of DHC in comparison to other pharmaceutical opioids and placebos in the detoxification and substitution of individuals with opiate use disorders.

Objectives

To investigate the effectiveness of DHC in reducing illicit opiate use and other health-related outcomes among adults compared to other drugs or placebos used for detoxification or substitution therapy.

Search methods

In February 2019 we searched Cochrane Drugs and Alcohol's Specialised Register, CENTRAL, PubMed, Embase and Web of Science. We also searched for ongoing and unpublished studies via ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and Trialsjournal.com. All searches included non-English language literature. We handsearched references of topic-related systematic reviews and the included studies.

Selection criteria

We included randomised controlled trials that evaluated the effect of DHC for detoxification and maintenance substitution therapy for adolescent (aged 15 years and older) and adult illicit opiate users.

The primary outcomes were abstinence from illicit opiate use following detoxification or maintenance therapy measured by self-report or urinalysis. The secondary outcomes were treatment retention and other health and behaviour outcomes.

Data collection and analysis

We followed the standard methodological procedures that are outlined by Cochrane. This includes the GRADE approach to appraise the quality of evidence.

Main results

We included three trials (in five articles) with 385 opiate-using participants that measured outcomes at different follow-up periods in this review. Two studies with 150 individuals compared DHC with buprenorphine for detoxification, and one study with 235 participants compared DHC to methadone for maintenance substitution therapy. We downgraded the quality of evidence mainly due to risk of bias and imprecision.

For the two studies that compared DHC to buprenorphine, we found low-quality evidence of no significant difference between DHC and buprenorphine for detoxification at six-month follow-up (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.25 to 1.39; P = 0.23) in the meta-analysis for the primary outcome of abstinence from illicit opiates. Similarly, low-quality evidence indicated no difference for treatment retention (RR 1.29, 95% CI 0.99 to 1.68; P = 0.06).

In the single trial that compared DHC to methadone for maintenance substitution therapy, the evidence was also of low quality, and there may be no difference in effects between DHC and methadone for reported abstinence from illicit opiates (mean difference (MD) −0.01, 95% CI −0.31 to 0.29). For treatment retention at six months' follow-up in this single trial**,** the RR calculated with an intention-to-treat analysis also indicated that there may be no difference between DHC and methadone (RR 1.04, 95% CI 0.94 to 1.16).

The studies that compared DHC to buprenorphine reported no serious adverse events, while the DHC versus methadone study reported one death due to methadone overdose.

Authors' conclusions

We found low-quality evidence that DHC may be no more effective than other commonly used pharmacological interventions in reducing illicit opiate use. It is therefore premature to make any conclusive statements about the effectiveness of DHC, and it is suggested that further high-quality studies are conducted, especially in low- to middle-income countries.

PLAIN LANGUAGE SUMMARY

Can dihydrocodeine reduce illegal opiate use in adolescents and adults?

Review question

We reviewed evidence on the effects of dihydrocodeine (DHC) to reduce illegal substance use among adolescents older than 15 years and adults.

Background

The use of illegal substances such as heroin is a world-wide problem, and can lead to other issues. What is especially concerning is the far-reaching health consequences of this substance use. This includes high numbers of deaths due to heroin and other opiates from overdoses, and the fact that it is a risk factor for Hepatitis C and HIV, particularly among those who inject their drugs.

We wanted to learn if DHC has a positive effect on decreasing this kind of drug use among those adolescents and adults. DHC is a type of opiate that is codeine-based.

Search date

The evidence is current to February 2019.

Study characteristics

We included three studies in this review with 385 participants in total with follow-up periods of different length. Two studies with 150 participants compared DHC to buprenorphine for detoxification (managing physical symptoms of withdrawal), while one study with 235 individuals compared DHC to methadone for maintenance substitution therapy (providing legal substance to reduce risk behaviour and other harm related to drug use over a longer period). All the studies took place in the UK.

Our primary outcome was abstinence or no longer using illegal substances; our secondary outcomes were completing treatment, as well as health-related consequences of substance use, and other behaviours often linked to substance use such as illegal activity. We also assessed the safety of DHC.

Key results

For detoxification from illegal substances such as heroin, DHC may not work any better than buprenorphine in reducing substance use, keeping individuals in treatment and other behaviours. The pattern stayed the same for follow-up appointments.

For maintenance treatment, DHC also may not work better than methadone in reducing substance use or any of the secondary outcomes, but participants may be more likely to stay in treatment. This finding remained the same across longer follow-up periods as well.

The only adverse event reported was one death from a methadone overdose in the study that compared DHC with methadone as maintenance therapy.

The pattern of results indicates that individuals who received DHC generally may not do better in reducing their substance use, completing treatment or other measures of substance-related behaviours than those that received other types of medication. However it is premature to make definitive statements about the efficacy of DHC for reducing illegal substance use, due to the low quality of evidence.

Quality of evidence

Overall, the evidence was of low quality. There were two major issues across the studies. There was no blinding of the participants or those who assessed the outcomes, so that they were aware of which group they were in. There was also a high level of participants who dropped out of two of the studies.

Study funding sources

All three studies were funded by government or research foundation organisations.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Dihydrocodeine compared to buprenorphine for detoxification in illicit-opiate-dependent individuals

Dihydrocodeine compared to buprenorphine for detoxification in illicit-opiate-dependent individuals

Patient or population: individuals dependent on illicit opiates
Setting: general medical setting and male prison
Intervention: dihydrocodeine (DHC)
Comparison: buprenorphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with buprenorphine	Risk with DHC				
Abstinence Assessed by urinalysis post-detoxification	Study population 429 per 1000	225 per 1000	RR 0.42 (0.11 to 1.57)	150 (2 RCTs)	⊕⊕⊖⊖ Low[1,2]	
Abstinence Self-report and urinalysis 3 months post-detoxification	Study population 329 per 1000	200 per 1000	RR 0.59 (0.26 to 1.31)	150 (2 RCTs)	⊕⊕⊖⊖ Low[1,2]	
Abstinence Self-report and urinalysis 6 months post-detoxification	Study population 170 per 1000	100 per 1000	RR 0.59 (0.25 to 1.39)	150 (2 RCTs)	⊕⊕⊖⊖ Low[1,2]	
Serious adverse events or **adverse events**	None reported			150 (2 RCTs)	⊕⊕⊖⊖ Low[1,2]	
Treatment retention Early dropout	Study population 414 per 1000	538 per 1000	RR 1.29 (0.99 to 1.68)	150 (2 RCTs)	⊕⊕⊖⊖ Low[1,2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DHC:** dihydrocodeine; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

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

Moderate quality Further research is likely to have an important effect on our confidence in the estimate of the effect and may change the estimate of the effect.
Low quality: Further research is very likely to have an important effect on our confidence in the estimate of the effect and is likely to change the estimate of the effect.
Very low quality: We are uncertain about the estimate.

[1]Risk of bias: marked down for lack of blinding of participants, personal and outcome assessor for self-report outcome, and incomplete outcome data, as high attrition in both studies.
[2]Imprecision: marked down as included studies have small sample sizes with small number of events, confidence intervals with range that includes estimate of no effect (RR=1), and both appreciable benefit and/or harm.

Summary of findings 2. Dihydrocodeine compared to methadone for substitution therapy in illicit-opiate-dependent individuals

Dihydrocodeine compared to methadone for substitution therapy in illicit-opiate-dependent individuals

Patient or population: individuals dependent on illicit opiates
Setting: general medical setting
Intervention: dihydrocodeine (DHC)
Comparison: methadone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with methadone	Risk with DHC				
Abstinence Assessed with illicit opiate score at 6-month follow-up		The mean DHC vs methadone illicit opiates mean difference was -0.01	MD −0.01 (−0.31 to 0.29)	204 (1 RCT)	⊕⊕⊖⊖ Low[1,2]	
Serious adverse events or **adverse events** Death due to methadone use	1 methadone death in a total of 399.5 person-years of follow-up		n/a	204 (1 RCT)	⊕⊕⊖⊖ Low[1,2]	
Treatment retention Assessed with number of individuals at 6-month follow-up	845 per 1000	880 per 1000	RR 1.04 (0.94 to 1.16)	204 (1 RCT)	⊕⊕⊖⊖ Low[1,2]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of the effect
Moderate quality: Further research is likely to have an important effect on our confidence in the estimate of the effect and may change the estimate of the effect.

Low quality: Further research is very likely to have an important effect on our confidence in the estimate of the effect and is likely to change the estimate of the effect.
Very low quality: We are uncertain about the estimate

[1]Risk of bias: marked down as blinding of participants, personnel and outcome assessors was not done.
[2]Imprecision: marked down, as data only come from one study with fewer than 400 participants, therefore viewed as imprecise.

BACKGROUND

Description of the condition

According to the World Drug Report, approximately a quarter of a billion people (5 percent of the world population aged 15 to 64 years) in 2015 had used drugs at least once in the previous year, with an estimated 28 million years of healthy life lost to drug use. It is estimated that 12 million years of healthy life were lost to opioid use specifically (UNODC 2017). Injection drug use is estimated at 12 million drug users worldwide (UNODC 2017). 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 2017). 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 interested in alternative opioid substitution therapy modalities within integrated HIV prevention and treatment programmes (Kermode 2011).

There are an estimated 15.5 to 17.7 million people worldwide aged 15 years and older who are dependent on illicit opiates (Degenhardt 2014; UNODC 2017), which is an estimated prevalence of 0.14% for men and 0.30% for women. In terms of illicit opiates and opioids, recent global trends indicate displacement between pharmaceutical or prescription opioids, or both, and heroin, dependent on pricing, availability and access in illicit drug markets (UNODC 2017). Severe opioid disorders were 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 (years lost 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 severe opioid disorders (Degenhardt 2014). In 2010 alone, a total of 43,000 deaths were attributed to illicit opiate use (Degenhardt 2014). Recently the USA has been experiencing an opioid epidemic, with an estimated 42,245 deaths in this country in 2016 alone (Gomes 2018).

Opioid disorders develop following the regular use of opioids, with severe opioid disorder defined as a chronic, relapsing disorder which may have serious consequences, including disability and even death (APA 2013). Opioid disorders may contribute 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). A distinct feature of opioid use is that it can lead to physical dependence after as little as one to two months of use. According to the DSM-V (APA 2013), opioid disorders are characterised by two or more of the following 11 symptoms occurring together in the previous year of use. Mild opioid disorders are defined by two or three criteria, moderate opioid disorders are defined by four or five criteria and severe opioid disorders are defined by six or more criteria:

1. taking opioids in larger amounts or over a longer period of time than intended;
2. difficulties in cutting down or controlling opioid use;
3. spending a large amount of time getting or using opioids or recovering from its effects;
4. craving or a strong desire to take opioids;
5. recurrent opioid use resulting in not fulfilling major obligations;
6. continued opioid use despite recurring social or interpersonal problems;
7. progressive neglect of alternative pleasures or interests because of opioid use;
8. recurrent opioid use in physically hazardous situations;
9. continued opioid use despite clear evidence of physical or psychological problems associated with use;
10. experiencing withdrawal or use of opioids to avoid or relieve withdrawal;
11. tolerance (APA 2013).

Opioid disorder 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 such 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 injection 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 use can cause harm beyond the individual who uses opiates. The use of illicit opiates such as heroin and morphine among pregnant women can have serious effects for their unborn babies including spontaneous abortion and infant mortality. Opiates are also transferable to the foetus and change the placental function, making preterm delivery a strong possibility. Babies can be born with congenital 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 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 people who inject drugs receive opioid substitution therapy, with lower figures in low- and middle-income countries (Mathers 2010). In addition, more recent reports indicate that donor funding has recently been decreased for harm reduction for people who inject drugs, which includes opiate users (Cook 2018).

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 people 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 opiate-dependent people; reduce barriers to admission; improve retention of people 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 remains 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 that 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). Several small trials have assessed the use of slow release oral morphine but there is insufficient 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 2017a). 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 2016). 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 2017b).

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 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 mild to moderate opiate use disorder, and to stabilise methadone patients (Banbery 2000; Krausz 1995; Krausz 1998). DHC is well tolerated orally and has a half-life of about four 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, may possibly increase 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 2017), has highlighted gaps in service provision for problem drug users receiving access to drug 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 mild to moderate opioid use disorder 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. DHC has the potential for use in treating such wider groups of drug users, particularly those with lower severity of opiate disorder, accessing community care and general health settings, and as an alternative for use in high-income as well as low- and middle-income countries. It 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 effectiveness of DHC in reducing illicit opiate use and other health-related outcomes among adults compared to other drugs or placebos used for detoxification or substitution therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We excluded from this review pre- and post-test studies and qualitative studies. We also excluded quasi-randomised studies, such as those allocating to interventions by alternate days of the week. We included studies involving additional psychological treatments if participants were randomly allocated to DHC or comparison medication, and groups were balanced in terms of proportion of participants receiving additional treatment.

Types of participants

Participants are adolescent (aged 15 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 (APA 2013).

We excluded participants who had serious pre-existing conditions (psychiatric conditions, pregnancy). We also excluded individuals with contraindications to DHC or the comparison pharmacological intervention.

Types of interventions

Experimental intervention

Interventions included 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, we expected that detoxification would 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 had to be treatment as usual, placebo or other types of pharmacological intervention. These included full (methadone, 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. Abstinence from illicit opiate use after detoxification or maintenance therapy, either through self-report or urinalysis, measured as the number of participants abstinent at the end of treatment and at follow-up.
2. Number of participants who experienced serious adverse events. According to the guidelines, serious adverse 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.
3. 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. 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. Drug overdose/admission to health services (symptoms of overdose and not limited to death due to overdose)
3. Physical health (typically related to substance use such as appetite, levels of energy, nausea)
4. Use of other substances of abuse (both legal and illegal)
5. Engagement in crime
6. Diversion (selling of drugs, use of prescribed opiates for illegal use)
7. Education and employment status

Search methods for identification of studies

Electronic searches

In February 2019, the Cochrane Drugs and Alcohol Information Specialist (IS) conducted systematic searches in the following databases for RCTs and controlled clinical trials without language, publication year or publication status restrictions:

1. Cochrane Drugs and Alcohol Group (CDAG) Specialised Register searched on 1 February 2019 (via CRSLive);
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 11) via onlinelibrary.wiley.com;
3. MEDLINE (PubMed; January 1966 to 1 February 2019);
4. Embase (OVID; January 1974 to 1 February 2019);
5. Web of Science (Thomson Reuters; January 1990 to 1 February 2019).

The IS developed a detailed search strategy in CENTRAL and then revised it accordingly for each database to take into account differences in controlled vocabulary and syntax rules. The search strategy combined the subject search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials, as referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

Search strategies for major databases are provided in Appendix 1.

We searched the following trials registries on 1 February 2019:

1. ClinicalTrials.gov (www.clinicaltrials.gov);
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
3. trialsjournal.com.

Searching other resources

We also contacted study authors as needed and searched reference lists in all relevant journal articles to obtain information on potential additional RCTs. In addition, the review authors also searched for other unpublished studies and assessed relevant conference proceedings for additional references.

The search included all studies with an English abstract, whether or not the full article was in a foreign language. After reading the abstract, we obtained all articles that appeared to possibly meet the inclusion criteria. All of the articles were in English.

Data collection and analysis

Selection of studies

Two authors (TC, IN) independently inspected the titles and abstracts that we found in the searches. We obtained potentially-relevant articles in full text and the same two review authors further assessed them for eligibility. There was no disagreement between these two authors that could not be resolved following their independent review of the full text, but another author (MCVH) was available to read the studies in order to assist with making a decision on whether to include or exclude the article if needed.

Data extraction and management

Two of the review authors (TC and IN) independently extracted data from the included studies using a data extraction form that was adapted from a standard extraction form used by Cochrane Drugs and Alcohol. We then entered these data into the Cochrane software, Review Manager 5, for data analysis (Review Manager 2014). We then extracted the following data: number of participants treated, participants' characteristics, 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 was information missing from the original studies on outcomes or other important information, we attempted to contact the corresponding author via email in order to request additional data.

Assessment of risk of bias in included studies

We performed the 'Risk of bias' assessment of RCTs in this review using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). 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 the study authors reported. 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 used the criteria indicated in the*Cochrane Handbook of Systematic Reviews of interventions,* adapted to the addiction field. See Table 1 for details.

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

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

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

Grading of evidence

We assessed the overall quality of the evidence for the primary outcome using the 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:

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

We decreased grading for the following reasons:

1. serious (−1) or very serious (−2) limitation to study quality;
2. important inconsistency (−1);
3. some (−1) or major (−2) concerns about directness;
4. imprecise or sparse data (−1);
5. high probability of reporting bias (−1).

We included and graded the primary outcomes and main secondary outcome in the 'Summary of findings' table (abstinence from illicit opiates following detoxification, abstinence from illicit opiates following maintenance or substitution therapy; retention in treatment, participants with severe adverse events, participants with adverse events) for DHC compared to other medication.

Measures of treatment effect

We compared the outcomes of the experimental and control groups at follow-up appointments. For dichotomous data, we calculated risk ratios (RR) with 95% confidence intervals (CIs). For continuous data, we calculated the mean difference (MD), with 95% CIs. In the case of continuous data, we used the standardised mean difference (SMD) as the treatment measure, again with 95% CIs if the studies measured the outcomes with different tools (Deeks 2017). If neither of these measures could be calculated, the treatment effects were reported as by the author in the study article.

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 (Deeks 2017) and we planned to 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 contacted the original investigators of the included studies up to three times to request any missing data (missing studies, outcomes, summary data, individuals, and study-level characteristics). We needed to decide whether the data were missing at random (not related to the actual data) or not missing at random (related to the actual data). When study data were assumed to be missing at random, only the available data were analysed. For data that were not missing at random, this needed to be addressed by performing a sensitivity analysis or, if this was not possible, by replacing missing data with specified values (Deeks 2017). We used intention-to-treat analyses for these studies.

Assessment of heterogeneity

As we found and included in the review more than one study, we checked for heterogeneity across the studies. We used the Chi^2 and I^2 statistical tests to assess if observed differences in study results occurred by chance alone or if these differences were estimates beyond chance. If P values for the Chi^2 test were 0.10 or lower, and when the I^2 statistic value was above 50%, this indicated a potential problem with heterogeneity (Deeks 2017).

Assessment of reporting biases

We originally planned to inspect the risk of publication bias by examining the symmetry of funnel plots if at least 10 studies were included in the meta-analyses.

In addition, when there seemed to be selective outcome reporting, we contacted the authors of the relevant studies to request additional information.

Data synthesis

We first summarised the main findings of the included studies, then we decided whether studies were appropriate for meta-analysis, namely if there were two or more individual studies 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 used the random-effects model for analysis. If there was more than one follow-up period for single studies, we performed separate analyses on the different follow-up periods. If possible, we grouped follow-up as short-term (one month or less), medium-term (two to six months) and long-term (seven months or more) follow-up. Where meta-analysis was not possible, we reported the findings narratively in the body of the review.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses for studies with low and unclear risk of bias and, if possible, for different ages, treatment history and mode of illicit opiate use for study participants.

Sensitivity analysis

We set out to explore the effects of risk of selection bias by conducting sensitivity analysis excluding studies at high risk of selection bias.

RESULTS

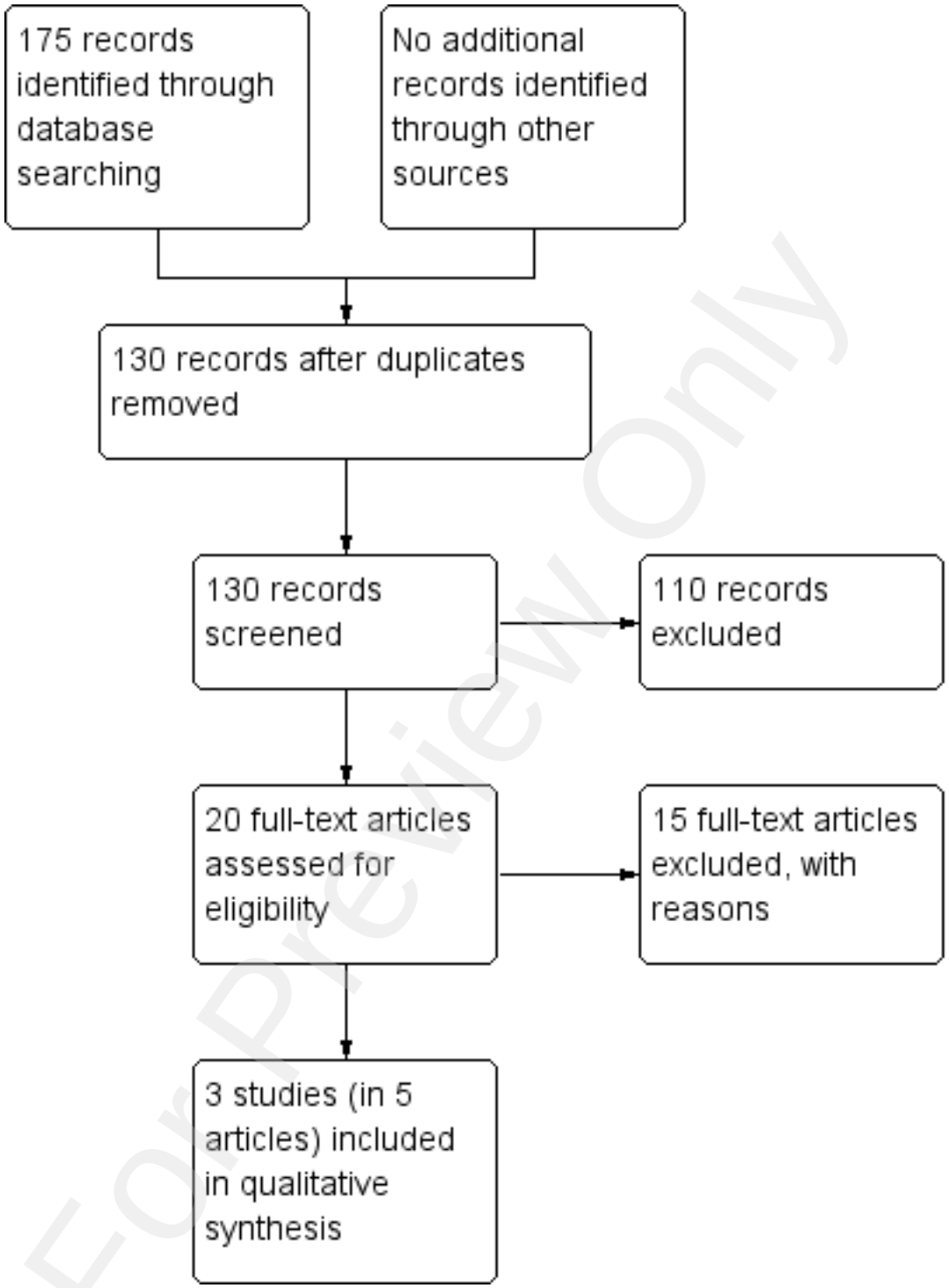
Description of studies

See Characteristics of included studies and Characteristics of excluded studies for detailed descriptions of each screened study.

Results of the search

We identified 130 potentially relevant articles through the search strategies (following the removal of duplicates). Based on the title and abstract, we excluded 110 studies, leaving 20 articles that we retrieved in full text so that we could conduct a more detailed evaluation. Of these, we excluded 15 and the remaining three trials (presented in five articles) were included in the review as they met all of the inclusion criteria (see Figure 1 for PRISMA flowchart (Moher 2009)).

Figure 1. Study flow diagram



Included studies

We included three studies (reported in five separate articles) that were published between 2004 and 2009 (Robertson 2006; Sheard 2009; Wright 2007). At study intake, this included a total of 385 opiate-using participants. All of the participants were opiate users, with two studies only including adults aged 18 years and older (Sheard 2009; Wright 2007), and the other including participants 15 years and older (up to 55 years of age; Robertson 2006). One of the studies (Sheard 2009), measured length of opiate use, with a mean length of 9.3 years opiate use (SD = 4.1). The other two studies included opiate dependency, with the mean opiate dependence score in one study being 10.2 (SD = 4.0), and 18 (30%) participants in the other study reported as severely dependent. The mean age of participants were 29.3 years (SD = 5.35) in Sheard 2009 and 29.5 years (SD = 6.2) in Wright 2007. Robertson 2006 did not provide participants' mean age.

Types of comparison

1. DHC versus buprenorphine as detoxification: two studies, 150 opiate-using participants at study intake (Sheard 2009; Wright 2007)
2. DHC versus methadone as maintenance therapy: one study, 235 opiate-using participants at study intake (Robertson 2006)

Location

All of the studies were based in the UK. Two of the studies took place in general medical settings (Robertson 2006; Wright 2007), while one took place in a male prison, therefore only male participants were included (Sheard 2009).

Length, dosage and description of intervention

The two detoxification studies provided participants with a daily dosage of 30 mg for 15 (Wright 2007), and 20 days (Sheard 2009), respectively. The studies dispensed this in the form of an oral tablet preparation. The substitution therapy study prescribed a daily, supervised 30 mg at the beginning of the study, which was titrated to reach a stabilising dose (up to 60 mg), and after three weeks this was dispensed on an individual basis (Robertson 2006).

Oucomes measures

All three of the studies used urinalysis to measure abstinence from opiate use by the end of detoxification or substitution therapy. However, Wright 2007 did not define abstinence by urinalysis only at the three-month and six-month follow-up periods post-detoxification, as it was obtained during tracking of participants. Therefore in order to make a comparison of outcomes, abstinence at these time periods for both Wright 2007 and Sheard 2009 contain self-report as well as urinalysis measures for the abstinence outcome.

Secondary outcome measures included treatment retention, which was reported as participants leaving detoxification or early for two studies (Sheard 2009; Wright 2007), and not attending treatment for substitution therapy in the third study (Robertson 2006). Measures of drug overdose included number of overdoses recorded at post-detoxification, as well as a proxy measure of number of Accident and Emergency (A&E) visits, and number of doctor (general practitioner) visits during the detoxification and follow-up period for two of the studies (Sheard 2009; Wright 2007). The remaining study measured percentage differences over the follow-up periods (Robertson 2006). Robertson 2006 measured physical health by the Maudley Addiction Profile (MAP) physical mean score. Two studies measured the number of participants who reported the inappropriate use of the allocated DHC at post-detoxification (Sheard 2009; Wright 2007), while Robertson 2006 provided the mean illicit opiate score. One study measured diversion by the percentage difference in selling drugs from baseline averaged over all of the follow-ups, while they measured the crime score by the mean difference in reported criminal activity from baseline averaged over all of the follow-up appointments (Robertson 2006).

Length of follow-up

The studies differed in terms of follow-up periods. Since two of the studies aimed to measure DHC's performance in detoxification, the first follow-up period was after the completion of detoxification services, with 150 participants, and then three and six months post detoxification, with 105 participants (Sheard 2009; Wright 2007). In Robertson 2006, where the aim was to measure DHC use as substitution therapy, and the primary outcome was treatment retention, follow-up was at 6, 12, 18, 24, 30 and 36 months respectively. A total of 181 participants across the studies completed the 12-month follow-up appointment.

Funding

Sheard 2009 and Wright 2007 received funding from the Leeds Primary Care Trusts Research Consortium Priorities and Needs Funding. Robertson 2006 received funding from the Chief Scientist Office of the Scottish Executive.

Excluded studies

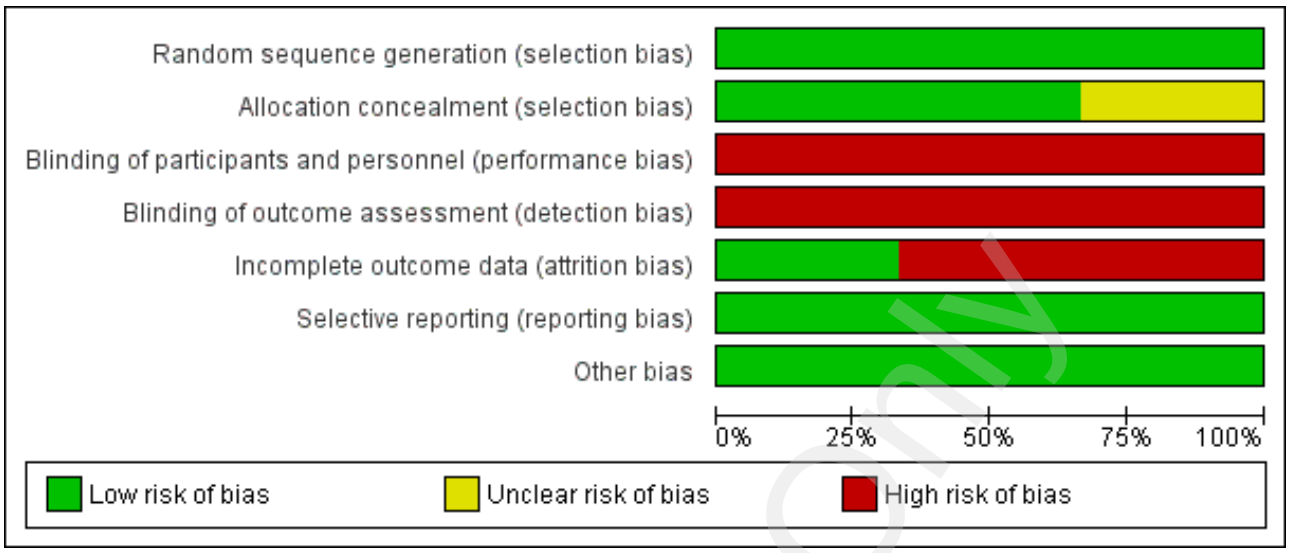
We excluded 15 potentially eligible studies for which the full-text articles were obtained and read after assessing the abstracts. The reasons for exclusion are not mutually exclusive, therefore one study may have more than one reason for exclusion: 13 of the studies were not RCTs, four studies did not report DHC as the intervention provided, and one study did not include the primary outcome.

Risk of bias in included studies

Figure 2 provides a summary of the risk of bias for each study and in each area of potential bias. Figure 3 provides a summary of the 'Risk of bias' assessments for our primary outcomes across all three studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Allocation

Generation of randomisation sequence

We deemed all studies at low risk of bias for sequence generation, with randomisation conducted by random block size (Robertson 2006; Sheard 2009; Wright 2007), stratified by sex by one of the studies (Robertson 2006). Two studies used Microsoft Excel RAND function to generate random block size (Sheard 2009; Wright 2007).

Concealment of allocation

Two of the studies used opaque envelopes to conceal allocation to study group, with an independent investigator confirming the order of opening the envelopes (Sheard 2009; Wright 2007). We therefore judged the risk of bias to be low. In the other study (Robertson 2006), the method of allocation concealment remained unclear despite attempts to contact the study author, and we deemed this study's risk of bias to be unclear.

Blinding

Performance Bias

We assessed all three studies to be at high risk of performance bias, as blinding did not take place consistently throughout the study. One study blinded personnel for a short period only, after which it was evident that participants and clinical staff members could distinguish between treatment groups, and blinding ceased (Robertson 2006). No blinding took place in the other studies (Sheard 2009; Wright 2007).

Detection bias

All staff members were unblinded in Robertson 2006. In the other two studies, where abstinence from illicit opiates was the primary outcome, we made the assumption that the staff in the laboratory where urinalysis was conducted was not aware of the treatment group to which the individual urine results belonged. However, since at follow-up some of the abstinence measures and other secondary outcome measures were self-reported (such as inappropriate use of prescribed medication), we assumed that the outcome assessor was not blinded (Sheard 2009; Wright 2007). For this reason, we rated all three studies as having a high risk of detection bias.

Incomplete outcome data

The rates of attrition were low at six-month follow-up in one of the studies, and they also conducted an intention-to-treat analysis; we therefore judged Robertson 2006 to be at low risk of attrition bias. The other two studies, although they used intention-to-treat data analysis, had high levels of attrition, which were different across the groups (Sheard 2009; Wright 2007). We therefore judged them to be at high risk of attrition bias.

Selective reporting

The studies reported on primary and secondary outcomes that they had stated in their study protocols (Sheard 2009; Wright 2007), or referred to in the study methods (Robertson 2006), and we therefore deemed reporting bias to be low.

Other potential sources of bias

Sheard 2009 declared that a primary author was part of a national pharmaceutical board, but no obvious issues of other bias were evident in any of the studies and we therefore judged all studies to have a low risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Dihydrocodeine compared to buprenorphine for detoxification in illicit-opiate-dependent individuals; **Summary of findings 2** Dihydrocodeine compared to methadone for substitution therapy in illicit-opiate-dependent individuals

1. Comparison of DHC to buprenorphine

We decided to exclude one-month post detoxification, as this is a very short-term follow-up and only one study reported it (Sheard 2009).

Primary outcomes

Abstinence (urinalysis)

Two studies measured abstinence through clean urine results at the end of the detoxification period (Sheard 2009; Wright 2007), using intention-to-treat analysis (n = 150). There was no significant difference between those who received DHC and those who received buprenorphine (RR 0.42, 95% CI 0.11 to 1.57; P = 0.20; Analysis 1.1).

Abstinence (self-report and urinalysis)

Two studies compared the primary outcome at three and six months post-detoxification (Sheard 2009; Wright 2007), by combining self-report and urinalysis results, and still using an intention-to-treat analysis (n = 150). There was no significant difference at three months' follow-up (RR 0.59, 95% CI 0.26 to 1.31; P = 0.19; Analysis 1.2) and at six months' follow-up between those who received DHC and those who received buprenorphine (RR 0.59, 95% CI 0.25 to 1.39; P = 0.23; Analysis 1.3).

Serious adverse events

Neither of the two studies reported any deaths at three- or six-month post-detoxification follow-up periods in (Sheard 2009; Wright 2007).

Adverse events

No other adverse events were reported.

Secondary outcomes

Treatment retention

The two studies (Sheard 2009; Wright 2007), that measured treatment retention only measured this outcome post-detoxification (n = 150). The results of the meta-analysis indicate that there was no significant difference between the two groups (RR 1.29, 95% CI 0.99 to 1.68; P = 0.06; Analysis 1.4).

Overdose

Two studies measured this explicitly only at the end of the detoxification period, and reported zero instances (Sheard 2009; Wright 2007). However, they measured this by proxy by number of A&E visits at three- and six-month post-detoxification follow-ups. At three months post-detoxification (n = 105) there was no difference between the number of visits to A&E services for the group of participants who received DHC and the group who received buprenorphine (RR 1.03, 95% CI 0.22 to 4.84; P = 0.97; Analysis 1.5). This difference was not significant at six months post-detoxification (n = 68) either (RR 0.58, 95% CI 0.06 to 5.66; P = 0.64) See Analysis 1.6. Another proxy measure of this was hospital attendance. At post-detoxification, there were zero reports of hospital visits in either of the studies. At three months post-detoxification, there was no significant difference in the number of hospital admissions between the DHC and buprenorphine groups (RR 1.06, 95% CI 0.20 to 5.55; P = 0.94; Analysis 1.7). There was also no significant difference in groups at six months post-detoxification (RR 1.39, 95% CI 0.23 to 8.37; P = 0.72; Analysis 1.8).

Diversion

Two studies (Sheard 2009; Wright 2007), measured this outcome at the end of the detoxification period, but it was not possible to conduct a meta-analysis for this outcome, as Wright 2007 reported zero instances of participants using prescribed opiates for illegal use. The results of Sheard 2009 were as follows: the risk ratio was 2.59 (95% CI 0.29 to 23.32) but there was no significant difference between groups.

2. Comparison of DHC to methadone

Only one study (Robertson 2006), reported on the comparison of DHC to methadone as substitution therapy. It was therefore not possible to conduct a meta-analysis, and we report on the results from this study in the narrative below.

Primary outcome

Abstinence (self-report)

We are only reporting on the level of abstinence at 6-month follow up as results were only provided for this time period. One (out of 105) participant who received DHC and two (out of 107) participants who received methadone, had clean urine for these substances and therefore the rest were retained on substitution therapy). There was no significant difference in the illicit opiate score across all follow-up periods as the mean difference was -0.01 (95% CI -0.31 to 0.29).

Serious adverse events

One death was reported by methadone overdose in a patient who had recently undergone detoxification.

Adverse events

No other adverse events reported.

Secondary outcomes

Retention to treatment

Robertson 2006 measured treatment retention by calculating the RRs using an intention-to-treat approach. At six-month follow-up, the analysis indicated that staying in treatment did not differ significantly between the DHC and methadone group (RR 1.04, 95% CI 0.94 to 1.16). At 12-month (RR 0.99, 95% CI 0.84 to 1.18) and 18-month follow-up (RR 1.27, 0.97 to 1.16), intention-to-treat results indicated no significant differences, although those participants in the DHC group at 18-month follow-up may be more likely to stay in treatment.

Overdose

There was a non-significant 1.7% (95% CI −2.8% to 6.1%) difference between the DHC and methadone group averaged over the follow-up periods.

Physical health

A non-significant mean difference in physical health score, as measured by the Maudsley Addiction Profile, across all available follow-up periods was found (MD −0.72, 95% CI −4.12 to 2.68).

Use of other substances of abuse

A non-significant −2.4% (95% CI −11.0% to 6.3%) difference between the DHC and methadone group averaged over the follow-up periods was found as reported by the study authors.

Engagement in crime

A non-significant 0.03 mean difference (95% CI −0.29 to 0.36) across all follow-up appointments was found.

Diversion

A non-significant 0.9% (95% CI −0.5% to 2.3%) difference between the DHC and methadone group averaged over the follow-up periods was found as reported by the study authors.

Employment and education

The percentage difference between the DHC and methadone group averaged across all follow-up appointments as reported by the study authors was not significant (3.7%, 95% CI −5.8% to 13.1%).

DISCUSSION

Summary of main results

This systematic review identified three RCTs with a total of 385 participants in total that compared DHC to methadone or buprenorphine respectively. There were different levels of bias in the three studies, but all were of low quality. When comparing DHC to buprenorphine in opiate detoxification, we cannot be certain of the difference in the following outcomes: adhering to treatment and overdose measured by proxy by attending A&E at three- and six-month post-detoxification follow-up periods. There were zero reports of overdose directly mentioned and zero participant deaths recorded in both Sheard 2009 and Wright 2007. Zero instances of illicit opiate use were reported in Wright 2007, with findings in Sheard 2009 indicating no differences between the groups. If better quality studies are conducted in the future, DHC may possibly be a viable alternative treatment option in opiate detoxification in addition to traditional options as it may perform just as well as buprenorphine in reducing opiate use.

When comparing DHC to methadone in opiate substitution, we included one study, with no meta-analysis possible (Robertson 2006). This study did not show any difference in illicit opiate use at long-term follow-up (6, 12, 18 months) between participants receiving DHC and those receiving methadone in shared care services. There was also no difference for retention in treatment, reported overdose, physical health score, engagement in crime, selling of drugs, employment and education. Again quality of evidence was low.

Overall completeness and applicability of evidence

The small number of included studies (n = 3) and participants across the range of settings is too small to permit definite conclusions around use of DHC in either opiate detoxification, or as substitution treatment modality. Evidence is compromised by high attrition, over-representation of male participants, varied doses of DHC and length of interventions, and the detoxification versus substitution approach. Because all of the studies were conducted in the UK, the findings are limited to this high-income setting. The application of this evidence in low- to middle-income countries may be limited.

Although the review focused on illicit opiate use as an outcome, our search strategy was not limited to only substances that are illegal. The findings of all three studies only included illicit opiate use, but there is no reason why the evidence presented in this review would not be pertinent to other problem opioid use. This is especially relevant due to the potential to use DHC substitution therapy in countries where opioids are widespread and there is a call to find innovative medications to treat opioid addiction (Volkow 2017). A future review could perhaps expand the focus to accommodate both illicit and legal opioid disorders.

Future studies may also need to include the severity of opioid use disorder, in order to ascertain DHC's use in treating mild, medium and severe opioid use disorders. Unfortunately this was not clarified in the studies included in the current review.

Quality of the evidence

We rated all three studies as having high rates of performance, attrition and detection bias and we judged their evidence overall to be of low quality due to risk of bias and imprecision of the estimates, resulting in greater uncertainty in the overall results.

Potential biases in the review process

We believe that we found and included all of the relevant studies that have compared DHC to other pharmaceutical opioids for detoxification and substitution therapy due to the often updated extensive searches on a wide range of databases. In addition, while it was not possible to assess the risk of publication bias formally by inspecting a funnel plot, the review authors included trials registers and contacted study authors for additional DHC studies.

We also tried to obtain the most accurate study data by contacting authors pf primary studies; however, in some cases they did not reply or provide the requested information.

Agreements and disagreements with other studies or reviews

We did not find any other systematic reviews on this topic. While most existing research looks at codeine as a substance with potential misuse, we did find a few studies that used DHC for treatment.

One study reports that DHC is more cost effective with a better safety and toxicity profile than methadone (Wright 2007), when used in primary care opiate detoxification. Additional literature reports that DHC is characterised by its short-acting properties, requiring frequent dosing or administration, and the potential for patients oscillating between sedation and withdrawal during detoxification (Backmund 2001; Banbery 2000). This requires a vigilant approach on the part of the prescriber (ideally experienced) in terms of reduced periods of relative withdrawal between doses (Bao 2009; Mitchell 2003; Wright 2007). Reduced opportunity for doctor-patient contact in DHC substitution (Backmund 2001), may also confound results, along with concerns for DHC diversion (Backmund 2001; Hickman 2007; Reith 2005; Wazaify 2005; Zamaprutti 2010).

Despite a comprehensive search of published and unpublished literature, we found only three studies, all based in the UK. The types of comparison were DHC versus buprenorphine in two detoxification studies with 150 opiate-using participants at intake (Sheard 2009; Wright 2007), and DHC versus methadone substitution with 235 opiate-using participants at study intake (Robertson 2006). Study settings varied, with two taking place in general medical settings (Robertson 2006; Wright 2007), and the other in a male prison (Sheard 2009).

AUTHORS' CONCLUSIONS

Implications for practice

The results indicated that there may be no difference of effect of dihydrocodeine (DHC) compared to buprenorphine for

detoxification or compared to methadone for maintenance of opiate use. Because of the low-quality evidence, it is premature to make any conclusive statements about the efficacy of DHC. However, the evidence base, although dated, should be made known to service providers who could use this information cautiously to consider and assess treatment options.

Implications for research

Further clinical investigation of DHC detoxification with specific groups of stabilised and non-stabilised individuals dependent on opiates and in varied settings is warranted. Further research is necessary to trial DHC with patients with less severe opiate disorder, with primary care substitution prescribing to achieve stabilisation in the community, and with a long follow-up period measuring a range of primary (abstinence) outcomes in clearly differentiated methods (self-report versus urinalysis) and secondary outcomes pertaining to retention, medical care visits, overdose, engagement in education and employment, and general health. Studies that included longer follow-up periods, such as 12 months or more (only one included study, Robertson 2006, reported a longer follow-up period), would also indicate if any changes in illicit opiate use is sustained over time. A recommendation is for the further investigation of DHC for detoxification or substitution therapy in low- to middle-income countries, through high-quality randomised controlled trials.

ACKNOWLEDGEMENTS

The review authors would like to thank Zuzana Mitrova of Cochrane Drugs and Alcohol (Rome, Italy) for all of her assistance with multiple search strategies and other administrative support for this review, and Linda Gowing and Franco De Crescenzo for peer-reviewing the manuscript.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Robertson 2006

Methods	RCT
Participants	Number of participants: 235 City and country: Lothian (including Edinburgh) Scotland

Robertson 2006 *(Continued)*

	Setting: community drug problem service and GP practices Gender: 71.5% male, 28.5% female Age range: 16-55 (mean or median age not available) Inclusion criteria: opiate users, adults, codeine/DHC provided Exclusion criteria: pregnant; have psychiatric morbidity Opiate dependency score (mean, SD): 10.2 (4.0)
Interventions	Intervention: DHC tablets as substitution therapy (n = 116) Dosage: 30 mg or 60 mg Control: methadone dispensed at 2.5 mg, supervised or unsupervised (n = 119) Length of intervention: 27 days induction phase, treatment up to 42 months
Outcomes	Follow up at 6, 12, 18, 24, 30, 36 months Measures: MAP, urine toxicology Primary outcomes 1. Retention in treatment Secondary outcomes 1. Overdoses and adverse events 2. Total illicit opiate use 3. Reported crime 4. Physical health 5. Mental health 6. Injection drug use 7. Selling drugs 8. Being in education or work
Notes	**Funding:** Chief Scientist Office of the Scottish Executive, grant number K/opr/2/2d3999 **Conflict of interest:** Dr Robertson is on an occasional advisory committee at the company that provided the DHC for the study: NAPP Pharmaceuticals, Cambridge, UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random block size, stratified by sex
Allocation concealment (selection bias)	Unclear risk	No information provided or available on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Initially staff entered participants without being aware of their allocated interventions, but after enrolment of 29 participants, personnel was not blinded after evidence that both participants and clinical staff were able to distinguish between treatments.
Blinding of outcome assessment (detection bias)	High risk	Blinding of outcome assessors for any of the outcomes was not done.

Robertson 2006 *(Continued)*

Abstinence measured by urinalysis		
Incomplete outcome data (attrition bias) Abstinence by urinalysis	Low risk	ITT analysis conducted and low attrition at 6 months' follow-up period (intervention group: 3/108; control group: 3/110)
Selective reporting (reporting bias)	Low risk	Primary outcome of treatment retention reported on, as well as secondary outcomes according to National Outcomes Treatment Report mentioned in the methods
Other bias	Low risk	No obvious other bias

Sheard 2009

Methods	RCT
Participants	Number of participants: 90 City and country: Leeds, England Setting: Her Majesty's Prison, Leeds Gender: male 100% Age (mean, SD): 29.3 (5.35) Inclusion criteria: opiate users, adults, codeine/DHC provided Exclusion criteria: < 18 and > 65 years; contra-indication to DHC or buprenorphine; had been previously randomised into trial; co-existing medical conditions; current detox from other illicit drugs Length of opiate use (mean, SD): 9.3 (4.1) years
Interventions	Intervention: DHC dispensed as oral tablet preparation for detox (n = 48) Dosage: 30 mg Control: buprenorphine dispensed under daily supervision for 20 days (n = 42) Length of intervention: 20 days
Outcomes	Follow-up end of detox and at 1, 3, 6 months Measures: medical records, urine toxicology Primary outcomes 1. Abstinence from illlicit opiates Secondary outcomes 1. SAEs and AEs 2. Leaving the study early 3. Inappropriate use of prescribed medication 4. Service utilisation
Notes	**Funding:** Leeds Primary Care Trusts Research Consortium Priorities and Needs Funding **Conflict of interest:** none

Sheard 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random block size generated using Microsoft Excel RAND function
Allocation concealment (selection bias)	Low risk	Opaque envelopes used so that intervention allocations not seen in advance
Blinding of participants and personnel (performance bias) All outcomes	High risk	All trial staff were aware of the condition that participants were in.
Blinding of outcome assessment (detection bias) Abstinence measured by urinalysis	High risk	Outcome assessor blinded in urinalysis: as urinalysis is primary outcome, assumption made that lab technician was not aware of which group the individual results belonged to. However at follow-up appointments, abstinence also included self-reporting of opiates where we assumed that the assessor was not blinded. We made the same assumption for the secondary outcomes.
Incomplete outcome data (attrition bias) Abstinence by urinalysis	High risk	Although similar in each arm and ITT analysis conducted, there was a high attrition rate (DHC group post-detox: 31/48, buprenorphine post-detox: 32/42; DHC group 1 month post-detox: 2/5, buprenorphine 1 month post-detox: 4/10; DHC 3 month post-detox: 1/4, buprenorphine 6 months post-detox: 2/8; DHC 3 months post-detox: 1/4, buprenorphine 6 months post-detox: 1/3)
Selective reporting (reporting bias)	Low risk	All outcomes reported on according to protocol ISRCTN07752728
Other bias	Low risk	No obvious other bias although primary author declared being on NAPP Pharmaceutical Board

Wright 2007

Methods	RCT
Participants	Number of participants: 60 City and country: Leeds, England Setting: general practice Gender: male 70%, female 30% Age (mean, SD): 29.5 (6.2) Inclusion criteria: opiate users, adults, codeine/DHC provided Exclusion criteria: < 18 years; contra-indication to DHC or buprenorphine; had been previously randomised into trial Number (%) severely dependent: 18 (30%)
Interventions	Intervention: DHC dispensed as oral tablet preparation for detox (unsupervised; n =32) Dosage: 30 mg

Wright 2007 *(Continued)*

	Control: buprenorphine dispensed under daily supervision for 15 days (n = 28) Length of intervention: 15 days
Outcomes	Follow-up end of detox and at 3, 6 months Measures: medical records, urine toxicology Primary 1. Abstinence from illlicit opiates Secondary 1. 1. SAEs and AEs 2. Inappropriate use of prescribed medication 3. Overdose 4. Service utilisation (admission to hospital or A&E and number of GP/drug worker visits during the detox period)
Notes	**Funding:** Leeds Primary Care Trusts Research Consortium Priorities and Needs Funding **Conflict of interest:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random block size, stratified by practice using Microsoft Excel RAND function
Allocation concealment (selection bias)	Low risk	Opaque, consecutively sealed envelopes, independent investigator confirmed order of opening of envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither staff nor participants were blinded to the condition once the envelopes had been opened
Blinding of outcome assessment (detection bias) Abstinence measured by urinalysis	High risk	Outcome assessor blinded. As urinalysis is primary outcome, we assumed that lab technician was not aware of which group the individual results belonged to. The risk increased at follow-up appointments where abstinence also included self-reporting of opiates where we assumed that the assessor was not blinded. We also assumed that the assessor was not blinded for other secondary outcomes.
Incomplete outcome data (attrition bias) Abstinence by urinalysis	High risk	High, differential rates of attrition, with only very small numbers completing detox (DHC group: 1/32 provided final urine sample at detox, buprenorphine group: 6/28 provided final urine sample at detox)
Selective reporting (reporting bias)	Low risk	All outcomes reported on compared with protocol ISRCTN07752728
Other bias	Low risk	No obvious evidence of other biases

A&E: Accident and Emergency Department; **AE:** adverse event; **detox:** detoxification; **DHC:** dihydrocodeine; **GP:** general practitioner; **ITT:** intention-to-treat; **MAP:** Maudsley Addiction Profile; **RCT:** randomised controlled trial; **SAE:** serious adverse event; **SD:** standard deviation

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

Study	Reason for exclusion
Backmund 2001	Not RCT
Banbery 2000	Not RCT
Bell 2007	Commentary on RCT
Carnwath 2002	Editorial
Day 2003	DHC not primary drug dispensed to participants for detox
Friessem 1991	Not RCT (epidemiology and case studies)
Hall 2007	Not RCT, DHC not primary drug dispensed to participants for detox
Krausz 1995	Not RCT
Krausz 1998	Not RCT
Pearson 2000	Not RCT
Seymour 2001	Commentary on retrospective study
Swadi 1990	Not RCT
Ulmer 2007	DHC not used for detox from other opiates, not RCT
Ulmer 2012	DHC not used for detox from other opiates, not RCT
Zamparutti 2010	Primary outcomes not measured, and not RCT

detox: detoxification; **DHC:** dihydrocodeine; **RCT:** randomised controlled trial

DATA AND ANALYSES

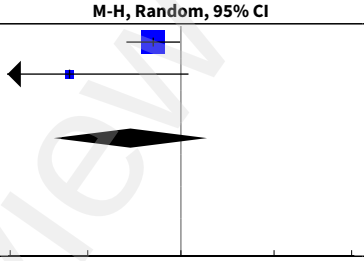
Comparison 1. Dihydrocodeine vs buprenorphine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinalysis: clean urine post-detoxification	2	150	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.57]
2 Abstinence self-report and urinalysis 3 months post-detoxification	2	150	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.31]
3 Abstinence self-report and urinalysis 6 months post-detoxification	2	150	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.25, 1.39]
4 Treatment retention: early dropout	2	150	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.99, 1.68]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 Overdose A&E attendance: 3 months post-detoxification	2	105	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.22, 4.84]
6 Overdose A&E attendance: 6 months post-detoxification	2	68	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.06, 5.66]
7 Overdose hospital attendance: 3 months post-detoxification	2	105	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.20, 5.55]
8 Overdose hospital attendance: 6 months post-detoxification	2	68	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.23, 8.37]

Analysis 1.1. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 1 Urinalysis: clean urine post-detoxification.

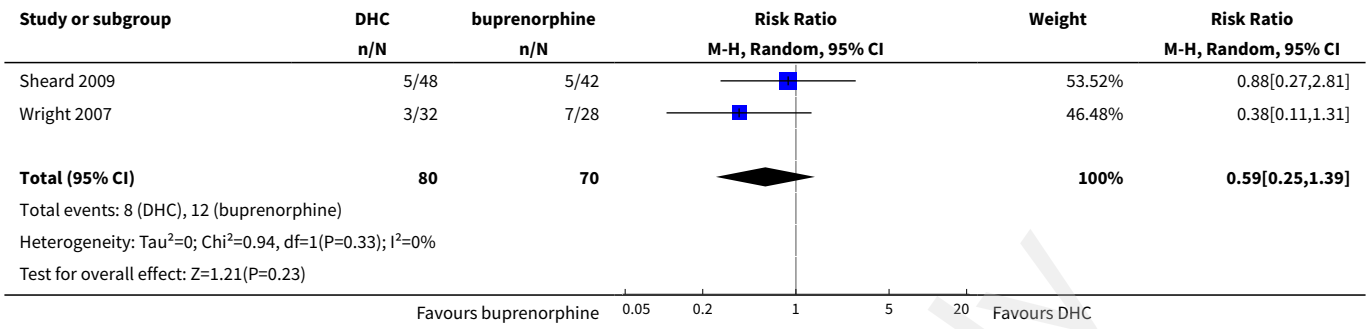
Study or subgroup	DHC n/N	buprenorphine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sheard 2009	17/48	24/42		72.75%	0.62[0.39,0.98]
Wright 2007	1/32	6/28		27.25%	0.15[0.02,1.14]
Total (95% CI)	**80**	**70**		**100%**	**0.42[0.11,1.57]**
Total events: 18 (DHC), 30 (buprenorphine)					
Heterogeneity: Tau^2=0.57; Chi^2=1.99, df=1(P=0.16); I^2=49.63%					
Test for overall effect: Z=1.29(P=0.2)					



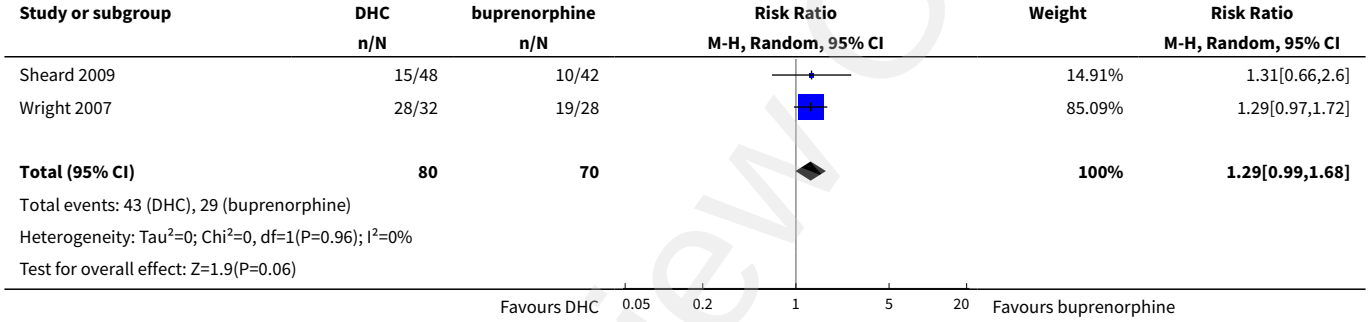
Analysis 1.2. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 2 Abstinence self-report and urinalysis 3 months post-detoxification.

Study or subgroup	DHC n/N	buprenorphine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Sheard 2009	12/48	13/42		61.84%	0.81[0.41,1.57]
Wright 2007	4/32	10/28		38.16%	0.35[0.12,0.99]
Total (95% CI)	**80**	**70**		**100%**	**0.59[0.26,1.31]**
Total events: 16 (DHC), 23 (buprenorphine)					
Heterogeneity: Tau^2=0.15; Chi^2=1.77, df=1(P=0.18); I^2=43.63%					
Test for overall effect: Z=1.3(P=0.19)					

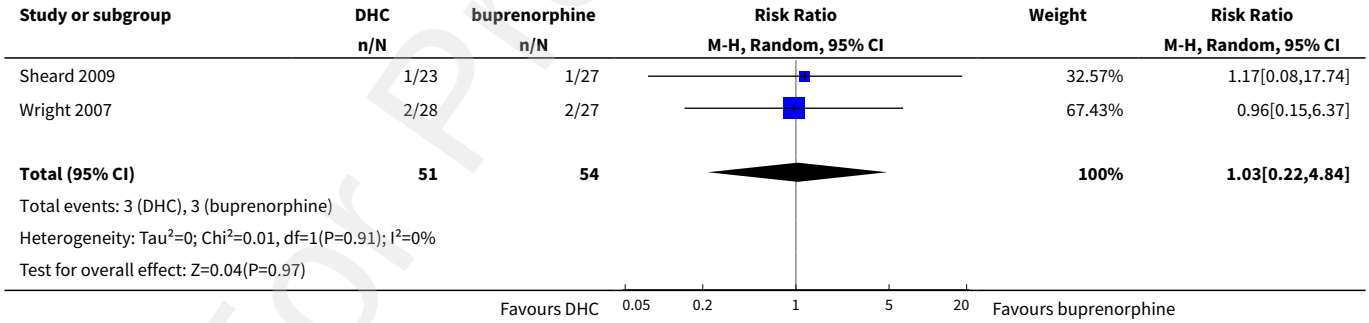
Analysis 1.3. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 3 Abstinence self-report and urinalysis 6 months post-detoxification.



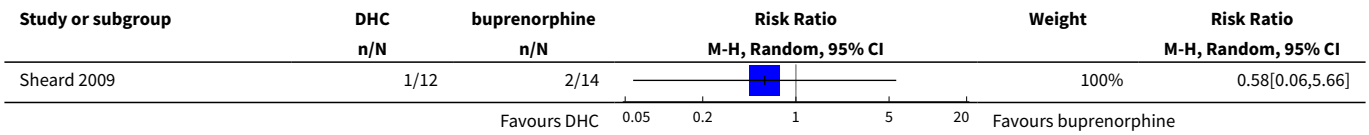
Analysis 1.4. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 4 Treatment retention: early dropout.

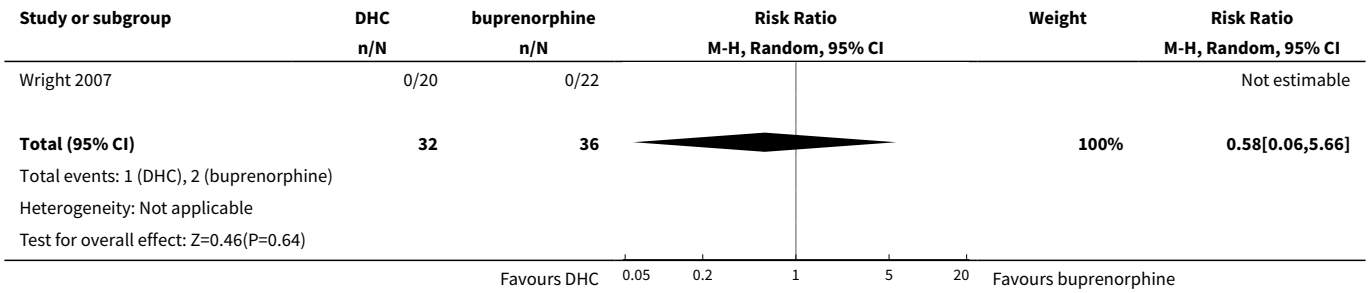


Analysis 1.5. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 5 Overdose A&E attendance: 3 months post-detoxification.

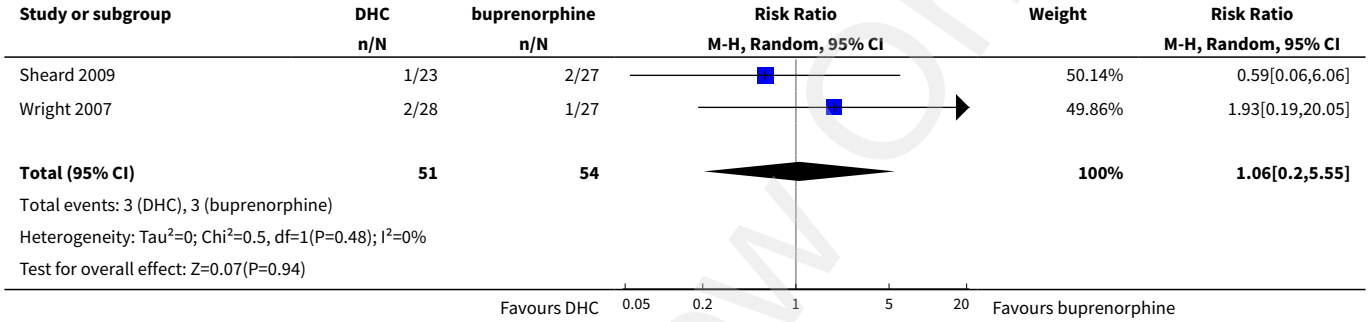


Analysis 1.6. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 6 Overdose A&E attendance: 6 months post-detoxification.

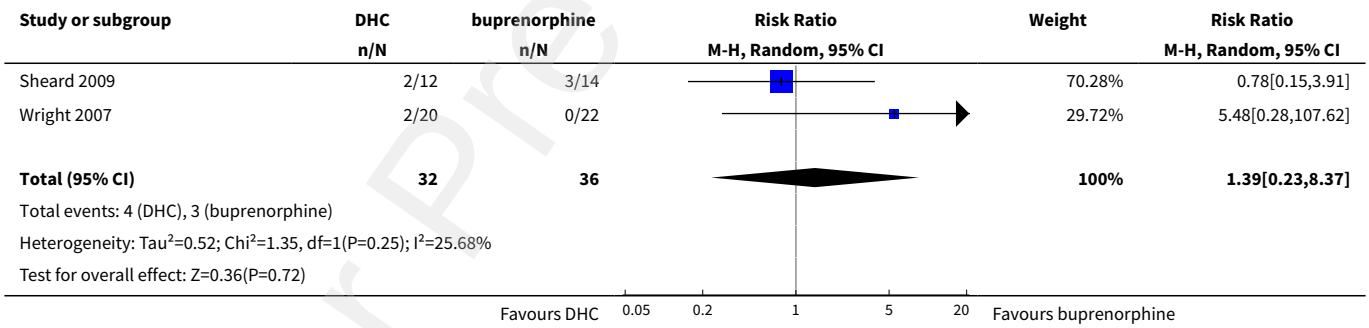




Analysis 1.7. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 7 Overdose hospital attendance: 3 months post-detoxification.



Analysis 1.8. Comparison 1 Dihydrocodeine vs buprenorphine, Outcome 8 Overdose hospital attendance: 6 months post-detoxification.



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 methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
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.
	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;

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

		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 dropout	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 imputed using appropriate methods All randomised participants are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts 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).

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

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. Search strategies

Cochrane Drugs and Alchohol Specialised Register (via CRSLive)

1 February 2019

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" AND INREGISTER

CENTRAL (via onlinelibrary.wiley.com)

2019, Issue 11

#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

#2 MeSH descriptor: [Opioid-Related Disorders] explode all trees

#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

#8 #1 and #6 in Trials

MEDLINE (PubMed)

1 February 2019

#1 "Opioid-Related Disorders"[MeSH]

#2 opiate*[tiab] OR opioid*[tiab] OR narcot*[tiab] OR heroin*[tiab] OR drug[tiab] OR substance[tiab]

#3 abstin*[tiab] OR abstinen*[tiab] OR abus*[tiab] OR addict*[tiab] OR depend*[tiab] OR detoxify*[tiab] OR desintoxi*[tiab] OR disintoxi*[tiab] OR overdos*[tiab] OR intoxicat*[tiab] OR withdraw*[tiab] OR relaps*[tiab]

#4 #2 OR #3

#5 #1 AND #4

#6 "dihydrocodeine"[Supplementary Concept] OR dihydrocodeine[tiab]

#7 randomized controlled trial[pt]

#8 controlled clinical trial[pt]

#9 randomized[tiab]

#10 placebo[tiab]

#11 drug therapy[sh]

#12 randomly[tiab]

#13 trial[tiab]

#14 groups[tiab]

#15 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

#16 animals[mh] NOT humans[mh]

#17 #15 NOT #16

#18 #5 AND #6 AND #17

Embase (OVID)

1 February 2019

1 exp opiate addiction/

2 ((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.

3 1 or 2

4 exp dihydrocodeine/

5 dihydrocodeine.tw.

6 (dh adj codeine).ti,ab.

7 di-hydrin.ti,ab.

8 (tiamon adj mono).ti,ab.

9 (codhydrin or codhydrine or codicontin or cohydrin or dehacodin or df118 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).ti,ab.

10 4 or 5 or 6 or 7 or 8 or 9

11 3 and 10

12 exp clinical trial/

13 (clin$ adj3 trial$).tw.

14 exp crossover procedure/

15 exp double blind procedure/

16 exp controlled clinical trial/

17 (placebo or assign* or allocat* or volunteer* or random* or factorial* or crossover).ti,ab.

18 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

19 12 or 13 or 14 or 15 or 16 or 17 or 18

20 11 and 19

Web of Science

1 February 2019

#1 TS= dihydrocodeine

#2 TS=((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 overdos* OR intoxicat* OR withdraw* OR relaps*))

#3 #1 AND #2

#4 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

#5 #3 AND #4

ICTRP

1 February 2019

dihydrocodeine

ClinicalTrials.gov

1 February 2019

dihydrocodeine

CONTRIBUTIONS OF AUTHORS

The concept for this review was developed by Tara Carney and Marie Claire van Hout. Tara Carney developed the data extraction form, was responsible for conducting the meta-analysis and overseeing the drafting of the review, and is the contact review author. Tara Carney and Ian Norman read all titles and abstracts included from the initial and updated search process and selected possibly relevant studies, and then Tara Carney obtained full copies of these studies, which both of these review authors used to undertake data extraction. Siphokazi Dada was responsible for entering data into the data extraction form. Nandi Siegfried assisted with critically appraising the study results before the meta-analysis, determining risk of bias, advising on the meta-analysis and assisting with grading the evidence. Charles Parry reviewed the meta-analysis and results. Tara Carney and Siphokazi Dada graded the evidence and developed the 'Summary of findings' tables. Marie Claire van Hout was primarily responsible for drafting the Discussion section. All review authors reviewed and commented on the drafts and final version of the review.

DECLARATIONS OF INTEREST

Tara Carney: none known

Marie Claire Van Hout: none known

Ian Norman: none known

Siphokazi Dada: none known

Nandi Siegfried: none known

Charles DH Parry: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Funding, Other.

The research leading to these results has received funding from the European Community's Seventh Framework Programme *FP7/2007-2013* under grant agreement no. 611736

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Following extensive discussion among the review authors, we reordered slightly the secondary outcomes included in the protocol (Carney 2016).
2. Nandi Siegfried was added as author in order to add methodological rigour to the review.
3. We changed terminology to match the updated and now widely used DSM-5 (APA 2013), namely use of substance use disorders as opposed to dependence.
4. Planned subgroup and sensitivity analysis was not performed because we only included three studies.
5. Since there were not more than 10 included studies in the meta-analysis, we were not able to consider the risk of publication bias by examining the symmetry of funnel plots.
6. We were not able to assess risk of performance and detection bias separately for objective and subjective primary outcomes, because the included studies reported abstinence results combining self-report and urinalysis results.