Opiate treatment for opiate withdrawal in newborn infants (Review)

Osborn DA, Jeffery HE, Cole MJ

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[Intervention Review]

Opiate treatment for opiate withdrawal in newborn infants

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

[1]Department of Mothers and Babies NICU, Royal Prince Alfred Hospital, Camperdown, Australia. [2]RPA Newborn Care, RPA Women and Babies, Royal Prince Alfred Hospital and University of Sydney, School of Public Health, Sydney, Australia. [3]Dept. of Neonatology, Westmead Hospital, Westmead, Australia

Contact address: David A Osborn, Department of Mothers and Babies NICU, Royal Prince Alfred Hospital, John Hopkins Drive, Camperdown, NSW, 2005, Australia. david.osborn@email.cs.nsw.gov.au.

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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.

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 methods

The review was updated in 2010 with additional searches CENTRAL, MEDLINE and EMBASE supplemented by searches of conference abstracts and citation lists of published articles.

Selection criteria

Randomized or quasi-randomized controlled trials of opiate treatment in infants with NAS born to mothers with opiate dependence.

Data collection and analysis

Each author assessed study quality and extracted data independently.

Main results

Nine studies enrolling 645 infants met inclusion criteria. There were substantial methodological concerns in all studies comparing an opiate with a sedative. Two small studies comparing different opiates were of good methodology.

Opiate (morphine) versus supportive care (one study): A reduction in time to regain birth weight and duration of supportive care and a significant increase in hospital stay was noted.

Opiate versus phenobarbitone (four studies): Meta-analysis found no significant difference in treatment failure. One study reported opiate treatment resulted in a significant reduction in treatment failure in infants of mothers using only opiates. One study reported a significant reduction in days treatment and admission to the nursery for infants receiving morphine. One study reported a reduction in seizures, of borderline statistical significance, with the use of opiate.

Opiate versus diazepam (two studies): Meta-analysis found a significant reduction in treatment failure with the use of opiate.

Different opiates (six studies): there is insufficient data to determine safety or efficacy of any specific opiate compared to another opiate.

Authors' conclusions

Opiates compared to supportive care may reduce time to regain birth weight and duration of supportive care but increase duration of hospital stay. When compared to phenobarbitone, opiates may reduce the incidence of seizures but 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. Compared to diazepam, opiates reduce the incidence of treatment failure. A post-hoc analysis generates the hypothesis that initial opiate treatment may be 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. This is an update of a previous review (Osborn 2002a; Osborn 2005). A separate review (Osborn 2010) 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 (e.g. clonidine, a benzodiazepine, barbiturate or neuroleptic agent); and 4) opiates versus non-pharmacological treatments (e.g. 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 (e.g. 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) apnoea, b) need for resuscitation, c) need for mechanical ventilation.
8. Duration of treatment of NAS (days).
9. Disruption to the mother infant relationship (e.g. separation of mother and infant, admission to a newborn nursery, failure to successfully breast feed, maternal depression, or parental dissatisfaction).

Search methods for identification of studies

Electronic searches

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 to 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 to 2002; Perinatal Society of Australia and New Zealand Annual Meetings 1999 to 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 to 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 to 2004; Perinatal Society of Australia and New Zealand Annual Meetings 2003-2005).
The search was updated in October 2010 by DO with additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2010), MEDLINE (1966 to April 2010), PREMEDLINE (to April 2010), EMBASE (1988 to April 2010), cross references of all new studies cited, abstracts and conference proceedings (American Pediatric Society/ Society for Pediatric Research Annual Meetings 2005 to 2010; Perinatal Society of Australia and New Zealand Annual Meetings 2005 to 2010).

Searching other resources

Electronic searches were supplemented by searches of citations of included studies and reviews, contact with authors and expert informants and searches of conference abstracts as documented above.
Clinical trials registries were also searched August 2010 for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp).

Data collection and analysis

Standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. A data extraction sheet was created for critical appraisal and data extraction from all potentially eligible studies.

Selection of studies

Two review authors (DO & HJ) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

Each author extracted data independently; authors then compared data and resolved differences for the 2002 review. DO and HJ extracted data independently; authors then compared data and resolved differences for the 2005 review update. DO extracted data for the 2010 review update. 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).

Assessment of risk of bias in included studies

The methodological quality of each trial was reviewed independently by the three authors for the 2002 review. DO performed the 2010 update. 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.
For the update in 2010, the authors assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009).

(1) Sequence generation (checking for possible selection bias)
For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the method as:
• adequate (any truly random process, e.g. random number table; computer random number generator);
• inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number);
• unclear.
(2) Allocation concealment (checking for possible selection bias)
For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:
• adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
• inadequate (open random allocation; unsealed or non opaque envelopes, alternation; date of birth);
• unclear.
(3) Blinding (checking for possible performance bias)
For each included study, we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:
• adequate, inadequate or unclear for participants;
• adequate, inadequate or unclear for personnel;
• adequate, inadequate or unclear for outcome assessors.
(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)
For each included study and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or can be supplied by the trial authors, we re-included missing data in the analyses. We assessed methods as:
• adequate (less than 20% missing data);
• inadequate;
• unclear.
(5) Outcome reporting bias
For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:
• adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
• inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
• unclear.
(6) Other sources of bias
For each included study, we described any important concerns we had about other possible sources of bias (e.g. early termination of trial due to data-dependant process, extreme baseline imbalance, etc). We assessed whether each study was free of other problems that could put it at risk of bias. We assessed other sources of bias as:
• yes;
• no;
• unclear.
(7) Overall risk of bias
We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). With reference to (1) and (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

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.

Unit of analysis issues

The unit of randomisation was the intended unit of analysis.

Dealing with missing data

The primary analysis was planned to be an intention-to-treat analysis reporting only available data (excluding cases where data are missing). For included studies, we planned to note levels of attrition. We planned to obtain missing data from the authors when possible. Where data remains missing, we planned to conduct sensitivity analysis of studies with < 10% losses after randomisation.

Assessment of heterogeneity

For the 2010 update, we planned to use the chi^2 statistic to detect statistically significant heterogeneity and the I^2 statistic to quantify

heterogeneity among the trials in each analysis. Had we identified substantial heterogeneity, we planned to explore it by pre-specified subgroup analysis. We planned to grade the degree of heterogeneity as 0 to 30% (might not be important), 31% to 50% (moderate heterogeneity); 51% to 75% (substantial heterogeneity); 76% to 100% (considerable heterogeneity).

Assessment of reporting biases

For the 2010 update, reporting bias was assessed by comparing stated primary and secondary outcomes and reported outcomes. Where study protocols are available, these will be compared to publications to determine the likelihood of reporting bias.

Data synthesis

The fixed effects model was assumed for meta-analysis.

Subgroup analysis and investigation of heterogeneity

Prespecified subgroup analyses included the following identified subcategories:
1. According to type of opiate used (e.g. tincture of opium, paregoric, morphine or methadone);
2. According to type of sedative used (e.g. 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;
5. According to age at treatment (e.g. early versus delayed treatment) and duration of treatment (e.g. short versus long course).
All outcomes where available were eligible for inclusion in subgroup analysis.
Heterogeneity was explored through subgroup analysis as above and sensitivity analysis according to study quality.

Sensitivity 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 ongoing studies.

Results of the search

The updated search (October 2010) identified an additional two eligible studies (Kraft 2009; Langenfeld 2005). Both studies compared different types of opiates for neonatal abstinence syndrome. An additional five studies (38 in total) are now included in the table of excluded studies. One additional ongoing study comparing oral morphine with sublingual buprenorphine for NAS treatment was found (Kraft 2010).

Included studies

Nine 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; Kraft 2009; Langenfeld 2005; 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. Seven studies were published in peer reviewed journals (Carin 1983; Jackson 2004; Kaltenbach 1986; Kandall 1983; Kraft 2009; Langenfeld 2005; Madden 1977). One study was a research monograph (Finnegan 1984) and one was an unpublished PhD thesis (Khoo 1995).
Carin 1983 enrolled infants born to mothers receiving methadone for more than three months. Infants were enrolled if the Finnegan score was $\geq$ 8. Polydrug use was disclosed by some mothers (see 'table of included studies'). Infants were randomly allocated to paregoric 0.42 to 2.1 ml/kg/day orally or phenobarbitone 5 to 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 to 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 nasogastric feeds, had severe withdrawal or were ad-

mitted 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 (e.g. 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 ml until score < 6, weaned after five days by 0.05 ml 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 to 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).
Kraft 2009 enrolled infants of mothers on methadone. Women using other drugs were excluded. Treatment was commenced for three consecutive modified Finnegan scores that added up to 24. Infants were randomised to sublingual buprenorphine 13.2 μg/kg/day with dose titration by 20% per day, or morphine 0.4 mg/kg/day with dose titration by 10% per day.
Langenfeld 2005 enrolled infants of mothers using an opiate with sporadic other drug use. Treatment was commenced for three consecutive modified Finnegan scores that added up to 24. Infants were randomised to tincture of opium, initial dose 0.192 mg/kg/day versus morphine 0.192 mg/kg/day titrated to keep Finnegan score < 8.
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 to 8 mg/kg/day in three divided doses) or diazepam (0.5 to 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.

Excluded studies

One study previously awaiting assessment (Pacifico 1989) that did not report method of treatment allocation has now been moved to the 'excluded studies'. A total of 39 studies or reports are included in the 'Excluded studies' table.

Risk of bias in included studies

Allocation

Three studies (Jackson 2004; Kraft 2009; Langenfeld 2005) 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.
Allocation concealment was adequately described by three studies (Jackson 2004; Kraft 2009; Langenfeld 2005), unclear for three studies (Carin 1983; Kandall 1983; Madden 1977) and inadequate for three studies (Finnegan 1984; Kaltenbach 1986; Khoo 1995).

Blinding

Blinding of treatment: Two studies reported blinding of treatment (Jackson 2004; Langenfeld 2005) by using identical appearing solutions and a standardised treatment protocol. Three studies (Finnegan 1984; Kaltenbach 1986; Kraft 2009) 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). Kraft 2009 did not blind measurement. No other study reported blinding of outcome measurement. The reporting by Finnegan 1984 according to drug of exposure in utero was not reported to be prespecified.

Incomplete outcome data

All infants were accounted for by six studies (Carin 1983; Finnegan 1984; Jackson 2004; Kraft 2009; Langenfeld 2005; Madden 1977). 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.

Selective reporting

Only two studies clearly prespecified primary and secondary outcomes (Jackson 2004; Langenfeld 2005). For the other eight studies, prespecified outcomes were unclear and whether reported outcomes were prespecified were unclear. Madden 1977 reported separately two infants receiving a second agent for duration of treatment and hospital stay (one allocated methadone and one to phenobarbitone).

Other potential sources of bias

Jackson 2004 reported infants randomly allocated to receive phenobarbitone tended to have been exposed to benzodiazepines (44 versus 22%) and other classes of drugs (23 versus 10%) more often than those randomly allocated to receive morphine sulphate. Two studies (Finnegan 1984; Kaltenbach 1986) reported stopping enrolment in the diazepam arm early due to an interim analysis demonstrating the possibility of adverse effects. Kraft 2009 did not report a prespecified sample size. Langenfeld 2005 was the only study that reported in sufficient detail to allow classification as not having other apparent sources of bias. None of the other studies provided sufficient detail of reporting to be clear about balance of groups after randomisation or other potential biases.

Effects of interventions

1. Opiate versus control (supportive therapy) (all infants)
Primary outcomes: Khoo 1995 reported no significant difference in treatment failure (80 infants, RR 1.29, 95% CI 0.41, 4.07) comparing infants receiving opiate and supportive care to supportive care alone.
Secondary outcomes: Khoo 1995 reported a significant increase in days treatment (MD 12.5 days, 95% CI 7.5, 17.5), days in hospital (MD 15.0 days, 95% CI 8.9, 21.1) and days in special care nursery (MD 16.7 days, 95% CI 10.7, 22.7) comparing infants receiving opiate and supportive care to supportive care alone. Infants receiving opiates had a significant reduction in days to regain birthweight (MD -2.8 days, 95% CI -5.3, -0.3) and days supportive care (MD -197.2 min/day, 95% CI -274.2, -120.3) compared to infants who received supportive care alone.
2. Opiate versus phenobarbitone (all infants)
Primary outcomes: Five studies (Finnegan 1984; Jackson 2004; Kaltenbach 1986; Khoo 1995; Madden 1977) reported treatment failure in infants of mothers using an opiate with or without other drugs. Is is unclear whether some of the infants reported by Kaltenbach 1986 were also enrolled in the study reported by Finnegan 1984 so this study was not included in meta-analysis. Kaltenbach 1986 reported a significant reduction in treatment failure (RR 0.16, 95% CI 0.04, 0.64). Meta-analysis of the other four studies found no significant difference in treatment failure (302 infants, typical RR 0.76, 95% CI 0.51, 1.11). This finding is sensitive to the inclusion of the study by Kaltenbach 1986.
Seizures: Kandall 1983 reported a reduction in seizures of borderline statistical significance in infants receiving paregoric compared to phenobarbitone (111 infants, 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 days 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 days treatment and days in hospital reported 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 days treatment (WMD -3.7 days, 95% CI -7.8, 0.3) or days in hospital (WMD -2.5 days, 95% CI -7.1, 2.0). Khoo 1995 reported no significant difference in days 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 reported no significant difference in median weight gain during the second and third weeks of life. Respiratory rates, whole blood pH and $PaCO_2$, blood pressure, serum thyroxine and platelet count on day four, seven and 14 were also similar except for a slightly higher blood $PaCO_2$ on day seven in phenobarbitone treated infants.

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

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

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

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.

5. Opiate versus diazepam (all infants)

Primary outcomes: Meta-analysis of two studies (Finnegan 1984; Madden 1977) found a significant reduction in treatment failure (86 infants, RR 0.43, 95% CI 0.23, 0.80) for infants treated with an opiate compared to diazepam. It is unclear whether some of the infants reported by Kaltenbach 1986 were also enrolled in the study reported by Finnegan 1984 so this study was not included in meta-analysis. Kaltenbach 1986 reported a significant difference in treatment failure (33 infants, RR 0.11, 95% CI 0.03, 0.36).

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 days treatment (MD 1.6 days, 95% CI -1.6, 4.7) or days in hospital (MD 2.3 days, 95% CI -1.8, 6.5) between infants receiving methadone compared to diazepam.

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

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 (19 infants, RR 0.11, 95% CI 0.02, 0.51). No study separately reported seizures, mortality or neurodevelopment in infants of mothers only on opiates.

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

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 (33 infants, RR 0.65, 95% CI 0.32, 1.32). No study separately reported seizures, mortality or neurodevelopment in infants of mothers using an opiate and other drugs.

8. Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

One study reported the effect of sublingual buprenorphine versus neonatal opium solution (Kraft 2009).

Primary outcomes: Kraft 2009 reported no significant difference in treatment failure (26 infants, RR 4.00, 95% CI 0.51, 31.13) and seizures (26 infants, RR 3.00, 95% CI 0.13, 67.51). In infants receiving buprenorphine three infants had treatment failure and one infant developed generalised seizures. In infants receiving neonatal opium solution one infant had treatment failure. No developmental outcomes were reported.

Secondary outcomes: Kraft 2009 reported no significant difference in days treatment (25 infants, MD -10.00, 95% CI -20.69, 0.69), but a significant reduction in days in hospital (25 infants, MD -11.00, 95% CI -21.69, -0.31). Severity of withdraw was not reported. Kraft 2009 reported that 35.6% of buprenorphine samples were below the limits of quantification and 98% below 0.6ng/ml, the therapeutic level reported for management of adult opioid replacement therapy.

9. Morphine versus tincture of opium (infants of mothers using only opiates)

One study reported the effect of morphine versus tincture of opium (Langenfeld 2005). No data was reported that could be included in meta-analysis tables.

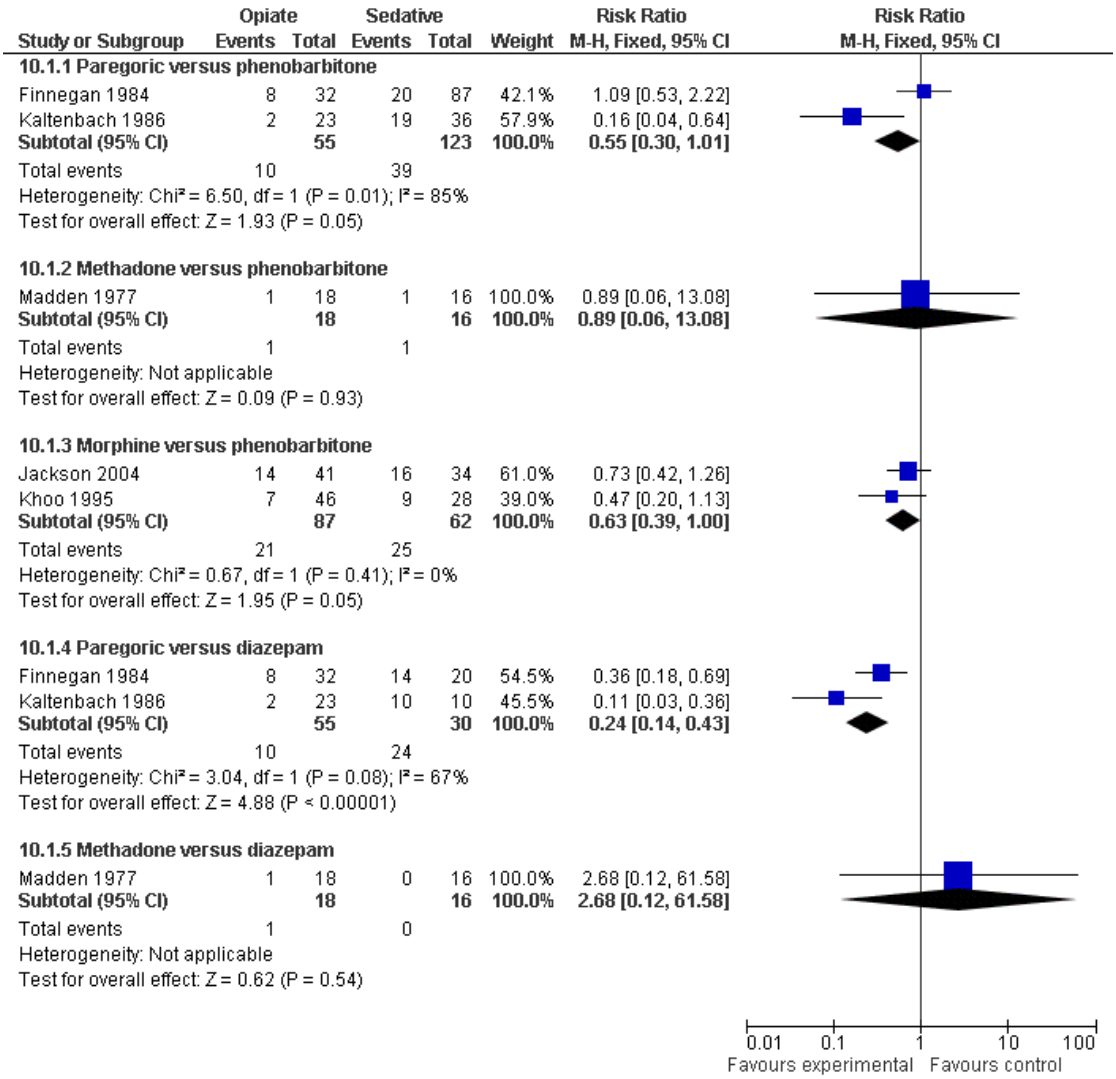
Primary outcomes: Langenfeld 2005 did not report treatment failure, seizures, mortality or neurodevelopment.

Seconday outcomes: Langenfeld 2005 reported the maximum Finnegan score values were almost equal in the tincture opium group (mean 15.4) and morphine group (mean 15.5). The area under the curve for the Finnegan score above 8 was not significantly different (P = 0.5; 95% CI difference −7.8 to 4.0 days). The weight gain per day during the therapy phase was 18.9 g per

day (morphine group) versus 24.9 g per day tincture opium group (P = 0.24; 95% CI difference 15.9, -4.1 g).

10. Specific opiate versus specific sedative (Figure 1)

Figure 1. Forest plot of comparison: 10 Specific opiate versus specific sedative, outcome: 10.1 Treatment failure.



Paregoric versus phenobarbitone: Meta-analysis of two studies (Finnegan 1984, Kaltenbach 1986) found no significant difference in treatment failure (RR 0.55, 95% CI 0.30, 1.01). There was substantial (I^2 = 85%) and statistically significant (p = 0.01) heterogeneity between studies. Kaltenbach 1986 reported a significant reduction in treatment failure (RR 0.16, 95% CI 0.04, 0.64). Kaltenbach 1986 may have reported some of the same patients reported by Finnegan 1984. Kandall 1983 reported no significant difference in seizures (RR 0.08, 95% CI 0.00, 1.44).

Methadone versus phenobarbitone: Madden 1977 reported no significant difference treatment failure (RR 0.89, 95% CI 0.06, 13.08), days treatment (RR -2.74, 95% CI-7.81, 2.33) and days in hospital (RR -0.74, 95% CI -6.37, 4.89).

Morphine versus phenobarbitone: meta-analysis of two studies (Jackson 2004; Khoo 1995) found a significant reduction in treatment failure (typical RR 0.63, 95% CI 0.39, 1.00). Khoo 1995 reported no significant difference in days treatment (MD -5.40, 95% CI -11.99, 1.19), days in hospital (MD -5.80, 95% CI -13.38, 1.78), days in special care nursery (MD -6.40, -13.81, 1.01), days to regain birthweight (MD -1.40, 95% CI -3.47, 0.67) and duration of supportive care (MD -35.10 minutes per day, 95% CI -86.87, 16.67).

Paregoric versus diazepam: Finnegan 1984 reported a significant reduction in treatment failure (RR 0.36, 95% CI 0.18, 0.69).

Methadone versus diazepam: Madden 1977 reported no significant difference in treatment failure (RR 2.68, 95% CI 0.12, 61.58).

Other comparisons

1. No study compared the effects of an opiate with chlorpromazine or clonidine.
2. No study reported tincture of opium.
3. Khoo 1995 compared morphine and supportive care to supportive care alone. The results are as documented above.
4. No study compared early versus delayed treatment of NAS, or short versus long courses of therapy for NAS.

Sensitivity analysis

Two studies met prespecified criteria for good methodology (Kraft 2009; Langenfeld 2005) with adequate allocation sequence and concealment and no losses. One study compared sublingual buprenorphine versus neonatal opium solution (Kraft 2009), although this study was unblinded. The results are as reported in **comparison 8**. The other study compared morphine versus tincture of opium (Langenfeld 2005). The results are as reported in **comparison 10.**

Only two studies reported blinding of intervention (Jackson 2004; Langenfeld 2005). 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 was not performed.

The other studies all had substantial methodological concerns. 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. As a result, no study comparing opiate to no treatment, or opiate versus phenobarbitone, or opiate versus diazepam met criteria for studies of good methodology.

DISCUSSION

Summary of main results

Opiate versus supportive care: This review finds limited evidence from one quasi-random study 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.

Opiate versus phenobarbitone: there is conflicting evidence whether use of an opiate results in a reduction of treatment failure for infants with opiate withdrawal. Meta-analysis of four studies found no significant difference in treatment failure. One study not included in the meta-analysis due to concerns regarding duplicate publication reported a significant reduction in treatment failure. The only study to report infants of mothers using only an opiate separately reported a significant reduction in treatment failure in infants treated with an opiate, but an increase in treatment failure in infants exposed to multiple drugs. The significance of the finding of one study reporting seizures in infants receiving phenobarbitone is unclear. No other study has reported this finding. One study incorporating blinding of treatment reported a significant reduction in special care nursery admission with use of morphine compared to phenobarbitone. The significance of this finding is unclear as there was no dose titration used. However, a relatively low dose of morphine was used (0.2 mg/kg/day) compared to a moderate dose of phenobarbitone (8mg/kg/day).

Opiate versus diazepam: meta-analysis of two studies found a significant reduction in treatment failure for infants treated with an opiate compared to diazepam, One of these studies reported this benefit was significant for infants born to mothers using only opiates, but not those using opiates and other drugs. No other outcomes were significantly different.

Specific opiate versus other opiate: two studies compared different opiates. One small pilot study comparing sublingual buprenorphine versus tincture of opium reported no significant difference in treatment failure or days treatment, one infant receiving buprenorphine had a seizure and infants receiving buprenorphine had a significant reduction in duration of hospital stay. However, 35.6% of buprenorphine samples were below the limits of quantification and 98% below 0.6 ng/ml, the therapeutic level reported for management of adult opioid replacement therapy. Given that the majority of treatment failure occurred in the sublingual buprenorphine group and apparently subtherapeutic levels were reported, the safety and efficacy of sublingual buprenorphine has not been confirmed. Another small study compared morphine to tincture of opium and reported no significant difference in maximum Finnegan score, area under the curve for the Finnegan score above 8 and weight gain per day during the therapy phase. Treatment failure and seizures were not reported.

Specific opiate versus specific sedative: Meta-analysis of two studies (Jackson 2004; Khoo 1995) comparing morphine and pheno-

barbitone found a significant reduction in treatment failure of borderline statistical significance. No significant difference in treatment failure rate were found for paregoric versus phenobarbitone, or methadone versus phenobarbitone.

Overall completeness and applicability of evidence

This review includes studies that report random or quasi-random allocation of infants with NAS to a sedative or non-opiate control. 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. However, few data are presented that differentiate response to treatment of infants of mothers using only opiates separately from those exposed to opiate using mothers with polydrug use. Only one study comparing use of an opiate versus a sedative (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. Two studies comparing different types of opiates enrolled infants of mothers using only opiates (Kraft 2009) or with infrequent other drug use (Langenfeld 2005). No study reported quality of mother-infant interaction, success of breast feeding, incidence of foster care or neurodevelopmental outcome (according to group of allocation). Most studies used a standardised score to determine need for treatment and response to treatment although few studies reported withdraw severity data that could be included in the review.

The initial dose of opiate and sedative varied between studies, with several studies using low initial doses of opiate and one study not titrating dose of morphine. Differences in treatment regimens has the potential to substantially affect the generalisability of this review.

The studies are insufficiently powered to detect important differences in treatment failure rate between different treatments.

Quality of the evidence

The validity of the results is affected by the methodological quality of the included studies. Three studies (Jackson 2004; Kraft 2009; Langenfeld 2005) reported adequate randomisation and allocation concealment procedures. However, one of these studies (Jackson 2004) 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. The other two studies (Kraft 2009; Langenfeld 2005) compared different types of opiates with only one of these studies (Langenfeld 2005) reporting a blinded comparison. 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. Two studies (Jackson 2004; Langenfeld 2005) 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. Few losses to follow up were reported by the individual studies, although this could have been by omission. In view of these limitations, the conclusions of this review should be treated with caution.

Potential biases in the review process

The review searched for published and unpublished studies in an attempt to avoid publication bias. The review included studies using quasi-random patient allocation increasing the risk of selection bias in the studies included in the review. This has been addressed using sensitivity analysis. This review prespecified the primary outcomes and the comparisons that have been made.

Agreements and disagreements with other studies or reviews

This review is consistent with recommendations made by other authors (Theis 1997) and the American Academy of Pediatrics (AAP 1998) recommendations for management of NAS due to opiate withdrawal. That is, if pharmacological treatment is chosen then a specific drug from the same class of drugs causing withdraw is preferable.

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. Trials should stratify randomisation of infants according to whether they were born to mothers using only opiates or using opiates and another drug. 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. Trials of different thresholds for initiating pharmacological treatment, different initial doses of opiate and different titration regimens are needed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Carin 1983

Methods	Randomised controlled trial.
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
Adequate sequence generation?	Unclear	Method not reported.
Allocation concealment?	Unclear	Unclear method sequence generation.
Blinding? Treatment	Unclear	Not reported.
Blinding? Short term outcomes	No	
Blinding? Long term outcomes	No	Not reported.
Incomplete outcome data addressed? All outcomes	Yes	None reported.
Free of selective reporting?	Unclear	Primary and secondary outcomes not clearly prespecified.

Finnegan 1984

Methods	Qusai-randomised controlled trial.
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 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
Adequate sequence generation?	No	Quasi-random, drug assignment from envelope designated according to first letter of last name (personal communication)
Allocation concealment?	No	Inadequate.
Blinding? Treatment	No	Not reported. Unlikely as different treatment regimens.
Blinding? Short term outcomes	No	Not reported.
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	None measured.
Free of selective reporting?	Unclear	Primary and secondary outcomes not clearly prespecified.

Jackson 2004

Methods	Randomised controlled trial.
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): 50μg/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 nasogastric 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**
Adequate sequence generation?	Yes	Computer generated random numbers.
Allocation concealment?	Yes	
Blinding? Treatment	Yes	Identical solutions labelled A or B.
Blinding? Short term outcomes	Yes	Yes.
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	Yes, none reported.
Free of selective reporting?	Yes	Clearly defined prespecified outcomes.
Free of other bias?	No	Infants randomly allocated to receive phenobarbitone tended to have been exposed to benzodiazepines (44 versus 22%) and other classes of drugs (23 versus 10%) more often than those randomly allocated to receive morphine sulphate

Kaltenbach 1986

Methods	Quasi-random study.
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): dose not reported. 3. Phenobarbitone titration (n = 16): dose 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 follow-up not reported according to assigned treatment group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Quasi-random, drug assignment from envelope designated according to first letter of last name
Allocation concealment?	No	Inadequate
Blinding? Treatment	No	Treatment regimens different.
Blinding? Short term outcomes	No	
Blinding? Long term outcomes	Yes	For Bayley's MDI / PDI
Incomplete outcome data addressed? All outcomes	Unclear	None reported.
Free of selective reporting?	Unclear	Unclear prespecified outcomes.

Kandall 1983

Methods	Randomised controlled trial.
Participants	Inclusion criteria: infants born to socioeconomically deprived mothers with opiate dependence. Infants with >= 7 on Lipsitz score or excessive individual sign (e.g. 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
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. EEG was abnormal 10 of 12 infants reported
Notes	Group numbers not balanced.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Method not reported.
Blinding? Treatment	No	Unlikely, treatment regimens different.
Blinding? Short term outcomes	Unclear	Not reported.
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Unclear	None reported.
Free of selective reporting?	Unclear	Unclear prespecified outcomes.

Khoo 1995

Methods	Quasi-random controlled trial.
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

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Used last number of the subject's hospital number.
Allocation concealment?	No	Inadequate.
Blinding? Treatment	No	
Blinding? Short term outcomes	Unclear	Not reported.
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	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

Khoo 1995 (*Continued*)

Free of selective reporting?	Unclear	Unclear prespecified primary outcome.

Kraft 2009

Methods	Randomised controlled trial.
Participants	Initiation of treatment any consecutive 3 modified Finnegan scale scores that added up to 24. Inclusion criteria >37 weeks' gestation, exposure to opioids in utero, and signs and symptoms of NAS that required treatment Exclusion criteria: major congenital malformations; intrauterine growth retardation; medical illness that required intensification of medical therapy, concomitant maternal benzodiazepine or severe alcohol abuse, maternal use of alcohol or of benzodiazepines in the 30 days before enrolment, concomitant neonatal use of cytochrome P450 3A inhibitors or inducers before initiation of NAS treatment, seizure activity or other neurologic abnormality, breastfeeding, and inability of mother to give informed consent as a result of comorbid psychiatric diagnosis Infants of polydrug using mothers excluded.
Interventions	Treatment (n=13): sublingual buprenorphine initially 13.2 μg/kg per day in 3 divided doses with dose titration by 20% per day for 2-3 scores totaling 24 or a single score $\geq$12. Buprenorphine solution 30% ethanol and 85 g sucrose per 100 mL. After 3 days of dose stabilisation, patients could begin weaning for scores of 8. Weaning was at intervals of 10%. Adjunctive treatment with phenobarbital initiated when the dose of buprenorphine reached 39 μg/kg per day Control (n=13): morphine 0.4 mg/kg/day (in the form of neonatal opium solution) in 6 divided doses with dose titration by 10% per day. Adjunctive treatment with phenobarbital initiated when the dose of NOS reached 1 mg/kg per day
Outcomes	Primary goal to determine of sublingual buprenorphine safe, tolerable, and feasible Secondary goals to determine buprenorphine efficacy on length of treatment and length of stay; and buprenorphine pharmacokinetics Treatment failure defined as need for adjunctive treatment.
Notes	Supported by the Commonwealth of Pennsylvania Tobacco Fund and National Institute on Drug Abuse

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated randomisation performed by the Hospital Investigational Drug Service
Allocation concealment?	Yes	
Blinding? Treatment	No	

Kraft 2009 (*Continued*)

Blinding? Short term outcomes	No	
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	1/26 withdrawn due to seizure (buprenorphine arm).
Free of selective reporting?	Unclear	Unclear prespecified primary and secondary outcomes.
Free of other bias?	Unclear	Unclear prespecified sample size.

Langenfeld 2005

Methods	Randomed controlled trial.
Participants	Newborn infants of opioid-addicted mothers. Treated if mean 3 Finnegan scores >8 Exclusion: if consent from parents was refused or additional severe diseases. No symptoms withdraw for 2 days Sporadic other drug use found in mother's urine.
Interventions	Treatment 1 (n=16): Tincture of opium 1% 2 drops/kg 4 hourly (25 drops per ml; morphine 0.4mg/ml) increased by 2 drops per dose until Finnegan score <8. Initial dose 0.32mg/kg 4 hourly = 0.192mg/kg/day Treatment 2 (n=17): Morphine 1% 2 drops/kg 4 hourly (25 drops per ml) (= 0.192mg/kg/day) increased by 2 drops per dose until Finnegan score <8
Outcomes	Primary outcome measures were the duration of therapy and the total dose of the particular formulation needed. The maximum values of the Finnegan score, the area under the score curve (AUC) above values of 8, as well as weight gain of the newborns were used as secondary parameters
Notes	Supported by the Maria Pesch-Stiftung of the Medical Faculty of the University of Cologne

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer random number generator to select random permuted blocks of 4
Allocation concealment?	Yes	
Blinding? Treatment	Yes	Identical solutions used.

Langenfeld 2005 (*Continued*)

Blinding? Short term outcomes	Yes	
Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	None.
Free of selective reporting?	Yes	Clear prespecified outcomes
Free of other bias?	Yes	

Madden 1977

Methods	Randomised controlled trial.
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**
Adequate sequence generation?	Unclear	Method not reported.
Blinding? Treatment	No	Unlikely, treatment regimens different.
Blinding? Short term outcomes	Unclear	Not reported.

Blinding? Long term outcomes	No	Not measured.
Incomplete outcome data addressed? All outcomes	Yes	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
Free of selective reporting?	Unclear	Unclear prespecified outcomes.

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

Study	Reason for exclusion
Alroomi 1988	Observational study.
Aurora 2008	Retrospective cohort study comparing diluted tincture of opium and phenobarbital
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.
Ebner 2007	Non-random (before-after) allocation to morphine or phenobarbitone
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
Guo 2006	Retrospective review of treatment of neonatal abstinence syndrome with methadone or tincture of opium

(*Continued*)

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
Lainwala 2003	Retrospective study comparing infants treated with methadone and oral morphine
Leikin 2009	Case series of clonidine treated infants for neonatal abstinence syndrome
Mack 1991	Observational study.
Mazurier 2008	Historicial control study morphine versus chlorpromazine.
Ostrea 1975	No study of treatment.
Ostrea 1976	Observational study.
Pacifico 1989	Study of newborns with neonatal abstinence syndrome treated with phenobarbital plus diazepam, phenobarbital plus diazepam plus morphine, or morphine alone. Method of allocation not reported
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.

(*Continued*)

Yaster 1996	Monograph review.
Zelson 1970	Letter documenting treatment observations.

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

Kraft 2010

Trial name or title	Buprenorphine for the Treatment of Neonatal Abstinence Syndrome
Methods	Randomised controlled trial
Participants	Inclusion Criteria: • ≥37 weeks gestation • exposure to opiates in utero • demonstration of signs and symptoms of neonatal abstinence syndrome requiring treatment Exclusion Criteria: • major congenital malformations and/or intrauterine growth retardation • medical illness requiring intensification of medical therapy • concomitant benzodiazepine or severe alcohol abuse, self-report of regular use of alcohol or of benzodiazepines use in the past 30 days, and/or receipt of benzodiazepines by prescription (as determined by self-report or intake urine) by the mother during pregnancy, • concomitant use of CYP 3A inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, HIV protease inhibitors) or inducers (rifampin, carbamazepine, phenobarbital) prior to initiation of NAS treatment • seizure activity or other neurologic abnormality • breast feeding • inability of mother to give informed consent due to co-morbid psychiatric diagnosis • hypoglycaemia requiring treatment with intravenous glucose
Interventions	Drug: Oral morphine solution 0.4 mg/kg/day morphine every 4 hours Drug: buprenorphine sublingual buprenorphine administered every 8 hours, titrated to control of abstinence symptoms
Outcomes	Primary Outcome Measures: Sublingual Buprenorphine safety and tolerability in the neonate Secondary Outcome Measures: Buprenorphine Pharmacokinetics Efficacy: Length of treatment Efficacy: Length of hospitalisation
Starting date	Study Start Date: April 2004; Estimated Study Completion Date: December 2010
Contact information	Walter K Kraft, MD, MS 215 955 9077 walter.kraft@jefferson.edu and Kevin Dysart, MD kcdysart@mac.com
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 Days treatment	1	80	Mean Difference (IV, Fixed, 95% CI)	12.50 [7.52, 17.48]
3 Days in hospital	1	80	Mean Difference (IV, Fixed, 95% CI)	15.0 [8.86, 21.14]
4 Days in special care nursery	1	80	Mean Difference (IV, Fixed, 95% CI)	16.7 [10.67, 22.73]
5 Days to regain birth weight	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-5.33, -0.27]
6 Duration supportive care (minutes/day)	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 Treatment failure	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.64]
3 Seizures	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
4 Days treatment	2	106	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-7.75, 0.29]
5 Days in hospital	2	106	Mean Difference (IV, Fixed, 95% CI)	-2.54 [-7.06, 1.98]
6 Days in special care nursery	1	74	Mean Difference (IV, Fixed, 95% CI)	-6.40 [-13.81, 1.01]
7 Days to regain birth weight	1	71	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.47, 0.67]
8 Duration supportive care (minutes/day)	1	74	Mean Difference (IV, Fixed, 95% CI)	-35.10 [-86.87, 16.67]
9 Admission to nursery	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.82]

Comparison 3. 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 4. 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 5. 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 Treatment failure	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.36]
3 Days treatment	1	33	Mean Difference (IV, Fixed, 95% CI)	1.56 [-1.59, 4.71]
4 Days in hospital	1	33	Mean Difference (IV, Fixed, 95% CI)	2.33 [-1.79, 6.45]

Comparison 6. 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 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]

Comparison 8. Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	26	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.51, 31.13]
2 Seizure	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.51]
3 Days treatment	1	25	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-20.69, 0.69]
4 Days in hospital	1	25	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-21.69, -0.31]

Comparison 9. Morphine versus tincture of opium (infants of mother using only opiates)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Seizure	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Days treatment	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Days in hospital	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 10. Specific opiate versus specific sedative

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Paregoric versus phenobarbitone	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 1.01]
1.2 Methadone versus phenobarbitone	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.06, 13.08]
1.3 Morphine versus phenobarbitone	2	149	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.39, 1.00]
1.4 Paregoric versus diazepam	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.43]
1.5 Methadone versus diazepam	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.12, 61.58]
2 Seizures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Paregoric versus phenobarbitone	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.44]
3 Days treatment	2	106	Mean Difference (IV, Fixed, 95% CI)	-3.73 [-7.75, 0.29]
3.1 Methadone versus phenobarbitone	1	32	Mean Difference (IV, Fixed, 95% CI)	-2.74 [-7.81, 2.33]
3.2 Morphine versus phenobarbitone	1	74	Mean Difference (IV, Fixed, 95% CI)	-5.40 [-11.99, 1.19]
4 Days in hospital	2	106	Mean Difference (IV, Fixed, 95% CI)	-2.54 [-7.06, 1.98]
4.1 Methadone versus phenobarbitone	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-6.37, 4.89]

4.2 Morphine versus phenobarbitone	1	74	Mean Difference (IV, Fixed, 95% CI)	-5.80 [-13.38, 1.78]
5 Days in special care nursery	1	74	Mean Difference (IV, Fixed, 95% CI)	-6.40 [-13.81, 1.01]
5.1 Morphine versus phenobarbitone	1	74	Mean Difference (IV, Fixed, 95% CI)	-6.40 [-13.81, 1.01]
6 Days to regain birthweight	1	71	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.47, 0.67]
6.1 Morphine versus phenobarbitone	1	71	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-3.47, 0.67]
7 Duration supportive care (minutes/day)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Morphine versus phenobarbitone	1	74	Mean Difference (IV, Fixed, 95% CI)	-35.10 [-86.87, 16.67]
8 Admission to nursery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Morphine versus phenobarbitone	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.82]

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 Days treatment.

Review: Opiate treatment for opiate withdrawal in newborn infants

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

Outcome: 2 Days treatment

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)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 3 Days in hospital.

Review: Opiate treatment for opiate withdrawal in newborn infants

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

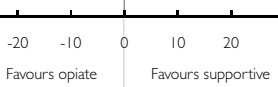
Outcome: 3 Days in hospital

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)

Test for subgroup differences: Not applicable

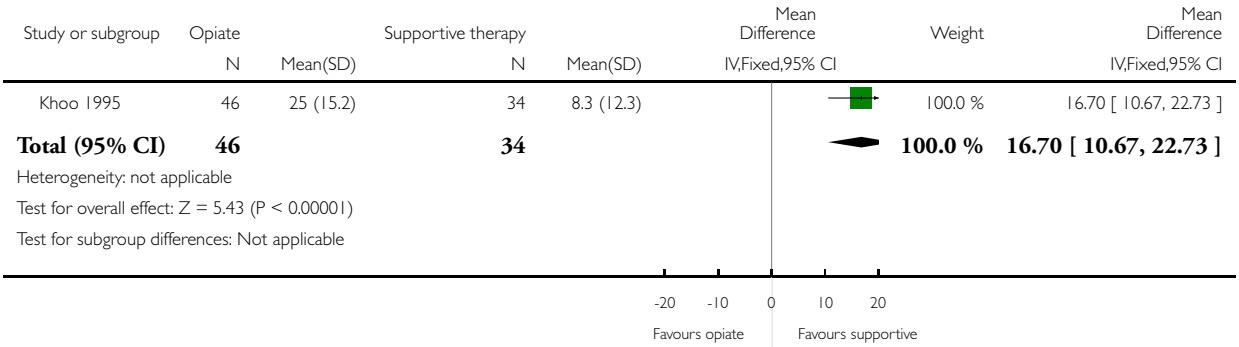


Analysis 1.4. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 4 Days in special care nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

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

Outcome: 4 Days in special care nursery

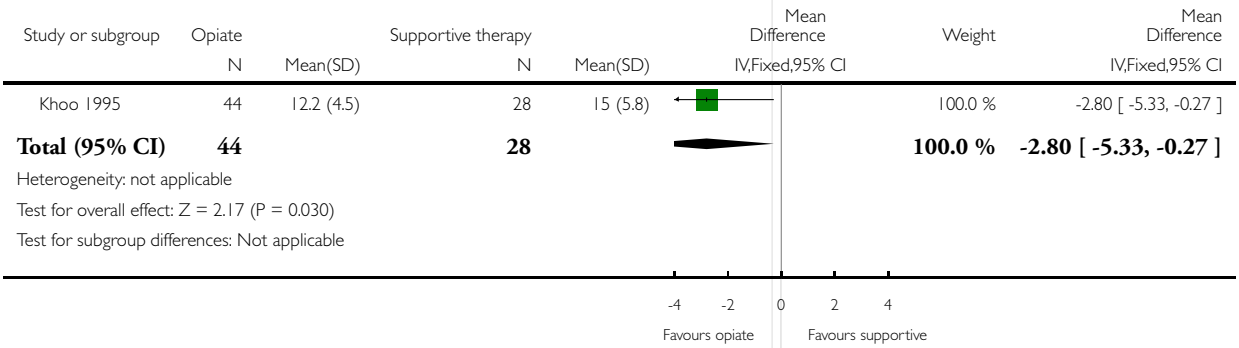


Analysis 1.5. Comparison 1 Opiate versus control (supportive therapy) (all infants), Outcome 5 Days to regain birth weight.

Review: Opiate treatment for opiate withdrawal in newborn infants

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

Outcome: 5 Days to regain birth weight



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

Review: Opiate treatment for opiate withdrawal in newborn infants

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

Outcome: 6 Duration supportive care (minutes/day)

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	112 (78.3)	34	309.2 (218.8)		100.0 %	-197.20 [-274.15, -120.25]
Total (95% CI)	**46**		**34**			**100.0 %**	**-197.20 [-274.15, -120.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.02 (P < 0.00001)

Test for subgroup differences: Not applicable

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)

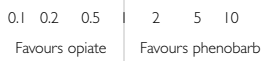
Analysis 2.2. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 2 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 2 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
Kaltenbach 1986	2/23	19/36		100.0 %	0.16 [0.04, 0.64]
Total (95% CI)	**23**	**36**		**100.0 %**	**0.16 [0.04, 0.64]**
Total events: 2 (Opiate), 19 (Phenobarbitone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.60 (P = 0.0093)					



Analysis 2.3. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 3 Seizures.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 3 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 2.4. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 4 Days treatment.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 4 Days treatment

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: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%

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

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 5 Days in hospital.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 5 Days in hospital

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)

Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 6 Days in special care nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

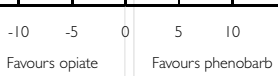
Outcome: 6 Days in special care nursery

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)

Test for subgroup differences: Not applicable

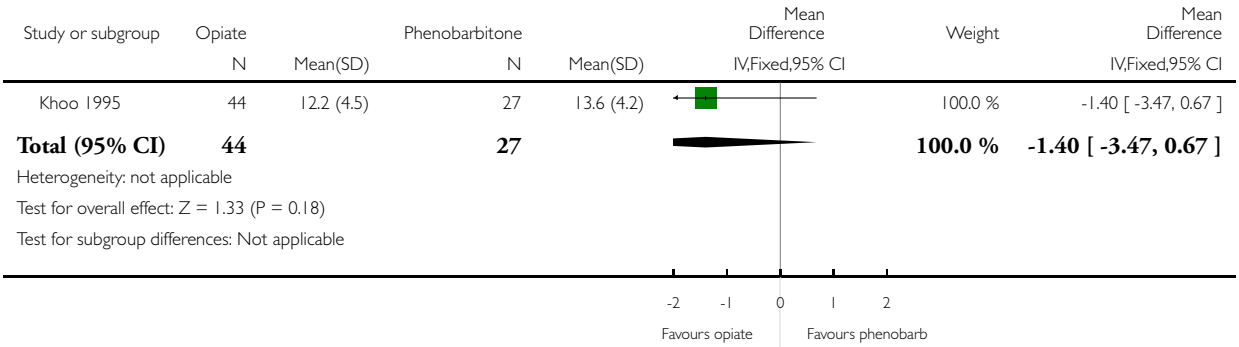


Analysis 2.7. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 7 Days to regain birth weight.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 7 Days to regain birth weight

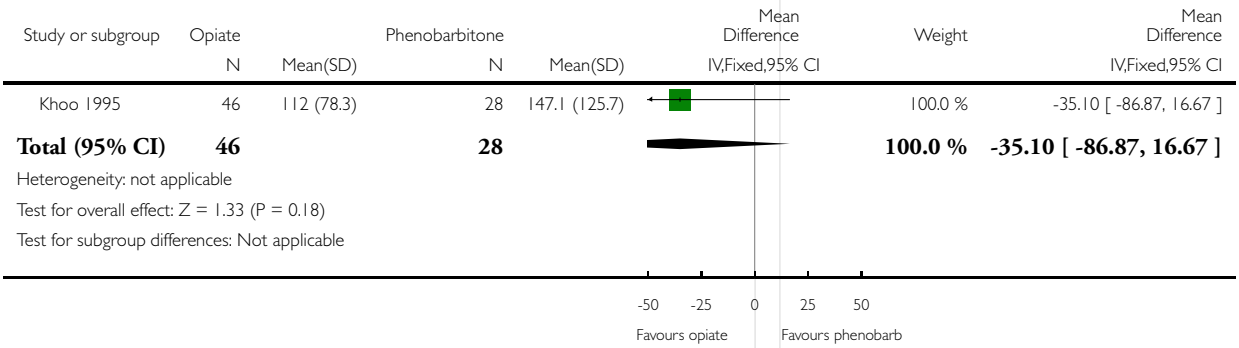


Analysis 2.8. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 8 Duration supportive care (minutes/day).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 8 Duration supportive care (minutes/day)



Analysis 2.9. Comparison 2 Opiate versus phenobarbitone (all infants), Outcome 9 Admission to nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 2 Opiate versus phenobarbitone (all infants)

Outcome: 9 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 phenobarbitone (infants of mother using only opiates), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 3 Opiate versus phenobarbitone (infants of mother using only opiates)

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	1/14	13/26		100.0 %	0.14 [0.02, 0.98]
Total (95% CI)	**14**	**26**		**100.0 %**	**0.14 [0.02, 0.98]**
Total events: 1 (Opiate), 13 (Phenobarbitone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.048)					

Analysis 4.1. Comparison 4 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: 4 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 5.1. Comparison 5 Opiate versus diazepam (all infants), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 5 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 5.2. Comparison 5 Opiate versus diazepam (all infants), Outcome 2 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 5 Opiate versus diazepam (all infants)

Outcome: 2 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
Kaltenbach 1986	2/23	10/10		100.0 %	0.11 [0.03, 0.36]
Total (95% CI)	**23**	**10**		**100.0 %**	**0.11 [0.03, 0.36]**
Total events: 2 (Opiate), 10 (Diazepam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.68 (P = 0.00023)					

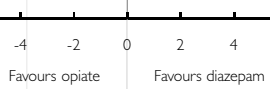
Analysis 5.3. Comparison 5 Opiate versus diazepam (all infants), Outcome 3 Days treatment.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 5 Opiate versus diazepam (all infants)

Outcome: 3 Days treatment

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)							
Test for subgroup differences: Not applicable							



Analysis 5.4. Comparison 5 Opiate versus diazepam (all infants), Outcome 4 Days in hospital.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 5 Opiate versus diazepam (all infants)

Outcome: 4 Days in hospital

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	19.13 (7.1)	16	16.8 (4.81)		100.0 %	2.33 [-1.79, 6.45]
Total (95% CI)	**17**		**16**			**100.0 %**	**2.33 [-1.79, 6.45]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Opiate versus diazepam (infants of mothers using only opiates), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 6 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 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)					

Analysis 8.1. Comparison 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates), Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

Outcome: 1 Treatment failure

Study or subgroup	Buprenorphine n/N	Opium solution n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraft 2009	4/13	1/13		100.0 %	4.00 [0.51, 31.13]
Total (95% CI)	**13**	**13**		**100.0 %**	**4.00 [0.51, 31.13]**
Total events: 4 (Buprenorphine), 1 (Opium solution)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
Test for subgroup differences: Not applicable					

Analysis 8.2. Comparison 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates), Outcome 2 Seizure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

Outcome: 2 Seizure

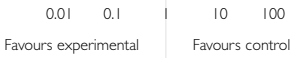
Study or subgroup	Buprenorphine n/N	Opium solution n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kraft 2009	1/13	0/13		100.0 %	3.00 [0.13, 67.51]
Total (95% CI)	**13**	**13**		**100.0 %**	**3.00 [0.13, 67.51]**

Total events: 1 (Buprenorphine), 0 (Opium solution)

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates), Outcome 3 Days treatment.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

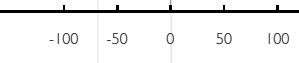
Outcome: 3 Days treatment

Study or subgroup	Buprenorphine N	Mean(SD)	Opium solution N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kraft 2009	12	22 (11)	13	32 (16)		100.0 %	-10.00 [-20.69, 0.69]
Total (95% CI)	**12**		**13**			**100.0 %**	**-10.00 [-20.69, 0.69]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates), Outcome 4 Days in hospital.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 8 Sublingual buprenorphine versus neonatal opium solution (infants of mother using only opiates)

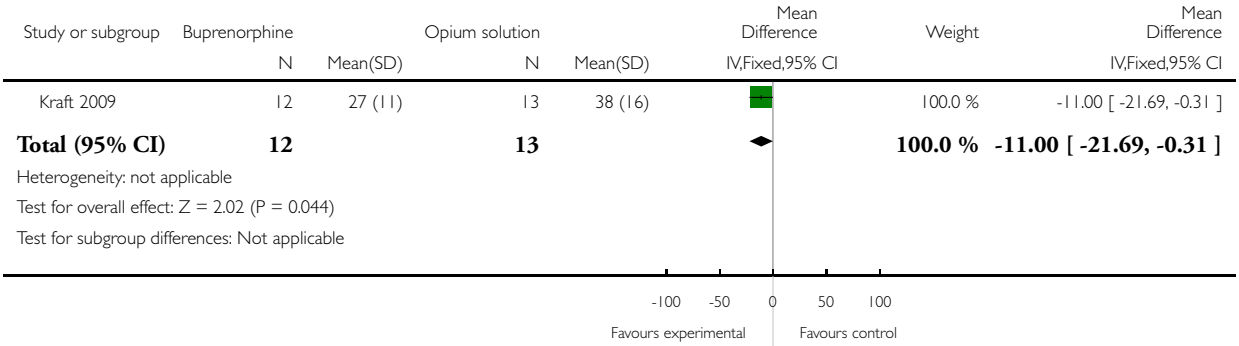
Outcome: 4 Days in hospital

Study or subgroup	Buprenorphine N	Mean(SD)	Opium solution N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kraft 2009	12	27 (11)	13	38 (16)		100.0 %	-11.00 [-21.69, -0.31]
Total (95% CI)	**12**		**13**			**100.0 %**	**-11.00 [-21.69, -0.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.02 (P = 0.044)

Test for subgroup differences: Not applicable

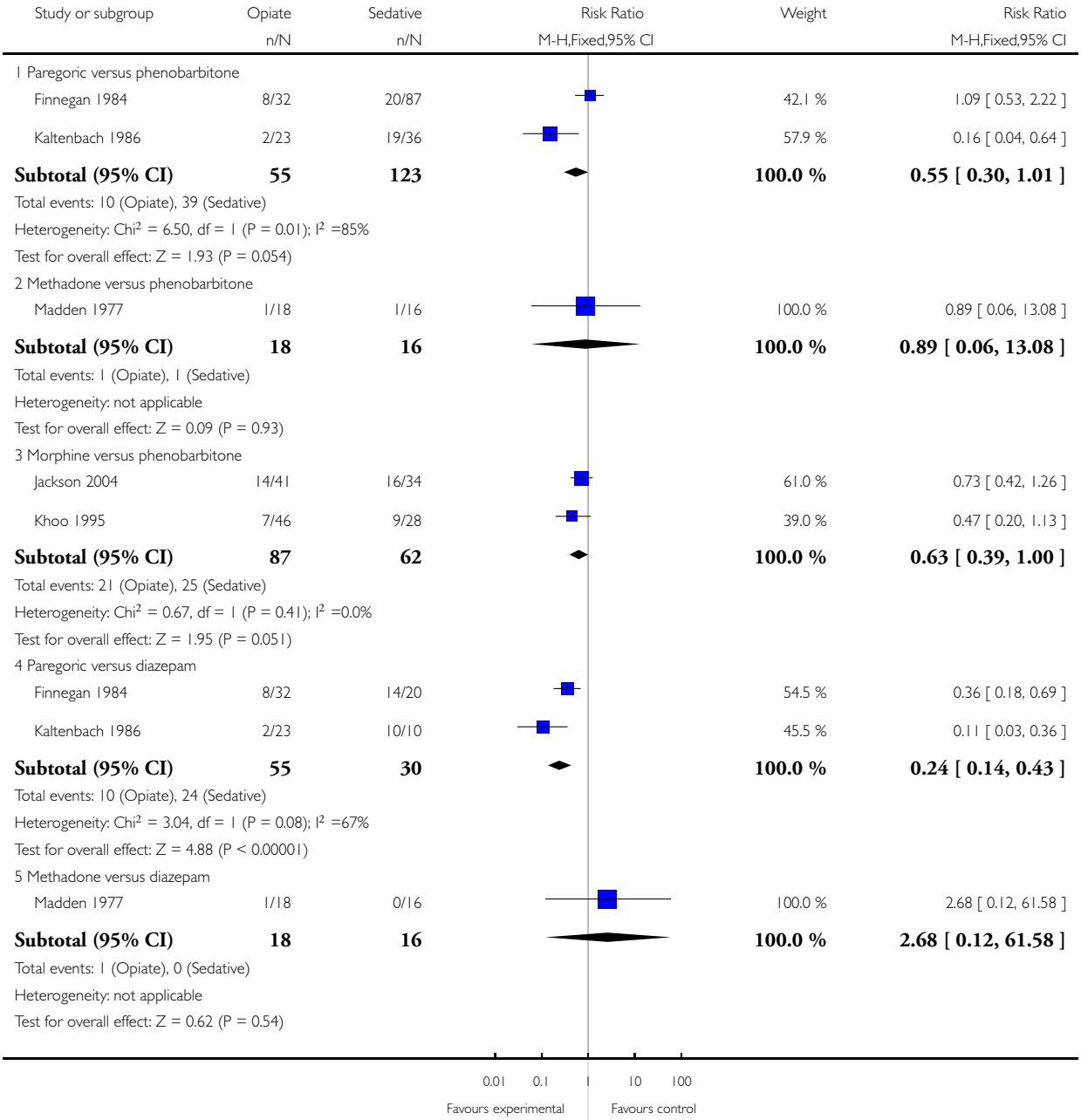


Analysis 10.1. Comparison 10 Specific opiate versus specific sedative, Outcome 1 Treatment failure.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 1 Treatment failure



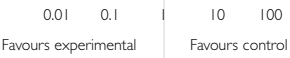
Analysis 10.2. Comparison 10 Specific opiate versus specific sedative, Outcome 2 Seizures.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 2 Seizures

Study or subgroup	Opiate n/N	Sedative n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Paregoric versus phenobarbitone					
Kandall 1983	0/49	7/62		100.0 %	0.08 [0.00, 1.44]
Subtotal (95% CI)	**49**	**62**		**100.0 %**	**0.08 [0.00, 1.44]**
Total events: 0 (Opiate), 7 (Sedative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.087)					



Analysis 10.3. Comparison 10 Specific opiate versus specific sedative, Outcome 3 Days treatment.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 3 Days treatment

Study or subgroup	Opiate N	Mean(SD)	Sedative N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Methadone versus phenobarbitone							
Madden 1977	17	11.76 (4.78)	15	14.5 (8.96)		62.8 %	-2.74 [-7.81, 2.33]
Subtotal (95% CI)	**17**		**15**			**62.8 %**	**-2.74 [-7.81, 2.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.06 (P = 0.29)							
2 Morphine versus phenobarbitone							
Khoo 1995	46	21.1 (14.1)	28	26.5 (14)		37.2 %	-5.40 [-11.99, 1.19]
Subtotal (95% CI)	**46**		**28**			**37.2 %**	**-5.40 [-11.99, 1.19]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.60 (P = 0.11)							
Total (95% CI)	**63**		**43**			**100.0 %**	**-3.73 [-7.75, 0.29]**
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Chi^2 = 0.39, df = 1 (P = 0.53), I^2 =0.0%							

Analysis 10.4. Comparison 10 Specific opiate versus specific sedative, Outcome 4 Days in hospital.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 4 Days in hospital

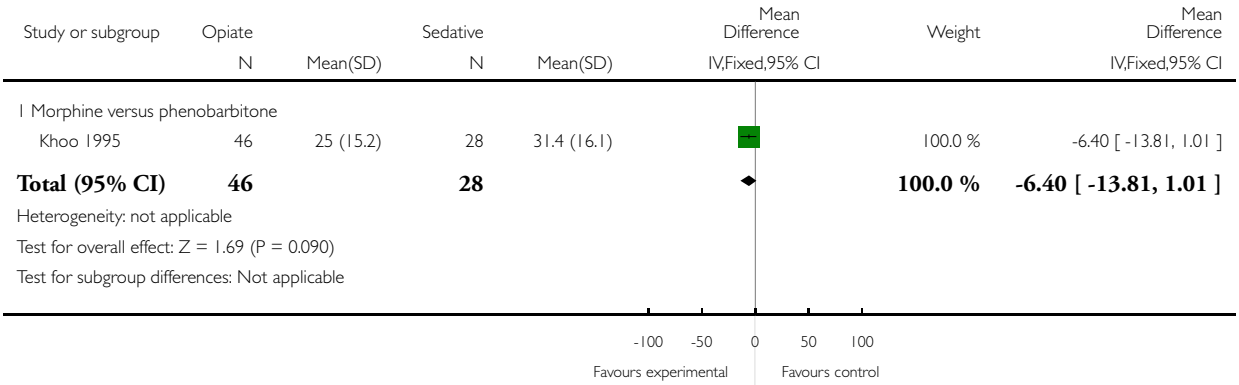
Study or subgroup	Opiate N	Mean(SD)	Sedative N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Methadone versus phenobarbitone							
Madden 1977	17	19.13 (7.1)	15	19.87 (8.91)		64.4 %	-0.74 [-6.37, 4.89]
Subtotal (95% CI)	**17**		**15**			**64.4 %**	**-0.74 [-6.37, 4.89]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.80)							
2 Morphine versus phenobarbitone							
Khoo 1995	46	29 (16.2)	28	34.8 (16.1)		35.6 %	-5.80 [-13.38, 1.78]
Subtotal (95% CI)	**46**		**28**			**35.6 %**	**-5.80 [-13.38, 1.78]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.50 (P = 0.13)							
Total (95% CI)	**63**		**43**			**100.0 %**	**-2.54 [-7.06, 1.98]**
Heterogeneity: Chi^2 = 1.10, df = 1 (P = 0.29); I^2 =9%							
Test for overall effect: Z = 1.10 (P = 0.27)							
Test for subgroup differences: Chi^2 = 1.10, df = 1 (P = 0.29), I^2 =9%							

Analysis 10.5. Comparison 10 Specific opiate versus specific sedative, Outcome 5 Days in special care nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 5 Days in special care nursery

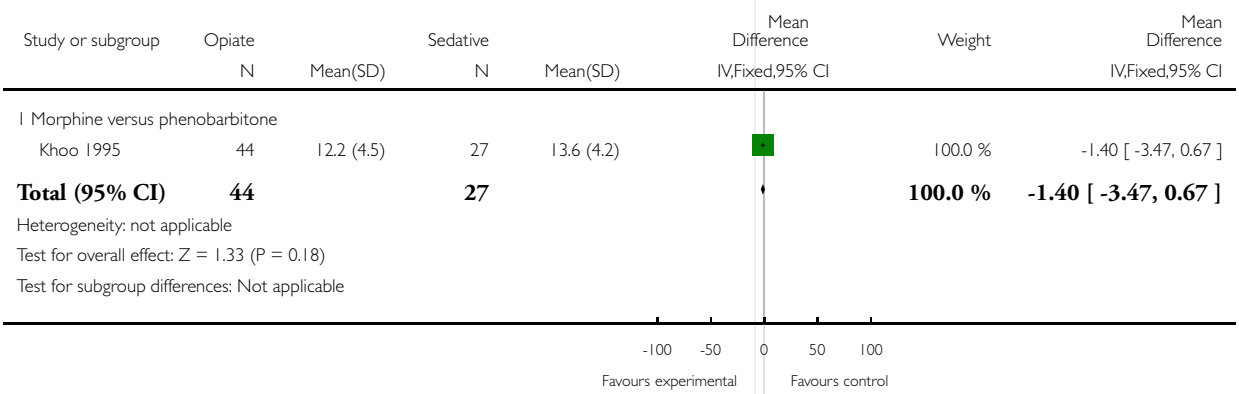


Analysis 10.6. Comparison 10 Specific opiate versus specific sedative, Outcome 6 Days to regain birthweight.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 6 Days to regain birthweight



Analysis 10.7. Comparison 10 Specific opiate versus specific sedative, Outcome 7 Duration supportive care (minutes/day).

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

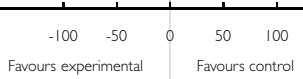
Outcome: 7 Duration supportive care (minutes/day)

Study or subgroup	Opiate N	Mean(SD)	Sedative N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Morphine versus phenobarbitone							
Khoo 1995	46	112 (78.3)	28	147.1 (125.7)		100.0 %	-35.10 [-86.87, 16.67]
Subtotal (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)

Test for subgroup differences: Not applicable



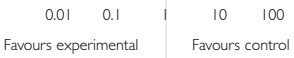
Analysis 10.8. Comparison 10 Specific opiate versus specific sedative, Outcome 8 Admission to nursery.

Review: Opiate treatment for opiate withdrawal in newborn infants

Comparison: 10 Specific opiate versus specific sedative

Outcome: 8 Admission to nursery

Study or subgroup	Opiate n/N	Sedative n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Morphine versus phenobarbitone					
Jackson 2004	12/41	21/34		100.0 %	0.47 [0.27, 0.82]
Subtotal (95% CI)	**41**	**34**		**100.0 %**	**0.47 [0.27, 0.82]**
Total events: 12 (Opiate), 21 (Sedative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.69 (P = 0.0072)					



WHAT'S NEW

Last assessed as up-to-date: 4 April 2010.

Date	Event	Description
28 April 2010	New citation required and conclusions have changed	Conclusions updated.
28 April 2010	New search has been performed	This updates the review "Opiate treatment for opiate withdrawal in newborn infants" published in the Cochrane Database of Systematic Reviews, Issue 3, 2005 (Osborn 2005). Search updated March 2010. Two additional trials included (Kraft 2009, Langenfeld 2005). Additional outcomes added.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 3, 2002

Date	Event	Description
16 October 2008	Amended	Converted to new review format.
29 March 2005	New citation required and conclusions have changed	Substantive amendment
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

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 2005, DO searched for new studies, assessed eligibility, critically appraised studies and extracted data. HJ critically appraised the new study and did data extraction. DO wrote the updated review.

For the updated review 2010, DO searched for new studies, assessed eligibility, critically appraised studies and extracted data. 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

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Updated to RevMan 5 format. Methods for assessment of heterogeneity, unit of analysis issues and reporting bias added.

INDEX TERMS

Medical Subject Headings (MeSH)

Diazepam [therapeutic use]; Hypnotics and Sedatives [therapeutic use]; Infant, Newborn; Morphine [therapeutic use]; 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