Opiate treatment for opiate withdrawal in newborn infants (Review)

Osborn DA, Jeffery HE, Cole MJ

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Opiate treatment for opiate withdrawal in newborn infants

David A Osborn[1], Heather E Jeffery[2], Michael J Cole[3]

[1]RPA Newborn Care, Royal Prince Alfred Hospital, Camperdown, Australia. [2]Neonatal Medicine, Royal Prince Alfred, Sydney, Australia. [3]Dept. of Neonatology, Westmead Hospital, Westmead, Australia

Contact address: David A Osborn, RPA Newborn Care, Royal Prince Alfred Hospital, Missenden Road, Camperdown, New South Wales, 2050, Australia. david.osborn@email.cs.nsw.gov.au.

Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 28 March 2005.

Citation: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD002059. DOI: 10.1002/14651858.CD002059.pub2.

ABSTRACT

Background

Neonatal abstinence syndrome (NAS) due to opiate withdrawal may result in disruption of the mother-infant relationship, sleep-wake abnormalities, feeding difficulties, weight loss and seizures. Treatments used to ameliorate symptoms and reduce morbidity include opiates, sedatives and non-pharmacological treatments.

Objectives

To assess the effectiveness and safety of using an opiate, compared to a sedative or non-pharmacological treatment, for treatment of NAS due to withdrawal from opiates.

Search strategy

The previous review was updated with additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2005), MEDLINE (1966-December 2004) and EMBASE (1980-December 2004) supplemented by searches of conference abstracts and citation lists of published articles.

Selection criteria

Trials enrolling infants with NAS born to mothers with an opiate dependence, with > 80% follow up and using random or quasi-random allocation to opiate or control. Control could include an opiate, sedative or non-pharmacological treatment.

Data collection and analysis

Each author assessed study quality and extracted data independently. Primary outcomes included control of symptoms, seizure occurrence, mortality and neurodevelopment. Treatment effect was expressed using relative risk (RR), risk difference (RD), mean difference (MD) and weighted mean difference (WMD). Meta-analysis was performed using a fixed effect model.

Main results

Seven studies enrolling a total of 585 infants met inclusion criteria (Carin 1983; Finnegan 1984; Jackson 2004; Kaltenbach 1986; Kandall 1983; Khoo 1995; Madden 1977); however, two (Finnegan 1984; Kaltenbach 1986) may be sequential reports that include some identical patients. The studies enrolled infants of mothers who had used opiates with or without other drugs during pregnancy. Methodological concerns included the use of quasi-random rather than random patient allocation methods in three studies; sizeable,

largely unexplained differences in reported numbers allocated to each group in four studies; and imbalances in group characteristics after randomisation in one study.

Opiate (morphine) vs supportive care only: One study (Khoo 1995) found no significant effect on treatment failure (RR 1.29, 95% CI 0.41, 4.07), a significant increase in hospital stay (MD 15.0 days, 95% CI 8.9, 21.1) and significant reductions in time to regain birthweight (MD -2.8 days, 95% -5.3, -0.3) and duration of supportive care (MD -197.2 minutes/day, 95% CI -274.2, -120.3).

Opiate vs phenobarbitone: Meta-analysis of four studies found no significant difference in treatment failure (typical RR 0.76, 95% CI 0.51, 1.11). One of these studies (Finnegan 1984) reported that opiate treatment resulted in a significant reduction in treatment failure among infants of mothers who had used only opiates; however, as this was a post-hoc analysis, this result should be interpreted with caution. One study (Jackson 2004) reported a significant reduction in duration of treatment and admission to the nursery for infants receiving morphine compared to phenobarbitone. One study (Kandall 1983) reported a reduction in seizures, of borderline statistical significance, with the use of opiate.

Opiate vs diazepam: Meta-analysis of two studies found a significant reduction in treatment failure (RR 0.43, 95% CI 0.23, 0.80) with the use of opiate.

No study reported neurodevelopment by allocated treatment group.

Authors' conclusions

Opiates, as compared to supportive care only, appear to reduce the time to regain birth weight and reduce the duration of supportive care, but increase the duration of hospital stay; there is no evidence of effect on treatment failure. When compared to phenobarbitone, opiates may reduce the incidence of seizures but, overall, there is no evidence of effect on treatment failure. One study reported a reduction in duration of treatment and nursery admission for infants on morphine. When compared to diazepam, opiates reduce the incidence of treatment failure. A post-hoc analysis generates the hypothesis that treatment effects may vary according to whether the population includes infants born to all opiate users (i.e. with or without other drug exposure) or is restricted to infants of mothers who used opiates only. In view of the methodologic limitations of the included studies the conclusions of this review should be treated with caution.

PLAIN LANGUAGE SUMMARY

Opiate treatment for opiate withdrawal in newborn infants

An opiate such as morphine or dilute tincture of opium should probably be used as initial treatment to ameliorate withdrawal symptoms in newborn infants with an opiate withdrawal due to maternal opiate use in pregnancy. Use of opiates (commonly prescribed methadone or illicit heroin) by pregnant women may result in a withdrawal syndrome in their newborn infants. This may result in disruption of the mother-infant relationship, sleeping and feeding difficulties, weight loss and seizures. Treatments for newborn infants used to ameliorate these symptoms and reduce complications include opiates, sedatives (phenobarbitone or diazepam) and supportive treatments (swaddling, settling, massage, relaxation baths, pacifiers or waterbeds). Trials of opiates compared to sedatives or other non-pharmacological treatments have generally been of poor quality. Individual trials have reported that using an opiate compared to phenobarbitone may reduce the incidence of seizures, duration of treatment and nursery admission rate. However, no overall effect was found on treatment failure rate. When compared to diazepam, opiates reduced the incidence of treatment failure. Opiates such as morphine or dilute tincture of opium should probably be used as initial treatment for opiate withdrawal in newborn infants.

BACKGROUND

Opiate use in pregnancy and neonatal abstinence syndrome (NAS) due to opiate withdrawal is currently a significant clinical and social problem. The US 1999 National Household Survey on Drug Abuse (NHSDA 1999) estimated that 39.7% of individuals over 12 years had ever used an illicit drug, with heroin use reported by 1.4%. Current illicit drug use (within last month) was reported by 6.7% (14.8 million people) and heroin by 0.1% (200,000 people). Rates of illicit drug use were almost half during pregnancy, with 3.4% of pregnant women reporting use of an illicit drug in the

past month. This represents an estimated 3,000 pregnant women who are current users of heroin in the US. These rates are similar to Australian data (NDSHS 1998).

Between 48% and 94% of infants exposed to opiates in utero develop clinical signs of withdrawal, with signs of withdrawal from methadone being more common than from heroin (Alroomi 1988, Doberczak 1991; Fricker 1978; Lam 1992; Maas 1990; Madden 1977; Olofsson 1983; Ostrea 1976). There is some evidence to correlate methadone dose and severity of withdrawal (Doberczak 1991; Harper 1977; Ostrea 1976). Clinically significant manifestations of withdrawal are uncommon if the methadone dose is below 20 mg/day (Strauss 1976). The onset of features of withdrawal from heroin tends to begin within 24 hours after birth and clinical manifestations are usually mild (Alroomi 1988, Bell 1995), whereas withdrawal from methadone usually begins between two and seven days after birth (Doberczak 1991) and may be delayed up to a month (Kandall 1974). Clinical features of neonatal opiate abstinence syndrome include neurological excitability, gastrointestinal dysfunction and autonomic signs (AAP 1998). There may be poor feeding, sleep-wake abnormalities (O'Brien 2002), vomiting, dehydration, poor weight gain and seizures. In addition, infants of mothers using illicit drugs may be at increased risk of neonatal mortality (Hulse 1998), sudden infant death syndrome (Kandall 1993), and abnormal neurodevelopmental outcomes (de Cubas 1993; Ornoy 1996).

Seizures occur in 2% to 11% of infants withdrawing from opiates (Herzlinger 1977; Kandall 1977; Doberczak 1991) and may be more common with methadone than heroin withdrawal (Herzlinger 1977). Although there is evidence in animals that withdrawal from opiates and opiate antagonists is eleptogenic (Olson 1997), there is little evidence that this is the case in humans. Case series of infants with neonatal opiate withdrawal in whom seizures have been reported (Herzlinger 1977; Kandall 1974) have not systematically controlled for maternal use of other drugs throughout pregnancy or reported seizures in infants exposed to only opiates in utero.

The American Academy of Pediatrics (AAP 1998) recommends that for infants with confirmed drug exposure the indications for drug therapy should be seizures, poor feeding, diarrhoea and vomiting resulting in excessive weight loss and dehydration, inability to sleep and fever unrelated to infection. An abstinence score such as the Lipsitz tool (Lipsitz 1975), Neonatal Abstinence Scoring System (Finnegan 1975a) and Neonatal Withdrawal Inventory (Zahorodny 1998) may document significant manifestations of withdrawal. Although the validity of these scoring systems is not proven, they may provide more objective criteria for assessing infants and deciding on treatment. When pharmacological treatment is chosen, the AAP recommends that for opiate withdrawal tincture of opium is the preferred drug. For sedative-hypnotic withdrawal, phenobarbitone is the agent of choice.

Opiates used for NAS due to opiate withdrawal have included tincture of opium, paregoric (contains anhydrous morphine with antispasmodics, camphor, 45% ethanol and benzoic acid), morphine, and methadone. Sedatives used for opiate withdrawal have included clonidine (an alpha2 presynaptic blocker), chlorpromazine, phenobarbitone and diazepam (Theis 1997; AAP 1998). Non-pharmacological treatments used have included swaddling, settling, massage, relaxation baths, pacifiers and waterbeds (Oro 1988).

The question to be addressed by this review is: what is the evidence, from random and quasi-random controlled trials, that an opiate is better than a sedative or non-pharmacological treatment of clinically significant NAS due to opiate withdrawal? The goal of treatment should be to provide comfort to the mother and infant in relieving symptoms, improve feeding and weight gain, prevent seizures, reduce unnecessary hospitalisation, improve mother-infant interaction and reduce the incidence of infant mortality and abnormal neurodevelopment. A separate review (Osborn 2002) examines the evidence for the use of sedatives in infants with NAS due to opiate withdrawal.

OBJECTIVES

To assess the effectiveness and safety of using an opiate for treatment of NAS due to withdrawal from opiates. Separate comparisons prespecified included: 1) opiates versus placebo or no treatment; 2) opiates versus other opiates; 3) opiates versus sedatives; and 4) opiates versus non-pharmacological treatments (including regular care). The evidence for use of different types of opiates, sedatives and non-pharmacological treatments was assessed in subgroup analyses.

METHODS

Criteria for considering studies for this review

Types of studies

Trials using random or quasi-random patient allocation.

Types of participants

Infants with NAS in the neonatal period born to mothers with an opiate dependence. Withdrawal may be determined by the presence of signs consistent with NAS or the use of a standardised score of NAS.

Types of interventions

Trials comparing the following were eligible: 1) opiates versus placebo or no treatment; 2) opiates (such as tincture of opium, paregoric, morphine or methadone) versus other opiates; 3) opiates versus sedatives (eg. clonidine, a benzodiazepine, barbiturate or neuroleptic agent); and 4) opiates versus non-pharmacological treatments (eg swaddling, settling, massage, relaxation baths, pacifiers or waterbeds).

Types of outcome measures

Primary outcomes:
1. Treatment failure: including failure to achieve control defined as a failure to reduce a standardised score of NAS from a clinically significant level to a clinically 'safe' level defined by author of trial, or the use of additional pharmacological treatments for control of NAS in the neonatal period,
2. Seizures
3. Neonatal and infant mortality
4. Neurodevelopmental outcome
Secondary outcomes:
1. Time to control of NAS (control of symptoms or reduction of NAS score to a clinically 'safe' level)
2. Duration of admission to a newborn nursery
3. Duration of hospitalisation (days)
4. Time to establishment of full sucking feeds
5. Success of breast feeding (eg absence of complementary formula feeds, adequate weight gain whilst breast feeding)
6. Rate of weight gain
7. Side effects occurring after commencement of therapy - a) apnea, b) need for resuscitation, c) need for mechanical ventilation
8. Duration of treatment of NAS (days).
9. Disruption to the mother infant relationship (eg separation of mother and infant, admission to a newborn nursery, failure to successfully breast feed, maternal depression, or parental dissatisfaction).
Subgroup analyses:
Prespecified subgroup analyses included the following identified subcategories:
1. According to type of opiate used (eg. tincture of opium, paregoric, morphine or methadone)
2. According to type of sedative used (eg. clonidine, a benzodiazepine, barbiturate or neurolept)
3. According to type of non-pharmacological treatment used
4. According to whether trials included mothers with only opiate dependence or with polydrug use, and
5. According to age at treatment (eg early versus delayed treatment) and duration of treatment (eg short versus long course).
All outcomes where available were eligible for inclusion in subgroup analysis.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. See Review Group details for more information. This was supplemented by additional searches of the Oxford Database of Perinatal Trials, Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2002), MEDLINE (1966-March 2002), PREMEDLINE (to March 2002), previous reviews including cross references (all studies cited), abstracts and conference proceedings (American Pediatric Society-Society for Pediatric Research Annual Meetings 1999-2002; Perinatal Society of Australia and New Zealand Annual Meetings 1999-2002).
The search of MEDLINE included both MeSH searches (using terms including: "[neonatal abstinence syndrome, opiate addiction, narcotics, methadone, morphine] and [infant-newborn or pregnancy]") and text word searches (using terms including: "[withdrawal, abstinence, addiction, opiate addiction, narcotics, methadone, morphine, paregoric, opium] and [infant-newborn or pregnancy]").
The search was updated in March 2005 by DO with additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2005), MEDLINE (1966-March 2005), PREMEDLINE (to March 2005), cross references of all new studies cited, abstracts and conference proceedings (American Pediatric Society-Society for Pediatric Research Annual Meetings 2003-4; Perinatal Society of Australia and New Zealand Annual Meetings 2003-2005).

Data collection and analysis

Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. The methodological quality of each trial was reviewed independently by the three authors. Particular emphasis was placed on allocation concealment, blinding, completeness of follow up and blinding of outcome assessment. Allocation concealment was ranked: Grade A: adequate; Grade B: uncertain; Grade C: clearly inadequate. Additional information where required was requested from authors of each trial to clarify methodology.
Methods used to collect data from the included trials: Each author extracted data independently. Authors then compared data and resolved differences. Additional data was requested from the authors of each trial. Additional information was provided by the authors for three trials (Finnegan 1984; Kaltenbach 1986; Khoo 1995).
Methods used to analyse the data: Standard methods of the Cochrane Neonatal Review Group. Treatment effect was expressed using relative risk (RR), risk difference (RD) and mean difference (MD) or weighted mean difference (WMD) where appropriate. The fixed effects model was assumed for meta-analysis.
We planned sensitivity analysis on the basis of methodological quality. Trials of good methodology were defined by studies with

adequate randomisation and allocation concealment, and > 90% follow up on an intention to treat basis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Seven studies reporting random or quasi-random allocation to treatment met criteria for inclusion (Carin 1983; Finnegan 1984; Jackson 2004; Kaltenbach 1986; Kandall 1983; Khoo 1995; Madden 1977). Two studies (Finnegan 1984; Kaltenbach 1986) may be sequential reports in which some of the patients are the same (author communication). In view of this uncertainty, outcomes that are reported by Kaltenbach 1986 that were previously reported by Finnegan 1984 are not included in the meta-analyses tables, but are reported separately in the text (see results). Five studies were published in peer reviewed journals (Carin 1983; Jackson 2004; Kaltenbach 1986; Kandall 1983; Madden 1977). One study was a research monograph (Finnegan 1984) and one was an unpublished PhD thesis (Khoo 1995). Thirty three reports or studies did not meet inclusion criteria (see 'table of excluded studies'). One study awaiting assessment (Pacifico 1989) did not report method of treatment allocation, although this was said to be non-random in another publication (AAP 1998).

Carin 1983 enrolled infants born to mothers receiving methadone for more than three months. Infants were enrolled if the Finnegan score was > = 8. Polydrug use was disclosed by some mothers (see 'table of included studies'). Infants were randomly allocated to paregoric 0.42 - 2.1 mls/kg/day orally or phenobarbitone 5-16 mg/kg/day in three divided doses titrated to symptom severity. Infants were weaned by a standard regimen depending on symptom scores.

Finnegan 1984 enrolled infants born to mothers using narcotics. Data were reported for infants of mothers a) using only opiates and b) using opiates and another drug. This stratification was not prespecified (author communication). The Neonatal Abstinence Scoring System (Finnegan score) was used to determine need and response to treatment. Infants were allocated to paregoric titrated to score (dose not reported), phenobarbitone loading dose regimen (20 mg/kg with maintenance 5 - 10 mg/kg/day) titrated against scores, phenobarbitone titration regimen (no loading dose), or diazepam (dose not reported) depending on scores. The two phenobarbitone groups (i.e. with or without loading dose) have been combined in the analyses reported in this review.

Jackson 2004 enrolled infants of mothers with a history of drug misuse and two sequential Lipsitz scores > 4. Exclusion of alternative diagnosis was by clinical examination and blood sample for electrolytes, calcium, magnesium and blood glucose. All mothers were on methadone. Other drug misuse was reported in 62 / 75 (82.7%) mothers. Infants were treated on postnatal wards unless they required naso-gastric feeds, had severe withdrawal or were admitted to special care baby unit for other problem. They were randomised to morphine (Oramorph) 50micrograms/kg/dose qid with no titration, or phenobarbitone 2 mg/kg qid with no titration. Second line treatment with chloral hydrate 15 kg/kg was according to standardised protocol. Treatment was weaned by 20% of original dose per day if the Lipsitz score was < = 4 for 48 hours.

Kaltenbach 1986 enrolled infants of women maintained on methadone. The Neonatal Abstinence Scoring System was used with scores averaging > = 8 for three consecutive scores determining need for treatment. Polydrug use was reported but incidence not given. Infants were allocated to paregoric, phenobarbitone loading dose followed by titration, phenobarbitone titration or diazepam (doses not reported). The two phenobarbitone groups (i.e. with or without loading dose) have been combined in the analyses reported in this review.

Kandall 1983 enrolled infants born to socioeconomically deprived mothers with opiate dependence. Infants with > = 7 on Lipsitz score or excessive single signs (eg diarrhoea or irritability) were treated. Polydrug use was reported (60 methadone only, 39 methadone and one other drug, 47 two other drugs, seven used heroin). Infants were randomly allocated to paregoric (0.2 ml q3h orally, increased by 0.05 mls until score < 6, weaned after five days by 0.05 mls every second day) or phenobarbitone (5 mg/kg/day intramuscular injection in three divided doses, increased by 1mg/kg/day until score < 6, then orally five days, weaned 1mg/kg every second day).

Khoo 1995 enrolled infants of mothers with an opiate dependence including 100 infants of mothers on at least two weeks of methadone, eight infants of mothers with a heroin dependency and three infants of mothers with a codeine dependency. The Neonatal Abstinence Scoring System was used with scores averaging > = 8 for three consecutive scores determining need for treatment. Of the mothers on methadone, 94.5% were on at least one other drug, and 76.4% of infants were exposed to more than two drugs in utero. Infants were allocated to morphine (0.5 mg/kg/day in 4 - 6 divided doses, titrated to score, up to a maximum dose of 0.9 mg/kg/day) plus supportive therapy, or phenobarbitone (loading dose 15 mg/kg intramuscularly, then 6 mg/kg/day in two divided doses, titrated to score up to maximum 10 mg/kg/day) plus supportive therapy, or to supportive therapy alone (included pacifier, swaddling, close wrapping, small frequent feeds, close skin contact by carrying in sling and other methods).

Madden 1977 enrolled infants of narcotic-addicted mothers in whom a clinical decision was made to treat. An abstinence score was not used. Polydrug use was reported (62 mothers on methadone only, 18 heroin and methadone, 19 heroin only, eight heroin and another agent, nine no drugs, one an agent other than heroin or methadone). Infants were randomly allocated to methadone

(0.25 mg q6h, increased every six hours to maximum 0.5 mg q6h), phenobarbitone (5-8 mg/kg/day in three divided doses) or diazepam (0.5 - 2.0 mg q8h with doses "tailored day to day").
Outcomes: No study reported mortality or long term neurodevelopmental outcome according to treatment group as allocated. Kaltenbach 1986 reported the Bayley MDI at six months according to treatments received (not allocated). Five studies reported treatment failure (Finnegan 1984; Jackson 2004; Kaltenbach 1986; Khoo 1995; Madden 1977), although Kaltenbach 1986 may have reported some of the same patients as Finnegan 1984. Four studies (Finnegan 1984; Jackson 2004; Kaltenbach 1986; Khoo 1995) reporting treatment failure used a standardised score to determine response to treatment. Madden 1977 reported need for a second agent but did not use a standardised score. One study reported seizure occurrence (Kandall 1983); seizures were clinically suspected (myoclonic, generalised motor or tonic-clonic) and infants had subsequent EEG, the majority of which were reported as abnormal although they were interictal.

Risk of bias in included studies

Randomisation: Jackson 2004 reported random allocation to treatment using a computer generated random number technique. Three studies (Carin 1983; Kandall 1983; Madden 1977) reported random allocation to treatment but did not report method of random allocation. Three studies (Finnegan 1984; Kaltenbach 1986; Khoo 1995) used quasi-random methods of patient allocation. Finnegan 1984 and Kaltenbach 1986 communicated "drug assignment pulled from envelopes which were designated according to first letter of last name". Khoo 1995 designated treatment according to the last number of the infant's hospital number. Several studies had sizeable and largely unexplained differences in the numbers of infants allocated to each group (Finnegan 1984; Jackson 2004; Kaltenbach 1986; Kandall 1983; Khoo 1995). Finnegan 1984 communicated that an interim analysis found the diazepam group had excessive complications (somnolence and respiratory depression), so enrolment in this group was stopped.
Blinding of treatment: Jackson 2004 reported blinding of the randomised treatment using solutions of identical appearance and a standardised treatment protocol. Two studies (Finnegan 1984; Kaltenbach 1986) did not blind treatment. No other study reported blinding of treatment and given the variable treatment regimens in each of the trials it is unlikely this was possible.
Blinding of outcome measurement: reported by three studies (Finnegan 1984; Jackson 2004; Kaltenbach 1986). No other study reported blinding of outcome measurement.
Losses to follow up: all infants were accounted for by four studies (Carin 1983; Finnegan 1984; Jackson 2004; Madden 1977). Madden 1977 reported separately two infants receiving a second agent for duration of treatment and hospital stay (one allocated methadone and one to phenobarbitone). Two studies did not report numbers entered so that any losses are unknown (Kaltenbach 1986; Kandall 1983). Khoo 1995 excluded three infants from analysis (one on phenobarbitone and two on supportive therapy) and nine infants did not have data available for days to regain birthweight.

Effects of interventions

INFANTS OF MOTHERS USING AN OPIATE - ALL INFANTS (The following comparisons include studies that enrolled infants of mothers using an opiate, with or without other drugs):
01 OPIATE VERSUS PLACEBO OR NO TREATMENT OR NON-PHARMACOLOGICAL TREATMENT
Primary outcomes: One study including 80 infants (Khoo 1995) reported no significant difference in treatment failure (RR 1.29, 95% CI 0.41, 4.07) when comparing infants receiving opiate and supportive treatment to supportive therapy alone.
Secondary outcomes: Khoo 1995 reported a significant increase in duration of treatment (MD 12.5 days, 95% CI 7.5, 17.5), duration of hospital stay (MD 15.0 days, 95% CI 8.9, 21.1) and duration of stay in special care nursery (MD 16.7 days, 95% CI 10.7, 22.7) for infants receiving opiates compared to supportive treatment alone. Infants receiving opiates had a significant reduction in days to regain birthweight (MD -2.8 days, 95% CI -5.3, -0.3) and duration of supportive care (MD -197.2 minutes per day, 95% CI -274.2, -120.3) compared to infants who received supportive care alone.
02 OPIATE VERSUS PHENOBARBITONE
Primary outcomes: Four studies (Finnegan 1984; Jackson 2004; Khoo 1995; Madden 1977) reported treatment failure in infants of mothers using an opiate with or without other drugs. No individual study found a significant difference in rate of treatment failure. Meta-analysis of these four studies including 302 infants found no significant difference in treatment failure comparing infants receiving an opiate to phenobarbitone (typical RR 0.76, 95% CI 0.51, 1.11). Kaltenbach 1986 reported a significant reduction in treatment failure in infants who received paregoric compared to phenobarbitone (RR 0.16, 95% CI 0.04, 0.64). As some of these infants may also have been reported by Finnegan 1984, this study is not included in the meta-analysis.
Seizures: One study (Kandall 1983) involving 111 infants reported a reduction in seizures of borderline statistical significance in infants receiving paregoric compared to phenobarbitone (RR 0.08, 95% CI 0.00, 1.44; RD -0.11, 95% CI -0.20, -0.03). All seizures (n = 7) occurred in the phenobarbitone group. It is unclear why this was the only study that reported a high incidence of seizures.
Mortality and neurodevelopment: Data for the Bayley MDI at six months were not reported by group of assignment in one study (Kaltenbach 1986). No other study reported mortality or neurodevelopment.
Secondary outcomes: Jackson 2004 reported a significant reduction in duration of treatment for infants on morphine compared to phenobarbitone (median 8 days versus 12 days, p = 0.02). As

this is reported as non-parametric data this has not been included in meta-analysis. Two others studies (Khoo 1995; Madden 1977) which reported duration of treatment and duration of hospital stay found no significant difference in either outcome between infants treated with an opiate compared to phenobarbitone. Meta-analysis of these two studies found no significant difference in duration of treatment (WMD -3.7 days, 95% CI -7.8, 0.3) or duration of hospital stay (WMD -2.5 days, 95% CI -7.1, 2.0). Khoo 1995 reported no significant difference in duration of stay in special care nursery (MD -6.4 days, 95% CI -13.8, 1.0), days to regain birthweight (MD -1.4 days, 95% CI -3.5, 0.7) or duration of supportive care (MD -35.1 minutes per day, 95% CI -86.9, 16.7). Carin 1983 reported a significant increase in median duration of treatment for paregoric compared to phenobarbitone treated infants (22 versus 17 days, $p < 0.01$). Jackson 2004 reported a significant reduction in admissions to the nursery for infants treated with morphine compared to phenobarbitone (RR 0.47, 95% CI 0.27, 0.82). Kandall 1983 reported severity scores (Lipsitz score) in infants on paregoric and phenobarbitone up to day 28. There was no significant difference in severity scores on day 3, 5, 7 or 14. A significant number of infants were no longer treated or reported on day 21 and 28.

Other outcomes reported: Carin 1983 found no difference in median weight gain during the second and third weeks of life. Respiratory rates, whole blood pH and PaCO2, blood pressure, serum thyroxine and platelet count on day four, seven and 14 were also similar except for a slightly higher blood PaCO2 on day seven in phenobarbitone treated infants.

03 OPIATE VERSUS DIAZEPAM

Primary outcomes: In 52 infants, Finnegan 1984 reported a significant reduction in treatment failure in infants receiving paregoric compared to diazepam (RR 0.36, 95% CI 0.18, 0.69). Madden 1977 reported only one infant treated with methadone who required a second agent compared to none who received diazepam. Meta-analysis of these two studies involving 86 infants found a significant reduction in rate of treatment failure in infants receiving an opiate (typical RR 0.43, 95% CI 0.23, 0.80). Kaltenbach 1986 found a significant reduction in need for a second drug in infants receiving paregoric compared to diazepam (RR 0.09, 95% CI 0.02, 0.33). As some of these infants may also have been reported by Finnegan 1984, this study is not included in the meta-analysis.

Mortality and neurodevelopment: Data for the Bayley MDI at six months were not reported by allocated treatment group in one study (Kaltenbach 1986). No other study reported mortality or neurodevelopment.

Secondary outcomes: Madden 1977 reported no significant difference in mean duration of treatment (MD 1.6 days, 95% CI -1.6, 4.7) or duration of hospital stay (MD 2.3 days, 95% CI -1.8, 6.5) between infants receiving methadone compared to diazepam.

SUBGROUP ANALYSES

1. ACCORDING TO WHETHER TRIALS INCLUDED INFANTS OF MOTHERS USING ONLY AN OPIATE OR AN OPIATE AND ANOTHER DRUG

A) INFANTS OF MOTHERS USING ONLY OPIATES

- OPIATE VERSUS PLACEBO OR NO-TREATMENT OR NON-PHARMACOLOGICAL TREATMENT

No eligible studies reported these comparisons.

- OPIATE VERSUS PHENOBARBITONE

Only one study (Finnegan 1984) separately reported infants of mothers on only opiates. Finnegan 1984 reported a significantly reduced treatment failure rate with paregoric compared to phenobarbitone (RR 0.14, 95% CI 0.02, 0.98) in 40 infants of mothers using only opiates. No study separately reported seizures, mortality or neurodevelopment in infants of mothers only on opiates.

- OPIATE VERSUS DIAZEPAM

Only one study (Finnegan 1984) separately reported infants of mothers on only opiates. Finnegan 1984 reported a significant reduction in treatment failure with paregoric compared to diazepam (RR 0.07, 95% CI 0.01, 0.47) in 19 infants of mothers using only opiates. No study separately reported seizures, mortality or neurodevelopment in infants of mothers only on opiates.

B) INFANTS OF MOTHERS USING AN OPIATE AND ANOTHER DRUG

- OPIATE VERSUS PLACEBO OR NO-TREATMENT OR NON-PHARMACOLOGICAL TREATMENT

No eligible studies reported these comparisons.

- OPIATE VERSUS PHENOBARBITONE

Only one study (Finnegan 1984) separately reported infants of mothers on opiates and other drugs. Finnegan 1984 reported a significantly increased treatment failure rate with paregoric compared to phenobarbitone (RR 3.39, 95% CI 1.37, 8.39) in 79 infants of mothers using opiates and other drugs. No study separately reported seizures, mortality or neurodevelopment in infants of mothers using an opiate and other drugs.

- OPIATE VERSUS DIAZEPAM

Only one study (Finnegan 1984) separately reported infants of mothers on opiates and other drugs. Finnegan 1984 reported no significant difference in treatment failure with paregoric compared to diazepam (RR 0.65, 95% CI 0.32, 1.32) in 33 infants of mothers using only opiates. No study separately reported seizures, mortality or neurodevelopment in infants of mothers using an opiate and other drugs.

2. ACCORDING TO TYPE OF OPIATE AND SEDATIVE USED

A) PAREGORIC VERSUS PHENOBARBITONE

Four studies (Carin 1983; Finnegan 1984; Kaltenbach 1986; Kandall 1983) compared paregoric to phenobarbitone. Finnegan 1984 reported no significant difference in treatment failure (RR 1.09, 95% CI 0.53, 2.22). Kaltenbach 1986 also reported a significant reduction in treatment failure (RR 0.16, 95% CI 0.04, 0.64), but this study may include some of the same patients as reported by Finnegan 1984. Kandall 1983 reported a reduction in seizures of borderline significance (RR 0.08, 95% CI 0.00, 1.44; RD -0.11, 95% CI -0.20, -0.03).

B) METHADONE VERSUS PHENOBARBITONE

One study (Madden 1977) compared methadone to phenobarbitone and found no significant difference in need for a second drug (RR 0.89, 95% CI 0.06, 13.08), duration of treatment or hospital stay.

C) MORPHINE VERSUS PHENOBARBITONE

Two studies (Jackson 2004; Khoo 1995) compared morphine to phenobarbitone. Jackson 2004 reported no significant difference in treatment failure (RR 0.73, 95% CI 0.42, 1.26), and a significant reduction in duration of treatment for infants receiving morphine (median 8 days versus 12 days, p = 0.02) and a reduction in admission to the nursery (RR 0.47, 95% CI 0.27, 0.82). Khoo 1995 reported no significant difference in treatment failure (RR 0.47, 95% CI 0.20, 1.13), duration of treatment (MD -5.4 days, 95% CI -12.0, 1.2), hospital stay (MD -5.8 days, 95% CI -13.4, 1.8), stay in special care nursery (MD -6.4 days, 95% CI -13.8, 1.1), time to regain birthweight (MD -1.4 days, 95% CI -3.5, 0.7) or duration of supportive care (-35.1 minutes per day, 95% CI -88.9, 16.7).

D) PAREGORIC VERSUS DIAZEPAM

Two studies (Finnegan 1984; Kaltenbach 1986) compared paregoric to diazepam although the studies may have included some of the same patients. Both Finnegan 1984 (RR 0.36, 95% CI 0.18, 0.69) and Kaltenbach 1986 (RR 0.09, 95% CI 0.02, 0.33) reported a significant reduction in treatment failure for infants receiving paregoric compared to diazepam.

E) METHADONE VERSUS DIAZEPAM

One study (Madden 1977) compared methadone with diazepam and reported no significant difference in need for a second drug (RR 2.68, 95% CI 0.12, 61.59), duration of treatment or hospital stay.

F) OTHER COMPARISONS

No study compared the effects of an opiate with chlorpromazine or clonidine. No study reported tincture of opium. No study compared different types of opiates.

3. ACCORDING TO TYPE OF NON-PHARMACOLOGICAL TREATMENT USED

Khoo 1995 compared morphine and supportive care to supportive care alone. The results are as documented above.

4. ACCORDING TO AGE AT TREATMENT OR DURATION OF TREATMENT

No study compared early versus delayed treatment of NAS, or short versus long courses of therapy for NAS.

SENSITIVITY ANALYSIS

No study met our pre-defined criteria for good methodology as three studies were quasi-randomised (Finnegan 1984; Kaltenbach 1986; Khoo 1995) and the other three studies (Carin 1983; Kandall 1983; Madden 1977) did not report method of randomisation or blinding of allocation concealment. Jackson 2004 had imbalances after randomisation with more infants in the phenobarbitone group exposed to benzodiazepines. Therefore, the planned sensitivity analysis according to methodological quality could not be performed.

DISCUSSION

This review includes studies that reported random or quasi-random allocation of infants with NAS to an opiate or sedative. Given the high rate of polydrug use in mothers of infants with NAS, the infants included in these studies are likely to represent the infants seen in clinical practice. Most studies used a standardised score to determine need for treatment and response to treatment. Few losses to follow up were reported by the individual studies, although this could have been by omission. This review prespecified the primary outcomes and the comparisons that have been made.

The validity of the results is affected by the methodological quality of the included studies. Only one study (Jackson 2004) reported adequate randomisation and allocation concealment procedures. However, this study had an imbalance after randomisation that resulted in significantly more infants in the phenobarbitone group whose mothers were on benzodiazepines, which has the potential to bias the results. Three studies reported quasi-random methods of patient allocation and the other studies failed to report method of random allocation. Several studies had large discrepancies in group allocations. Only one study (Jackson 2004) reported blinding of treatment and only three studies reported blinding of outcome measurement. Communication with the author of two studies (Finnegan 1984; Kaltenbach 1986) has revealed that the studies may be sequential reports including some of the same patients. Original data are not available. The outcomes of these studies were not combined in meta-analysis. In view of these limitations, the conclusions of this review should be treated with caution. Only one study (Finnegan 1984) differentiated infants of mothers only using opiates to those born to mothers on an opiate and another drug, although this was not prespecified. No study reported quality of mother-infant interaction, success of breast feeding, incidence of foster care or neurodevelopmental outcome (according to group of allocation).

This review finds evidence from one quasi-random study (Khoo 1995) that morphine and supportive care compared to supportive care alone does not affect treatment failure rate, but results in a

significant reduction in time to regain birthweight and duration of supportive care at the cost of increased hospital stay. It is unclear whether the effect on duration of hospital stay was due to a policy of keeping the infants in hospital whilst receiving pharmacological therapy. Comparing use of an opiate to phenobarbitone, meta-analysis of four studies found no significant difference in incidence of treatment failure. One study (Jackson 2004) reported a significant reduction in duration of treatment and a reduction in admission to the nursery for infants receiving morphine compared to phenobarbitone. Evidence from one study (Kandall 1983) suggests that infants treated with an opiate may be less likely to have seizures, although this is not reported by any other study and is of borderline significance. Possible reasons include delayed treatment of withdrawing infants due to the use of an insensitive score (Lipsitz score) for NAS, the use of a low dose of phenobarbitone (5mg/kg/day) without a loading dose, or that the difference was found by chance or due to study bias. This review also finds evidence from a quasi-random study (Finnegan 1984) that infants with NAS born to mothers using only opiates are more likely to have symptom control and less likely to have a second agent commenced if they are treated with an opiate compared to phenobarbitone, although this subgroup analysis was not prespecified. Which opiate to use for NAS due to opiate withdrawal is not answered by the studies in this review. Paregoric was the opiate used in four of the studies. However, concerns regarding its high alcohol content have resulted in recommendations to use tincture of opium (AAP 1998). Two studies compared morphine to phenobarbitone with one study (Jackson 2004) reporting a significant reduction in duration of treatment and a reduction in admission to the nursery for infants receiving morphine compared to phenobarbitone. No trial compared different opiates or used tincture of opium. One study (Madden 1977) failed to demonstrate a benefit for methadone compared to phenobarbitone or diazepam. No study compared different treatment thresholds or compared different dose regimens. Further research is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Opiates, as compared to supportive care only, appear to reduce the time to regain birth weight and reduce the duration of supportive care, but increase the duration of hospital stay; there is no evidence of effect on treatment failure. When compared to phenobarbitone, opiates may reduce the incidence of seizures but, overall, there is no evidence of effect on treatment failure. One study reported a reduction in duration of treatment and nursery admission for infants on morphine. When compared to diazepam, opiates reduce the incidence of treatment failure. A post-hoc analysis generates the hypothesis that treatment effects may vary according to whether the population includes infants born to all opiate users (i.e. with or without other drug exposure) or is restricted to infants of mothers who used opiates only. In view of the methodologic limitations of the included studies the conclusions of this review should be treated with caution.

Implications for research

In infants of mothers using only opiates, further well designed studies are required to determine which opiate is most effective and what treatment threshold should be used. Studies should measure effects on infant signs of withdrawal, quality of mother-infant interaction, growth and long term development. Objective and validated infant symptom severity scores should be used. In infants of mothers using an opiate and another drug, further trials of an opiate versus phenobarbitone or opiate combined with a sedative are warranted.

ACKNOWLEDGEMENTS

Dr Loretta Finnegan and Dr Katie Khoo who kindly provided additional information regarding their studies.

REFERENCES

References to studies included in this review

Carin 1983 *{published data only}*
Carin I, Glass L, Parekh A, Solomon N, Steigman J, Wong S. Neonatal methadone withdrawal. Effect of two treatment regimens. *American Journal of Diseases of Children* 1983;**137**:1166–9.

Finnegan 1984 *{published and unpublished data}*
Finnegan LP, Michael H, Leifer B, Desai S. An evaluation of neonatal abstinence treatment modalities. *NIDA Research Monograph* 1984;**49**:282–8.

Jackson 2004 *{published data only}*
Jackson L, Ting A, McKay S, Galea P, Skeoch C. A randomised controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome. *Archives of Disease in Childhood* 2004;**89**: F300–4.

Kaltenbach 1986 *{published and unpublished data}*
Kaltenbach K, Finnegan LP. Neonatal abstinence syndrome, pharmacotherapy and developmental outcome. *Neurobehavioral Toxicology and Teratology* 1986;**8**:353–5.

Kandall 1983 *{published data only}*
Kandall SR, Doberczak TM, Mauer KR, Strashun RH, Korts DC. Opiate v CNS depressant therapy in neonatal drug abstinence syndrome. *American Journal of Diseases of Children* 1983;**137**: 378–82.

Khoo 1995 *{unpublished data only}*
Khoo KT. The effectiveness of three treatment regimens used in the management of neonatal abstinence syndrome. University of Melbourne. PhD Thesis 1995.

Madden 1977 *{published data only}*
Madden JD, Chappel JN, Zuspan F, Gumpel J, Mejia A, Davis R. Observation and treatment of neonatal narcotic withdrawal. *American Journal of Obstetrics and Gynecology* 1977;**127**:199–201.

References to studies excluded from this review

Alroomi 1988 *{published data only}*
Alroomi LG, Davidson J, Evans TJ, Galea P, Howat R. Maternal narcotic abuse and the newborn. *Archives of Disease in Childhood* 1988;**63**:81–3.

Bier 2000 *{published data only}*
* Bier JB, Ferguson AE, Grenon D, Mullane E, Coyle M. The effect of phenobarbital on developmental outcomes in infant with methadone withdrawal: results of a randomized trial. *Pediatric Research* 2000;**47**:175A.
Ferguson A, Coyle M, LaGasse L, Liu E, Lester B. Neurobehavioural effects of treatment for opiate withdrawal. *Pediatric Research* 2001;**49**:18A.

Calabrese 1985 *{published data only}*
Calabrese JR, Gulledge AD. The neonatal narcotic abstinence syndrome: a brief review. *Canadian Journal of Psychiatry* 1985;**30**: 623–6.

Connaughton 1977 *{published data only}*
Connaughton JF, Reeser D, Schut J, Finnegan LP. Perinatal addiction: outcome and management. *American Journal of Obstetrics and Gynecology* 1977;**129**:679–86.

Coyle 2002 *{published data only}*
Bier JB, Ferguson AE, Grenon D, Mullane E, Coyle M. The effects of phenobarbital on developmental outcomes in infants with methadone withdrawal: results of a randomized trial. *Pediatric Research* 2000;**47**:175A.
* Coyle MG, Ferguson A, Lagasse L, Oh W, Lester B. Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. *Journal of Pediatrics* 2002;**140**:561–4.
Ferguson AE, Coyle M, LaGasse L, Liu E, Lester B. Neurobehavioural effects of treatment for opiate withdrawal. *Pediatric Research* 2001;**49**:18A.

Doberczak 1991 *{published data only}*
Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. *Journal of Pediatrics* 1991; **118**:933–7.

Finnegan 1975a *{published data only}*
Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addictive Diseases* 1975;**2**:141–58.

Finnegan 1975b *{published data only}*
Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1975;**12**:19–32.

Finnegan 1979 *{published data only}*
Finnegan LP, Mitros TF, Hopkins LE. Management of neonatal narcotic abstinence utilizing a phenobarbital loading dose method. *NIDA Research Monograph* 1979;**27**:247–53.

Finnegan 1985 *{published data only}*
Finnegan LP. Effects of maternal opiate abuse on the newborn. *Federation Proceedings* 1985;**44**:2314–7.

Fischer 1999 *{published data only}*
Fischer G, Jagsch R, Eder H, Gombas W, Etzersdorfer P, Schmidl-Mohl K. Schatten C, Weninger M, Aschauer HN. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. *Addiction* 1999;**94**:231–9.

Fosnot 2000 *{published data only}*
Fosnot J, Spinner SS, Florio A, Desai SA, Greenspan JS. The efficacy of paregoric versus tinture of opium in the treatment of neonatal abstinence syndrome (NAS). *Pediatric Research* 1999;**45**: 197A.

Harper 1977 *{published data only}*
Harper RG, Solish G, Feingold E, Gersten Woolf NB, Sokal MM. Maternal ingested methadone, body fluid methadone, and the neonatal withdrawal syndrome. *American Journal of Obstetrics and Gynecology* 1977;**129**:417–24.

Herzlinger 1977 *{published data only}*
Herzlinger RA, Kandall SR, Vaughan HG Jr. Neonatal seizures associated with narcotic withdrawal. *Journal of Pediatrics* 1977;**91**: 638–41.

Kahn 1969 *{published data only}*
Kahn EJ, Neumann LL, Polk GA. The course of the heroin withdrawal syndrome in newborn infants treated with phenobarbital or chlorpromazine. *Journal of Pediatrics* 1969;**75**: 495–500.

Kaltenbach 1987 *{published data only}*
Kaltenbach K, Finnegan LP. Perinatal and developmental outcome of infants exposed to methadone in-utero. *Neurotoxicology and Teratology* 1987;**9**:311–3.

Kandall 1977 *{published data only}*
Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman A, Lowinson J. The narcotic-dependent mother: fetal and neonatal consequences. *Early Human Development* 1977;**1**:159–69.

Kron 1975a *{published data only}*
Kron RE, Kaplan SL, Finnegan LP, Litt M, Phoenix MD. The assessment of behavioural change in infants undergoing narcotic withdrawal: comparative data from clinical and objective methods. *Addictive Diseases* 1975;**2**:257–75.

Kron 1975b *{published data only}*
Kron RE, Litt M, Finnegan LP. Narcotic addiction in the newborn: differences in behaviour generated by methadone and heroin. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1975;**12**:63–9.

Kron 1976 *{published data only}*
Kron RE, Litt M, Eng D, Phoenix MD, Finnegan LP. Neonatal narcotic abstinence: Effects of pharmacotherapeutic agents and maternal drug usage on nutritive sucking behavior. *Journal of Pediatrics* 1976;**88**:637–41.

Lainwala 2002 *{published data only}*
Lainwala S, Brown E, Weinschenk N, Blackwell M, Hagadorn J. Comparison of length of hospital stay of infants treated with methadone vs oral morphine preparations for narcotic abstinence syndrome. *Pediatric Research* 2002;**51**:360A.

Lainwala 2003 *{published data only}*
Lainwala S, Brown E, Weinschenk N, Blackwell M, Hagadorn J. Length of hospital stay (LOS) of infants treated with oral morphine preparations for neonatal abstinence syndrome (NAS). *Pediatric Research* 2003;**53**:A2753.

Mack 1991 *{published data only}*
Mack G, Thomas D, Giles W, Buchanan N. Methadone levels and neonatal withdrawal. *Journal of Paediatrics and Child Health* 1991; **27**:96–100.

Ostrea 1975 *{published data only}*
Ostrea EM, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. *Addictive Diseases* 1975;**2**:187–99.

Ostrea 1976 *{published data only}*
Ostrea EM, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. *Journal of Pediatrics* 1976;**88**:642–5.

Rivers 1986 *{published data only}*
Rivers RP. Neonatal opiate withdrawal. *Archives of Disease in Childhood* 1986;**61**:1236–9.

Rosen 1982 *{published data only}*
Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *Pediatrics* 1982;**101**: 192–6.

Sutton 1990 *{published data only}*
Sutton LR, Hinderliter SA. Diazepam abuse in pregnant women on methadone maintenance. Implications for treatment. *Clinical Pediatrics* 1990;**29**:108–11.

Tunis 1984 *{published data only}*
Tunis SL, Webster DM, Izes JK, Finnegan LP. Maternal drug use and the effectiveness of pharmacotherapy for neonatal abstinence. *NIDA Research Monograph* 1984;**55**:158.

Wijburg 1991 *{published data only}*
Wijburg FA, de Kleine MJ, Fleury P, Soepatmi S. Morphine as an anti-epileptic drug in neonatal abstinence syndrome. *Acta Paediatrica Scandinavica* 1991;**80**:875–7.

Wolman 1989 *{published data only}*
Wolman I, Niv D, Yoval I, Pausner D, Geller E, David MP. Opioid-addicted parturient, labor, and outcome: a reappriasal. *Obstetrical & Gynecological Survey* 1989;**44**:592–7.

Yaster 1996 *{published data only}*
Yaster M, Kost-Byerly S, Berde C, Billet C. The management of opioid and benzodiazepine dependence in infants, children, and adolescents. *Pediatrics* 1996;**98**:135–40.

Zelson 1970 *{published data only}*
Zelson C. Heroin withdrawal syndrome. *Journal of Pediatrics* 1970; **76**:483–6.

References to studies awaiting assessment

Pacifico 1989 *{published data only}*
Pacifico P, Nardelli E, Pantarotto MF. Neonatal heroin withdrawal syndrome; evaluation of different pharmacological treatments. *Pharmacological Research* 1989;**21 (S 1)**:63–4.

Additional references

AAP 1998
American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. *Pediatrics* 1998;**101**:1079–88.

Bell 1995
Bell GL, Lau K. Perinatal and neonatal issues of substance abuse. *Pediatric Clinics of North America* 1995;**42**:261–81.

de Cubas 1993
de Cubas MM, Field T. Children of methadone-dependent women: developmental outcomes. *American Journal of Orthopsychiatry* 1993;**63**:266–76.

Fricker 1978
Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *American Journal of Diseases of Children* 1978;**132**:360–6.

Hulse 1998
Hulse GK, Milne E, English DR, Holman CD. Assessing the relationship between maternal opiate use and neonatal mortality. *Addiction* 1998;**93**:1033–42.

Kandall 1974
Kandall SR, Gartner LM. Late presentation of drug withdrawal symptoms in newborns. *American Journal of Diseases of Children* 1974;**127**:58–61.

Kandall 1993
Kandall SR, Gaines J, Habel L, Davidson G, Jessop D. Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring. *Journal of Pediatrics* 1993;**123**:120–6.

Lam 1992
Lam SK, To WK, Duthie SJ, Ma HK. Narcotic addiction in pregnancy with adverse maternal and perinatal outcome. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 1992;**32**: 216–21.

Lipsitz 1975
Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. *Clinical Pediatrics* 1975;**14**:592–4.

Maas 1990
Maas U, Kattner E, Weingart Jesse B, Schafer A, Obladen M. Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. *Journal of Perinatal Medicine* 1990;**18**:111–8.

Madden 1977
Madden JD, Chappel JN, Zuspan F, Gumpel J, Mejia A, Davis R. Observation and treatment of neonatal narcotic withdrawal. *American Journal of Obstetrics and Gynecology* 1977;**127**:199–201.

NDSHS 1998
Adhikari P, Summerill A. 1998 National Drug Strategy Household Survey: Detailed findings. AIHW cat. no. PHE 27. Canberra: AIHW (Drug Statistics Series No. 6)..

NHSDA 1999
Office of Applied Statistics, Substance Abuse and Mental Health Administration (SAMHSA). National household survey on drug abuse. 1999. http://www.DrugAbuseStatistics.samhsa.gov/ 2001.

O'Brien 2002
O'Brien C, Jeffery HE. Sleep deprivation, disorganization and fragmentation during opiate withdrawal in newborns. *Journal of Paediatrics and Child Health* 2002;**38**:66–71.

Olofsson 1983
Olofsson M, Buckley W, Andersen GE, Friis Hansen BSO. Investigation of 89 children born by drug-dependent mothers. I. Neonatal course. *Acta Paediatrica Scandinavica* 1983;**72**:403–6.

Olson 1997
Olson GA, Olson RD, Kastin AJ. Endogenous opiates: 1996. *Peptides* 1997;**18**:1651–88.

Ornoy 1996
Ornoy A, Michailevskaya V, Lukashov I, Bar Hamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. *Child Abuse & Neglect* 1996;**20**:385–96.

Oro 1988
Oro AS, Dixon SD. Waterbed care of narcotic-exposed neonates. A useful adjunct to supportive care. *American Journal of Diseases of Children* 1988;**142**:186–8.

Osborn 2002a
Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD002053]

Strauss 1976
Strauss ME, Andresko M, Stryker JC, Wardell JN. Relationship of neonatal withdrawal to maternal methadone dose. *American Journal of Drug and Alcohol Abuse* 1976;**3**:339–45.

Theis 1997
Theis JG, Selby P, Ikizler Y, Koren GS. Current management of the neonatal abstinence syndrome: a critical analysis of the evidence. *Biology of the Neonate* 1997;**71**:345–56.

Zahorodny 1998
Zahorodny W, Rom C, Whitney W, Giddens S, Samuel M, Maichuk G, Marshall R. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *Journal of Dvelopmental and Bhavioral Pdiatrics* 1998;**19**:89–93.

References to other published versions of this review

Osborn 2002b
Osborn DA, Jeffery HE, Cole M. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD002059]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Carin 1983

Methods	Randomisation: yes, method not reported. Blinding of treatment: not reported. Blinding of measurement: no. Losses to follow up: none.
Participants	Inclusion criteria: Infants born to mothers receiving methadone for more than 3 months, parental consent, Finnegan score >= 8. Exclusion criteria: Asphyxia, infection, congenital, metabolic or haematologic abnormality. Polydrug use: in paregoric group, mothers disclosed the use of heroin (4), cocaine (3) and diazepam (3). In the phenobarbitone group 3 mothers disclosed cocaine use.
Interventions	1. Paregoric (n = 16): 0.42 to 2.1 mls/kg/day orally titrated to severity of symptoms. 2. Phenobarbitone (n = 15): 5-16mg/kg/day in 3 divided doses titrated to symptoms. Co-interventions: none reported. Weaning: Finnegan score <= 4 for 2 days, both groups weaned by 20% every 2nd day. Therapy ceased when phenobarbitone 1.0mg/kg/day or paregoric 0.1mls/kg/day.
Outcomes	Primary outcome: effects on physical and biochemical findings. Other outcomes: duration of treatment. Median weight gain.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Finnegan 1984

Methods	Randomisation: quasi-random, drug assignment from envelope designated according to first letter of last name. Blinding of treatment: no, treatment regimens different. Blinding of measurement: yes. Losses to follow up: none reported.
Participants	Inclusion criteria: Infants born to mothers with a) narcotic use only and b) narcotic and other drug use. Finnegan score determined need for treatment. Exclusion criteria: none reported.
Interventions	1. Paregoric (n = 32): titrated to score, dose not reported. 2. Phenobarbitone (n=87) with or without loading dose (20 mg/kg) with maintenance 5-10 mg/kg/day titrated against score. Dose increased until control obtained, serum level > 70mcg/ml or evidence of

Finnegan 1984 (*Continued*)

	toxicity. 3. Diazepam (n = 20): dose not reported. Co-interventions: none reported. Subgroup analysis according to whether mother on narcotic alone or narcotic and other drug.
Outcomes	Primary outcome: need for 2nd pharmacological intervention. Other outcomes: none.
Notes	Additional information obtained from authors. Group numbers not balanced. Interim analysis found diazepam group had excessive number of complications (somnolence and respiratory depression), so enrolment in this group stopped. May include some of the infants as reported by Kaltenbach 1986. Randomisation not stratified according to type of antenatal drug use.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Jackson 2004

Methods	Randomisation: yes, computer generated random numbers. Blinding of treatment: yes, identical solutions labelled A or B. Blinding of measurement: yes. Losses to follow up: none reported.
Participants	Infants with mothers with a history of drug misuse and 2 sequential Lipsitz scores >4. Exclusion of alternative diagnosis by clinical examination and blood sample for electrolytes, calcium, magnesium and blood glucose. All mothers on methadone. Other drug misuse: 62 / 75 (82.7%).
Interventions	Morphine (Oramorph) (n = 41): 50micrograms/kg/dose qid. No titration. Phenobarbitone (n = 34): 2mg/kg qid. No titration. Second line treatment (chloral hydrate 15kg/kg) according to standardised protocol. Treatment weaned by 20% of original dose/day if Lipsitz score <=4 for 48 hours.
Outcomes	Primary outcome: total duration of pharmacological treatment required to achieve symptom resolution. Other outcomes; admission to SCBU, use of second line therapies.
Notes	Infants treated on postnatal wards unless required naso-gastric feeds, had severe withdrawal or admitted to special care baby unit for other problem. Significantly more infants born to mothers using benzodiazepines in group allocated phenobarbitone.

Risk of bias

Item	Authors' judgement	Description

Jackson 2004 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Kaltenbach 1986

Methods	Randomisation: quasi-random, drug assignment from envelope designated according to first letter of last name. Blinding of treatment: no, treatment regimens different. Blinding of measurement: yes. Losses to follow up: none reported.
Participants	Inclusion criteria: Infants of drug dependant women maintained on methadone. Neonatal Abstinence Scoring System score averaging >= 8 for 3 consecutive scores. Exclusion criteria: none reported. Polydrug use: yes, of mothers on methadone, 94.5% were on at least one other drug, and 76.4% of infants were exposed to more than 2 drugs.
Interventions	1. Paregoric (n = 23): dose not reported. 2. Phenobarbitone loading dose followed by titration (n = 20): doses not reported. 3. Phenobarbitone titration (n = 16): doses not reported. 4. Diazepam (n = 10): dose not reported. Co-interventions: none reported.
Outcomes	Primary outcome: Bayley Scale of Mental Development at 6 months (not reported by groups as allocated) . Other outcomes: need for second agent to control symptoms.
Notes	Additional information obtained from authors. Group numbers not balanced. May include some of the infants as reported by Finnegan 1984. Randomisation not stratified according to type of antenatal drug use. Developmental followup not reported according to assigned treatment group.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Kandall 1983

Methods	Randomisation: yes, method not reported. Blinding of treatment: unlikely, treatment regimens different. Blinding of measurement: not reported. Losses to follow up: none reported.
Participants	Inclusion criteria: infants born to socioeconomically deprived mothers with opiate dependence. Infants with >= 7 on Lipsitz score or excessive individual sign (eg diarrhoea or irritability). Exclusion criteria: none reported. Polydrug use: yes, 60 methadone only, 39 methadone and one other drug, 47 two other drugs, 7 used heroin.

Kandall 1983 (*Continued*)

Interventions	1. Paregoric (n = 49): 0.2ml q3h orally, increased by 0.05mls until score < 6. Weaned after 5 days by 0.05mls every 2nd day. 2. Phenobarbitone (n = 62): 5mg/kg/day IMI in 3 divided doses, increased by 1mg/kg/day until score < 6. Then weaned after 5 days by 1mg/kg every 2nd day. Co-interventions: none reported.
Outcomes	Primary outcome: none reported. Other outcomes: Lipsitz NAS severity score, symptoms and seizures. Seizures were clinically suspected (myoclonic, generalised motor or tonic-clonic) and had subsequent EEG.
Notes	Group numbers not balanced.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Khoo 1995

Methods	Randomisation: quasi-random, used last number of the subject's hospital number. Blinding of treatment: no. Blinding of measurement: not reported. Losses to follow up: 1 infant allocated phenobarbital and 2 supportive therapy excluded from analysis. Data available for days to regain birthweight from 44/46 infants on morphine, 27/28 on phenobarbitone and 28/34 on supportive therapy.
Participants	Inclusion criteria: infants of mothers with an opiate dependence who had 3 Finnegan NASS scores averaging >=8 in 3 consecutive 4-hour periods. Urine drug screens performed during pregnancy. Of 111 infants entered into trial, 100 had been exposed to methadone, 8 to heroin, 3 to codeine. Polydrug use was reported by 95% of methadone mothers. 76% of infants had been exposed to more than 2 drugs in utero.
Interventions	1. Morphine (n=46); 0.5mg/kg/day in 4-6 divided doses, titrated to score up to maximum 0.9mg/kg/day; and supportive therapy. 2. Phenobarbitone loading dose (n=29) 15mg/kg (intramuscular) then 6mg/kg/day in 2 divided doses, titrated to score up to maximum 10mg/kg/day; and supportive therapy. 3. Supportive therapy alone (n=36) (included pacifier, swaddling, close wrapping, small frequent feeds, close skin contact by carrying in sling and other methods).
Outcomes	Primary outcome: unclear. Other outcomes: need for second drug (failure to settle measured using Finnegan score), duration of supportive intervention, numbers of dose increments on therapy, number of treatment days, days in baby special care nursery, days in hospital, treatment days and days to regain weight. Brazelton Neonatal Behavioural Assessment Scale performed in the neonatal period, and an infant temperament questionnaire at 2, 4, 8 and 12 months.
Notes	Methods and data obtained from author's PhD thesis and the author. Group numbers not balanced.

Khoo 1995 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Madden 1977

Methods	Randomisation: yes, method not reported. Blinding of treatment: unlikely, treatment regimens different. Blinding of measurement: not reported. Losses to follow up: none reported. One infant given diazepam non-randomly excluded. One infant in each of methadone and phenobarbital groups treated with second drug not included in duration of treatment and hospital stay.
Participants	Inclusion criteria: infants of narcotic-addicted mothers. Clinical Inclusion criteria: infants of narcotic-addicted mothers. Clinical decision to treat. Abstinence score not used. Exclusion criteria: none reported. Polydrug use: yes, of 123 pregnancies studied, 62 mothers on methadone only, 18 heroin and methadone, 19 heroin only, 8 heroin and another agent, 9 no current drugs, one an agent other than heroin or methadone. Fifty one infants required treatment.
Interventions	1. Methadone (n = 18): 0.25mg q6h, increased every 6 hours to maximum 0.5mg q6h. 2. Phenobarbitone (n = 16): 5-8mg/kg/day (3 divided doses). 3. Diazepam (n = 16): 0.5-2.0mg q8h. Doses "tailored day to day". Co-interventions: none reported.
Outcomes	Primary outcome: none reported. Other outcomes: use of second drug, duration of treatment and day of hospital discharge.
Notes	Note not intention to treat analysis - infants requiring second agent not included in initial treatment group for outcomes duration of treatment and day of discharge.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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

Alroomi 1988	Observational study.
Bier 2000	Randomised trial of tincture of opium and phenobarbitone versus tincture of opium.
Calabrese 1985	Monograph review.
Connaughton 1977	Observational report.
Coyle 2002	Compared addition of phenobarbitone versus placebo in infants initially treated with diluted tincture of opium.
Doberczak 1991	Observational study.
Finnegan 1975a	Observational study.
Finnegan 1975b	Observational study.
Finnegan 1979	Case series report.
Finnegan 1985	Monograph review.
Fischer 1999	Randomised trial of SR morphine and methadone in pregnant women to prevent neonatal abstinence syndrome.
Fosnot 2000	Historical control study of paregoric versus tincture of opium.
Harper 1977	Observational study.
Herzlinger 1977	Observational study.
Kahn 1969	Randomised study of phenobarbitone versus chlorpromazine for neonatal heroin withdrawal.
Kaltenbach 1987	Observational study.
Kandall 1977	Observational study. Not treatment study.
Kron 1975a	Observational study.
Kron 1975b	Observational study.
Kron 1976	Non-randomised control study comparing paregoric, phenobarbitone and diazepam treated infants with neonatal abstinence syndrome.
Lainwala 2002	Retrospective study comparing infants treated with methadone and oral morphine.

(*Continued*)

Lainwala 2003	Retrospective study comparing infants treated with methadone and oral morphine.
Mack 1991	Observational study.
Ostrea 1975	No study of treatment.
Ostrea 1976	Observational study.
Rivers 1986	Monograph review.
Rosen 1982	Observational study.
Sutton 1990	Case report.
Tunis 1984	Control study of infants with neonatal abstinence syndrome given paregoric, phenobarbitone or diazepam. Method of allocation not stated. No data given.
Wijburg 1991	Case reports.
Wolman 1989	Monograph review.
Yaster 1996	Monograph review.
Zelson 1970	Letter documenting treatment observations.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Pacifico 1989

Methods	Not known
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	

DATA AND ANALYSES

Comparison 1. Opiate versus control (supportive therapy) (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.41, 4.07]
2 Duration of treatment (days)	1	80	Mean Difference (IV, Fixed, 95% CI)	12.50 [7.52, 17.48]
3 Duration of hospital stay (days)	1	80	Mean Difference (IV, Fixed, 95% CI)	15.0 [8.86, 21.14]
4 Duration of stay in special care nursery (days)	1	80	Mean Difference (IV, Fixed, 95% CI)	16.7 [10.67, 22.73]
5 Time to regain birth weight (days)	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-5.33, -0.27]
6 Duration of supportive care per day (minutes)	1	80	Mean Difference (IV, Fixed, 95% CI)	-197.2 [-274.15, -120.25]

Comparison 2. Opiate versus phenobarbitone (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	4	302	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.11]
2 Seizures	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
3 Duration of treatment (days)	2	106	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-7.75, 0.29]
4 Duration of hospital stay (days)	2	106	Mean Difference (IV, Fixed, 95% CI)	-2.54 [-7.06, 1.98]
5 Duration of stay in special care nursery (days)	1	74	Mean Difference (IV, Fixed, 95% CI)	-6.40 [-13.81, 1.01]
6 Time to regain birth weight (days)	1	71	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.47, 0.67]
7 Duration of supportive care per day (minutes)	1	74	Mean Difference (IV, Fixed, 95% CI)	-35.10 [-86.87, 16.67]
8 Admission to nursery	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.82]

Comparison 3. Opiate versus diazepam (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.23, 0.80]
2 Duration of treatment (days)	1	33	Mean Difference (IV, Fixed, 95% CI)	1.56 [-1.59, 4.71]
3 Duration of hospital stay (days)	1	33	Mean Difference (IV, Fixed, 95% CI)	2.33 [-1.79, 6.45]

Comparison 4. Opiate versus phenobarbitone (infants of mother using only opiates)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 0.98]

Comparison 5. Opiate versus diazepam (infants of mothers using only opiates)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.02, 0.51]

Comparison 6. Opiate versus phenobarbitone (infants of mothers using opiates and other drugs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	79	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.37, 8.39]

Comparison 7. Opiate versus diazepam (infants of mothers using opiates and other drugs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.32, 1.32]

Analysis 1.1. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Supportive therapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Khoo 1995	7/46	4/34		100.0 %	1.29 [0.41, 4.07]
Total (95% CI)	**46**	**34**		**100.0 %**	**1.29 [0.41, 4.07]**

Total events: 7 (Opiate), 4 (Supportive therapy)

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

Analysis 1.2. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 2 Duration of treatment (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 2 Duration of treatment (days)

Study or subgroup	Opiate N	Mean(SD)	Supportive therapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	21.1 (14.1)	34	8.6 (8.5)		100.0 %	12.50 [7.52, 17.48]
Total (95% CI)	**46**		**34**			**100.0 %**	**12.50 [7.52, 17.48]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.92 (P < 0.00001)

Analysis 1.3. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 3 Duration of hospital stay (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 3 Duration of hospital stay (days)

Study or subgroup	Opiate N	Mean(SD)	Supportive therapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	29 (16.2)	34	14 (11.8)		100.0 %	15.00 [8.86, 21.14]
Total (95% CI)	**46**		**34**			**100.0 %**	**15.00 [8.86, 21.14]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.79 (P < 0.00001)

Analysis 1.4. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 4 Duration of stay in special care nursery (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 4 Duration of stay in special care nursery (days)

Study or subgroup	Opiate N	Mean(SD)	Supportive therapy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	25 (15.2)	34	8.3 (12.3)		100.0 %	16.70 [10.67, 22.73]
Total (95% CI)	**46**		**34**			**100.0 %**	**16.70 [10.67, 22.73]**

Heterogeneity: not applicable

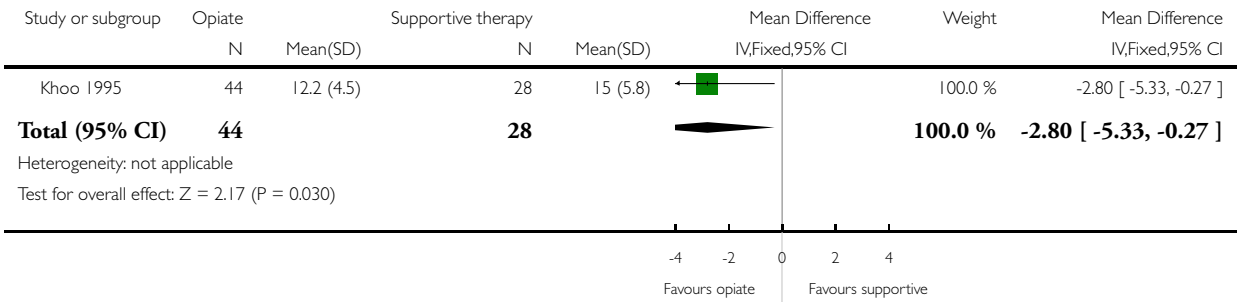
Test for overall effect: Z = 5.43 (P < 0.00001)

Analysis 1.5. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 5 Time to regain birth weight (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 5 Time to regain birth weight (days)

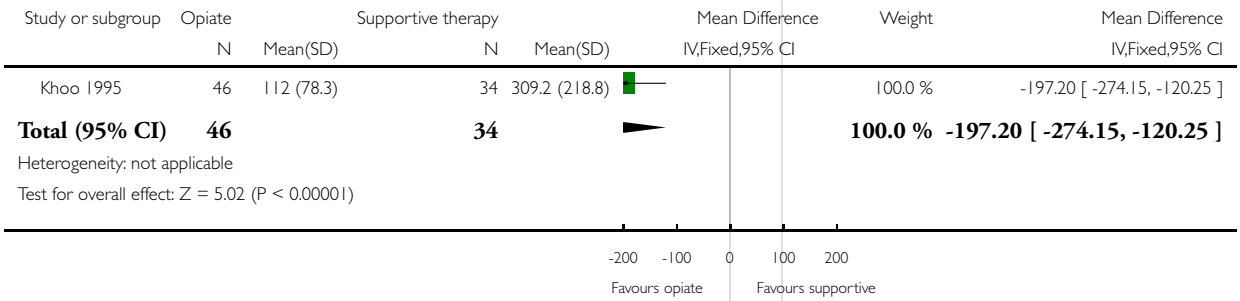


Analysis 1.6. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 6 Duration of supportive care per day (minutes).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 1 Opiate versus control (supportive therapy) (all infants)

Outcome: 6 Duration of supportive care per day (minutes)



Analysis 2.1. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Phenobarbitone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Finnegan 1984	8/32	20/87		26.6 %	1.09 [0.53, 2.22]
Jackson 2004	14/41	16/34		43.2 %	0.73 [0.42, 1.26]
Khoo 1995	7/46	9/28		27.6 %	0.47 [0.20, 1.13]
Madden 1977	1/18	1/16		2.6 %	0.89 [0.06, 13.08]
Total (95% CI)	**137**	**165**		**100.0 %**	**0.76 [0.51, 1.11]**

Total events: 30 (Opiate), 46 (Phenobarbitone)

Heterogeneity: Chi^2 = 2.15, df = 3 (P = 0.54); I^2 =0.0%

Test for overall effect: Z = 1.42 (P = 0.16)

Analysis 2.2. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 2 Seizures.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 2 Seizures

Study or subgroup	Opiate n/N	Phenobarbitone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kandall 1983	0/49	7/62		100.0 %	0.08 [0.00, 1.44]
Total (95% CI)	**49**	**62**		**100.0 %**	**0.08 [0.00, 1.44]**

Total events: 0 (Opiate), 7 (Phenobarbitone)

Heterogeneity: not applicable

Test for overall effect: Z = 1.71 (P = 0.087)

Analysis 2.3. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 3 Duration of treatment (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 3 Duration of treatment (days)

Study or subgroup	Opiate N	Mean(SD)	Phenobarbitone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	21.1 (14.1)	28	26.5 (14)		37.2 %	-5.40 [-11.99, 1.19]
Madden 1977	17	11.76 (4.78)	15	14.5 (8.96)		62.8 %	-2.74 [-7.81, 2.33]
Total (95% CI)	**63**		**43**			**100.0 %**	**-3.73 [-7.75, 0.29]**

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² =0.0%

Test for overall effect: Z = 1.82 (P = 0.069)

Analysis 2.4. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 4 Duration of hospital stay (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 4 Duration of hospital stay (days)

Study or subgroup	Opiate N	Mean(SD)	Phenobarbitone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	29 (16.2)	28	34.8 (16.1)		35.6 %	-5.80 [-13.38, 1.78]
Madden 1977	17	19.13 (7.1)	15	19.87 (8.91)		64.4 %	-0.74 [-6.37, 4.89]
Total (95% CI)	**63**		**43**			**100.0 %**	**-2.54 [-7.06, 1.98]**

Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² =9%

Test for overall effect: Z = 1.10 (P = 0.27)

Analysis 2.5. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 5 Duration of stay in special care nursery (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 5 Duration of stay in special care nursery (days)

Study or subgroup	Opiate N	Mean(SD)	Phenobarbitone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	25 (15.2)	28	31.4 (16.1)		100.0 %	-6.40 [-13.81, 1.01]
Total (95% CI)	**46**		**28**			**100.0 %**	**-6.40 [-13.81, 1.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.69 (P = 0.090)

Analysis 2.6. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 6 Time to regain birth weight (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 6 Time to regain birth weight (days)

Study or subgroup	Opiate N	Mean(SD)	Phenobarbitone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	44	12.2 (4.5)	27	13.6 (4.2)		100.0 %	-1.40 [-3.47, 0.67]
Total (95% CI)	**44**		**27**			**100.0 %**	**-1.40 [-3.47, 0.67]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)

Analysis 2.7. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 7 Duration of supportive care per day (minutes).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 7 Duration of supportive care per day (minutes)

Study or subgroup	Opiate N	Mean(SD)	Phenobarbitone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Khoo 1995	46	112 (78.3)	28	147.1 (125.7)		100.0 %	-35.10 [-86.87, 16.67]
Total (95% CI)	**46**		**28**			**100.0 %**	**-35.10 [-86.87, 16.67]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)

Analysis 2.8. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 8 Admission to nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 8 Admission to nursery

Study or subgroup	Opiate n/N	Phenobarbitone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jackson 2004	12/41	21/34		100.0 %	0.47 [0.27, 0.82]
Total (95% CI)	**41**	**34**		**100.0 %**	**0.47 [0.27, 0.82]**

Total events: 12 (Opiate), 21 (Phenobarbitone)

Heterogeneity: not applicable

Test for overall effect: Z = 2.69 (P = 0.0072)

Analysis 3.1. Comparison 3 Opiate versus diazepam (all infants), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 3 Opiate versus diazepam (all infants)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Finnegan 1984	8/32	14/20		97.0 %	0.36 [0.18, 0.69]
Madden 1977	1/18	0/16		3.0 %	2.68 [0.12, 61.58]
Total (95% CI)	**50**	**36**		**100.0 %**	**0.43 [0.23, 0.80]**

Total events: 9 (Opiate), 14 (Diazepam)

Heterogeneity: Chi^2 = 1.60, df = 1 (P = 0.21); I^2 =37%

Test for overall effect: Z = 2.63 (P = 0.0085)

Analysis 3.2. Comparison 3 Opiate versus diazepam (all infants), Outcome 2 Duration of treatment (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

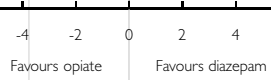
Comparison: 3 Opiate versus diazepam (all infants)

Outcome: 2 Duration of treatment (days)

Study or subgroup	Opiate N	Mean(SD)	Diazepam N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Madden 1977	17	11.76 (4.78)	16	10.2 (4.45)		100.0 %	1.56 [-1.59, 4.71]
Total (95% CI)	**17**		**16**			**100.0 %**	**1.56 [-1.59, 4.71]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

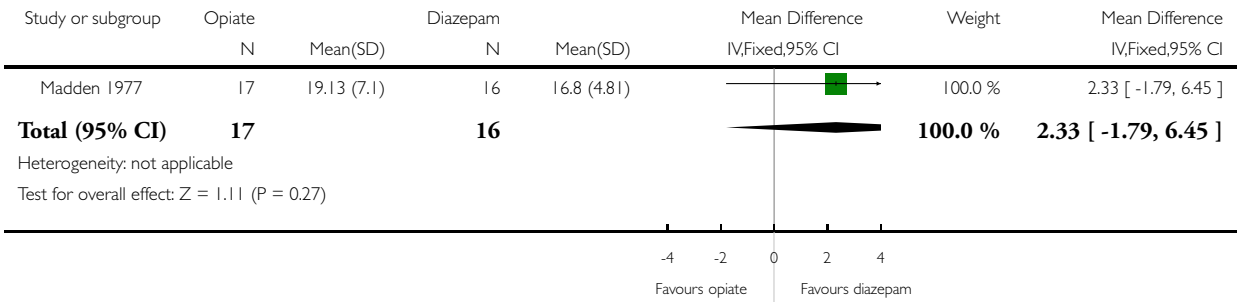


Analysis 3.3. Comparison 3 Opiate versus diazepam (all infants), Outcome 3 Duration of hospital stay (days).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 3 Opiate versus diazepam (all infants)

Outcome: 3 Duration of hospital stay (days)

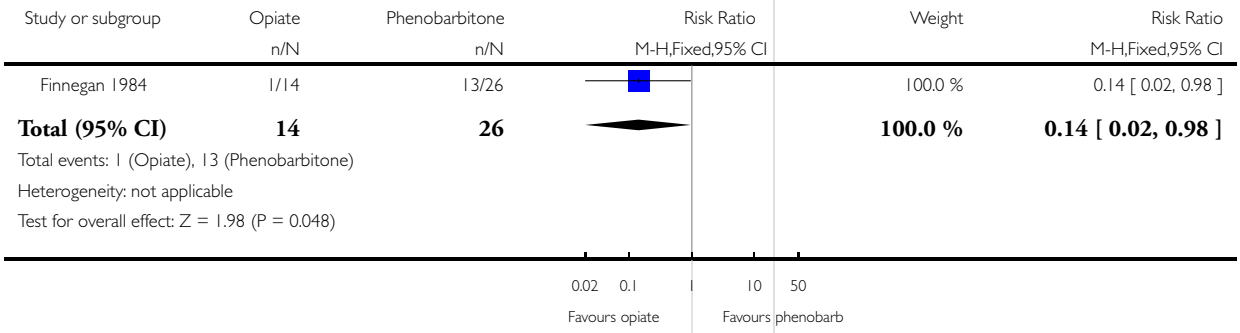


Analysis 4.1. Comparison 4 Opiate versus phenobarbitone (infants of mother using only opiates), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 4 Opiate versus phenobarbitone (infants of mother using only opiates)

Outcome: 1 Treatment failure



Analysis 5.1. Comparison 5 Opiate versus diazepam (infants of mothers using only opiates), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 5 Opiate versus diazepam (infants of mothers using only opiates)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Finnegan 1984	1/14	5/5		100.0 %	0.11 [0.02, 0.51]
Total (95% CI)	**14**	**5**		**100.0 %**	**0.11 [0.02, 0.51]**
Total events: 1 (Opiate), 5 (Diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.82 (P = 0.0047)					

Analysis 6.1. Comparison 6 Opiate versus phenobarbitone (infants of mothers using opiates and other drugs), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 6 Opiate versus phenobarbitone (infants of mothers using opiates and other drugs)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Phenobarbitone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Finnegan 1984	7/18	7/61		100.0 %	3.39 [1.37, 8.39]
Total (95% CI)	**18**	**61**		**100.0 %**	**3.39 [1.37, 8.39]**
Total events: 7 (Opiate), 7 (Phenobarbitone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0083)					

Analysis 7.1. Comparison 7 Opiate versus diazepam (infants of mothers using opiates and other drugs), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 7 Opiate versus diazepam (infants of mothers using opiates and other drugs)

Outcome: 1 Treatment failure

Study or subgroup	Opiate n/N	Diazepam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Finnegan 1984	7/18	9/15		100.0 %	0.65 [0.32, 1.32]
Total (95% CI)	**18**	**15**		**100.0 %**	**0.65 [0.32, 1.32]**
Total events: 7 (Opiate), 9 (Diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.23)					

WHAT'S NEW

Last assessed as up-to-date: 28 March 2005.

16 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 3, 2002

29 March 2005	New search has been performed	This updates the existing review "Opiate treatment for opiate withdrawal in newborn infants" published in The Cochrane Library, Issue 3, 2002 (Osborn 2002b). One new included study (Jackson 2004) comparing morphine with phenobarbitone was included. Three further abstracts of conference proceedings and one published trial of phenobarbitone plus dilute tincture of opium (DTO) versus DTO alone were excluded.
29 March 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DO wrote the original protocol and review. All reviewers independently searched for studies, assessed eligibility, critically appraised included studies and extracted data. DO entered the characteristics of included and excluded studies data and data tables and HJ and MC checked accuracy and checked the final version of the review.

For the updated review, DO searched for new studies, assessed eligibility, critically appraised studies and extracted data independently. HJ critcally appraised the new study and did data extaction. DO wrote the updated review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- RPA Newborn Care, Royal Prince Alfred Hospital, Sydney, Australia.

External sources

- Centre for Perinatal Health Services Research, University of Sydney, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Diazepam [therapeutic use]; Infant, Newborn; Narcotics [*therapeutic use]; Neonatal Abstinence Syndrome [*drug therapy]; Opioid-Related Disorders [*drug therapy]; Phenobarbital [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans