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Zankl A, Martin J, Davey JG, Osborn DA

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[Intervention Review]

Sedatives for opioid withdrawal in newborn infants

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ABSTRACT

Background

Neonatal abstinence syndrome (NAS) due to opioid withdrawal may result in disruption of the mother–infant relationship, sleep–wake abnormalities, feeding difficulties, weight loss, seizures and neurodevelopmental problems.

Objectives

To assess the effectiveness and safety of using a sedative versus control (placebo, usual treatment or non-pharmacological treatment) for NAS due to withdrawal from opioids and determine which type of sedative is most effective and safe for NAS due to withdrawal from opioids.

Search methods

We ran an updated search on 17 September 2020 in CENTRAL via CRS Web and MEDLINE via Ovid. We searched clinical trials databases, conference proceedings and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials**.**

Selection criteria

We included trials enrolling infants with NAS born to mothers with an opioid dependence with more than 80% follow-up and using randomised, quasi-randomised and cluster-randomised allocation to sedative or control.

Data collection and analysis

Three review authors assessed trial eligibility and risk of bias, and independently extracted data. We used the GRADE approach to assess the certainty of the evidence.

Main results

We included 10 trials (581 infants) with NAS secondary to maternal opioid use in pregnancy. There were multiple comparisons of different sedatives and regimens. There were limited data available for use in sensitivity analysis of studies at low risk of bias.

Phenobarbital versus supportive care: one study reported there may be little or no difference in treatment failure with phenobarbital and supportive care versus supportive care alone (risk ratio (RR) 2.73, 95% confidence interval (CI) 0.94 to 7.94; 62 participants; very low-certainty evidence). No infant had a clinical seizure. The study did not report mortality, neurodevelopmental disability and adverse events. There may be an increase in days' hospitalisation and treatment from use of phenobarbital (hospitalisation: mean difference (MD) 20.80, 95% CI 13.64 to 27.96; treatment: MD 17.90, 95% CI 11.98 to 23.82; both 62 participants; very low-certainty evidence).

Phenobarbital versus diazepam: there may be a reduction in treatment failure with phenobarbital versus diazepam (RR 0.39, 95% CI 0.24 to 0.62; 139 participants; 2 studies; low-certainty evidence). The studies did not report mortality, neurodevelopmental disability and adverse events. One study reported there may be little or no difference in days' hospitalisation and treatment (hospitalisation: MD 3.89, 95% CI −1.20 to 8.98; 32 participants; treatment: MD 4.30, 95% CI −0.73 to 9.33; 31 participants; both low-certainty evidence).

Phenobarbital versus chlorpromazine: there may be a reduction in treatment failure with phenobarbital versus chlorpromazine (RR 0.55, 95% CI 0.33 to 0.92; 138 participants; 2 studies; very low-certainty evidence), and no infant had a seizure. The studies did not report mortality and neurodevelopmental disability. One study reported there may be little or no difference in days' hospitalisation (MD 7.00, 95% CI −3.51 to 17.51; 87 participants; low-certainty evidence) and 0/100 infants had an adverse event.

Phenobarbital and opioid versus opioid alone: one study reported no infants with treatment failure and no clinical seizures in either group (low-certainty evidence). The study did not report mortality, neurodevelopmental disability and adverse events. One study reported there may be a reduction in days' hospitalisation for infants treated with phenobarbital and opioid (MD −43.50, 95% CI −59.18 to −27.82; 20 participants; low-certainty evidence).

Clonidine and opioid versus opioid alone: one study reported there may be little or no difference in treatment failure with clonidine and dilute tincture of opium (DTO) versus DTO alone (RR 0.09, 95% CI 0.01 to 1.59; 80 participants; very low-certainty evidence). All five infants with treatment failure were in the DTO group. There may be little or no difference in seizures (RR 0.14, 95% CI 0.01 to 2.68; 80 participants; very low-certainty evidence). All three infants with seizures were in the DTO group. There may be little or no difference in mortality after discharge (RR 7.00, 95% CI 0.37 to 131.28; 80 participants; very low-certainty evidence). All three deaths were in the clonidine and DTO group. The study did not report neurodevelopmental disability. There may be little or no difference in days' treatment (MD −4.00, 95% CI −8.33 to 0.33; 80 participants; very low-certainty evidence). One adverse event occurred in the clonidine and DTO group. There may be little or no difference in rebound NAS after stopping treatment, although all seven cases were in the clonidine and DTO group.

Clonidine and opioid versus phenobarbital and opioid: there may be little or no difference in treatment failure (RR 2.27, 95% CI 0.98 to 5.25; 2 studies, 93 participants; very low-certainty evidence). One study reported one infant in the clonidine and morphine group had a seizure, and there were no infant mortalities. The studies did not report neurodevelopmental disability. There may be an increase in days' hospitalisation and days' treatment with clonidine and opioid versus phenobarbital and opioid(hospitalisation: MD 7.13, 95% CI 6.38 to 7.88; treatment: MD 7.57, 95% CI 3.97 to 11.17; both 2 studies, 91 participants; low-certainty evidence). There may be little or no difference in adverse events (RR 1.55, 95% CI 0.44 to 5.40; 2 studies, 93 participants; very low-certainty evidence). However, there was oversedation only in the phenobarbital and morphine group; and hypotension, rebound hypertension and rebound NAS only in the clonidine and morphine group.

Authors' conclusions

There is very low-certainty evidence that phenobarbital increases duration of hospitalisation and treatment, but reduces days to regain birthweight and duration of supportive care each day compared to supportive care alone. There is low-certainty evidence that phenobarbital reduces treatment failure compared to diazepam and very low-certainty evidence that phenobarbital reduces treatment failure compared to chlorpromazine. There is low-certainty evidence of an increase in days' hospitalisation and days' treatment with clonidine and opioid compared to phenobarbital and opioid. There are insufficient data to determine the safety and incidence of adverse events for infants treated with combinations of opioids and sedatives including phenobarbital and clonidine.

PLAIN LANGUAGE SUMMARY

Sedatives for opioid withdrawal in newborn infants

Review question

To determine the effectiveness and safety of using a sedative (sleep-inducing medicine) compared to a non-opioid or a non-medicine control for the treatment of neonatal abstinence syndrome (NAS) due to withdrawal from opioids.

Background

Use of opioids (prescribed or illicit) by pregnant women may result in their newborn infant experiencing withdrawal symptoms collectively referred to as NAS, which may result in disruption of the mother–infant relationship, sleeping and feeding difficulties, weight loss and seizures (fits). Treatments for newborn infants used to ameliorate NAS and reduce complications include supportive treatments such as a dummy (pacifier); swaddling or close wrapping; small frequent feeds; close skin contact by carrying in sling and other methods; and prescription of opioids or sedatives, or both.

Study characteristics

The search was up-to-date to September 2020.

Key results

We included 10 trials, enrolling 581 infants with NAS caused by maternal opioid use in pregnancy, in the review. There were multiple comparisons of different sedatives and regimens. The addition of phenobarbital to supportive care increased duration of hospitalisation and treatment, but reduced duration supportive care each day compared to supportive care alone. Phenobarbital reduced treatment failure compared to both diazepam and chlorpromazine. Clonidine and opioid compared to phenobarbital and opioid increased in days of hospitalisation and days of treatment. There were insufficient data to determine the safety and incidence of side effects for infants treated with combinations of opioids and sedatives including phenobarbital and clonidine. Side effects reported in infants treated with an opioid included oversedation from the addition of phenobarbital, and low blood pressure from the addition of clonidine with rebound high blood pressure and NAS reported after stopping clonidine. We found one ongoing study of clonidine plus morphine for NAS.

Certainty of the evidence

This was low to very low for all results.

Summary of findings 1. Phenobarbital versus supportive care for opioid withdrawal in newborn infants

Phenobarbital vs supportive care for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal

Settings: hospital, Australia

Intervention: phenobarbital vs supportive care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive care	Phenobarbital				
Treatment failure To discharge	**Study population**		**RR 2.73** (0.94 to 7.94)	62 (1 study)	⊕⊖⊖⊖ **Very low** [a],[b]	—
	118 per 1000	**321 per 1000** (111 to 934)				
Seizures To discharge	No events	No events	Not estimable	62 (1 study)	⊕⊖⊖⊖ **Very low** [a],[b],[c]	—
Neonatal and infant mortality	—	—	—	—	—	Not reported
Neurodevelopmental disability	—	—	—	—	—	Not reported
Days' hospitalisation	Mean 14.0 days (9.9 to 18.1)	The mean days' hospitalisation was **20.8 higher** (13.64 to 27.96 higher) in the phenobarbital group.	—	62 (1 study)	⊕⊖⊖⊖ **Very low** [a],[b]	—
Days' pharmacological treatment	Mean 8.6 days (5.6 to 11.6)	The mean days' treatment was **17.9 higher** (11.98 to 23.82 higher) in the phenobarbital group.	—	62 (1 study)	⊕⊖⊖⊖ **Very low** [a],[b]	—
Adverse events To discharge	—	—	—	—	—	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded two levels for very serious risk of bias (quasi-random allocation, no blinding).
[b]Downgraded one level for serious imprecision (wide confidence intervals).
[c]No events.

Summary of findings 2. Phenobarbital versus diazepam for opioid withdrawal in newborn infants

Phenobarbital vs diazepam for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal
Settings: hospital, USA
Intervention: phenobarbital vs diazepam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Diazepam	Phenobarbital				
Treatment failure To discharge	**389 per 1000**	**152 per 1000** (93 to 241)	**RR 0.39** (0.24 to 0.62)	139 (2 studies)	⊕⊕⊖⊖ **Low** [a],[b]	—
Seizures To discharge	—	—	—	—	—	Not reported
Neonatal and infant mortality	—	—	—	—	—	Not reported
Neurodevelopmental disability	—	—	—	—	—	Not reported

Days' hospitalisation	Mean 16.8 days (14.2 to 19.4)	The mean days' hospitalisation was **3.89 higher** (1.2 lower to 8.98 higher) in the phenobarbital group	—	32 (1 study)	⊕⊕⊖⊖ **Low** [a],[c]	—
Days' pharmacological treatment	Mean 10.2 days (7.8 to 12.6)	The mean days' treatment was **4.3 higher** (0.73 lower to 9.33 higher) in the phenobarbital group	—	31 (1 study)	⊕⊕⊖⊖ **Low** [a],[c]	—
Adverse events To discharge	—	—	—	—	—	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for serious risk of bias (high-risk allocation procedures).
[b]Downgraded one level for serious inconsistency (moderate heterogeneity).
[c]Downgraded one level for serious imprecision (wide confidence intervals).

Summary of findings 3. Phenobarbital versus chlorpromazine for opioid withdrawal in newborn infants

Phenobarbital vs chlorpromazine for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal
Settings: hospital, USA and Switzerland
Intervention: phenobarbital vs chlorpromazine

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Chlorpromazine	**Phenobarbital**				
Treatment failure	**288 per 1000**	**357 per 1000** (219 to 587)	**RR 0.55** (0.33 to 0.92)	138 (2 studies)	⊕⊖⊖⊖ **Very low** [a],[b],[c]	—

To discharge						
Seizures To discharge	No events	No events	Not estimable	140 (2 studies)	⊕⊖⊖⊖ **Very low** [a,d]	—
Neonatal and infant mortality	—	—	—	—	—	Not reported
Neurodevelopmental disability	—	—	—	—	—	Not reported
Days' hospitalisation	Mean 25.0 days (16.1 to 33.9)	The mean days' hospitalisation was **7 higher** (3.51 lower to 17.51 higher) in the phenobarbital group	—	87 (1 study)	⊕⊕⊖⊖ **Low** [c,e]	—
Days' pharmacological treatment	—	—	—	—	—	Not reported
Adverse events To discharge	No events	No events	Not estimable	100 (1 study)	⊕⊕⊖⊖ **Low** [d]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for serious risk of bias (single study at low risk of bias).
[b]Downgraded one level for serious inconsistency (high heterogeneity).
[c]Downgraded one level for serious imprecision (wide confidence intervals).
[d]Downgraded two levels for very serious imprecision (no events).
[e]Downgraded one level for serious risk of bias (incomplete outcome data).

Summary of findings 4. Phenobarbital and opioid versus opioid alone for opioid withdrawal in newborn infants

Phenobarbital and opioid vs opioid alone for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal
Settings: hospital, USA

Intervention: phenobarbital and opioid vs opioid alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dilute tincture of opium	Phenobarbital and dilute tincture of opium				
Treatment failure To discharge	No events	No events	Not estimable	20 (1 study)	⊕⊝⊝⊝ **Very low** [a],[b]	—
Seizures To discharge	No events	No events	Not estimable	20 (1 study)	⊕⊝⊝⊝ **Very low** [a],[b]	—
Neonatal and infant mortality	—	—	—	—	—	Not reported
Neurodevelopmental disability	—	—	—	—	—	Not reported
Days' hospitalisation	Mean 80.8 days (66.8 to 94.7)	The mean days' hospitalisation was **43.5 lower** (59.18 to 27.82 lower) in the phenobarbital and dilute tincture of opium group	—	20 (1 study)	⊕⊕⊝⊝ **Low** [a],[c]	—
Days' pharmacological treatment	—	—	—	—	—	Not reported
Adverse events To discharge	—	—	—	—	—	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for serious risk of bias (high-risk allocation procedures).

[b]Downgraded two levels for very serious imprecision (single small study, no events).
[c]Downgraded one level for serious imprecision (single small study, wide confidence intervals).

Summary of findings 5. Clonidine and opioid versus opioid alone for opioid withdrawal in newborn infants

Clonidine and opioid vs opioid alone for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal
Settings: hospital, USA
Intervention: clonidine and opioid vs opioid alone (all infants)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dilute tincture of opium	Clonidine and dilute tincture of opium				
Treatment failure To discharge	**125 per 1000**	**11 per 1000** (1 to 199)	**RR 0.09** (0.01 to 1.59)	80 (1 study)	⊕⊖⊖⊖ **Very low** [a],b	—
Seizures To discharge	**75 per 1000**	**10 per 1000** (1 to 201)	**RR 0.14** (0.01 to 2.68)	80 (1 study)	⊕⊖⊖⊖ **Very low** [a],b	—
Mortality post discharge Follow-up: 2 months	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 7** (0.37 to 131.28)	80 (1 study)	⊕⊖⊖⊖ **Very low** [a],b	3 infants in the clonidine group died from unrelated causes.
Neurodevelopmental disability	—	—	—	—	—	Not reported
Days' hospitalisation	—	—	—	—	—	Not reported
Days' pharmacological treatment	Mean 15.0 days (13.0 to 17.0)	The mean days' treatment was **4 lower** (8.33 lower to 0.33 higher) in the clonidine and dilute tincture of opium group	—	80 (1 study)	⊕⊖⊖⊖ **Very low** [a],b	—
Adverse events (treatment related)	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3.00** (0.13 to 71.51)	80 (1 study)	⊕⊖⊖⊖ **Very low** [a],b	1 infant with supraventricu-

To discharge						lar tachycardia in clonidine group.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for serious inconsistency (single small study).
[b]Downgraded two levels for very serious imprecision (wide confidence intervals).

Summary of findings 6. Clonidine and opioid versus phenobarbital and opioid for opioid withdrawal in newborn infants

Clonidine and opioid vs phenobarbital and opioid for opioid withdrawal in newborn infants

Patient or population: newborn infants with opioid withdrawal
Settings: hospital, USA
Intervention: clonidine and opioid vs phenobarbital and opioid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenobarbital and morphine	Clonidine and morphine				
Treatment failure To discharge	**89 per 1000**	**202 per 1000** (87 to 467)	**RR 2.27** (0.98 to 5.25)	93 (2 studies)	⊕⊖⊖⊖ **Very low** [a],[b]	—
Seizures To discharge	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3** (0.13 to 71.15)	68 (1 study)	⊕⊖⊖⊖ **Very low** [a],[b]	—
Mortality to discharge Follow-up: 8 months	No events	No events	Not estimable	68 (1 study)	⊕⊖⊖⊖ **Very low** [a],[c]	—

Neurodevelopmental disability	—	—	—	—	—	Not reported
Days' hospitalisation	Mean 26.3 days (22.7 to 29.9)	The mean days' hospitalisation was **7.13 higher** (6.38 to 7.88 higher) in the clonidine and morphine group	—	91 (2 studies)	⊕⊕⊖⊖ **Low** [a]	—
Days' pharmacological treatment	Mean 24.0 days (20.4 to 27.7)	The mean days' treatment was **7.57 higher** (3.97 to 11.17 higher) in the clonidine and morphine group	—	91 (2 studies)	⊕⊕⊖⊖ **Low** [a,d]	—
Adverse events (treatment related) To discharge	**67 per 1000**	**103 per 1000** (29 to 360)	**RR 1.55** (0.44 to 5.4)	93 (2 studies)	⊕⊖⊖⊖ **Very low** [a,b,e]	1 study reported oversedation in 3 infants receiving phenobarbital and morphine. The other study reported 6 infants with hypotension, rebound hypertension (1 infant) and rebound NAS (1 infant) in infants treated with clonidine and morphine.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for serious risk of bias (no study at low risk of bias).
[b]Downgraded two levels for very serious imprecision (very wide confidence intervals).
[c]Downgraded two levels for very serious imprecision (single study with no events).
[d]Downgraded one level for serious imprecision (single small study with wide confidence intervals).
[e]Downgraded one level for serious inconsistency (heterogeneity, $I^2 = 77\%$).

BACKGROUND

Description of the condition

Opioid use in pregnancy and neonatal abstinence syndrome (NAS) due to opioid withdrawal is currently a significant clinical and social problem. Since the previous review update on this topic (Osborn 2010), rates of illicit drug use by pregnant women in the USA as reported by the National Household Survey on Drug Abuse have increased from 3.4% in 1999 to 5.4% in 2013, with heroin abuse still being most common (NHSDA 1999; NHSDA 2013). Prescription of methadone and buprenorphine are standard maintenance treatments for pregnant women with an opioid addiction (Brogly 2014; Coyle 2012; Jones 2010; Kocherlakota 2014; Siu 2014). Of growing concern is the use and abuse of prescription opioid analgesic medications by pregnant women for non-cancer related pain (Kocherlakota 2014; Kraft 2016; Patrick 2015; Stover 2015). The flow on effect of the illicit and prescribed opioid usage rates across the USA by pregnant women is a nationwide increase in admission of newborn infants to neonatal intensive care units for NAS from 0.6% (7 cases per 1000) in 2004 to 4.0% (27 cases per 1000) in 2013 (Tolia 2015). As the reported mean length of stay for infants requiring treatment for NAS in the USA is 16 days, cost estimates of treatment are USD 159,000 to USD 238,000 greater than for healthy infants (Peltz 2015). These data are reflected outside the USA across several European countries, Canada and Australia (Allegaert 2016; Bauchinger 2015; Brogly 2017; Davies 2016; Kirchner 2014; NDSHS 2013; Turner 2015; Unger 2012), indicating that NAS is a globally significant clinical and social problem with concomitant fiscal burdens for healthcare providers. Such is the global concern that the World Health Organization (WHO) has published guidelines for clinicians regarding the management of substance use in pregnancy and NAS (WHO 2014).

Between 48% and 94% of infants exposed to opioids 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 1975). Onset of NAS in the case of heroin withdrawal is usually within 24 hours after birth and has a shorter (8 to 10 days) and milder manifestation of clinical symptoms (Alroomi 1988; Bell 1995; Kocherlakota 2014; Siu 2014). Conversely, withdrawal from methadone or buprenorphine has a usual onset of NAS from 48 hours to 72 hours with a more protracted (up to 30 days or more) and more pronounced manifestation of clinical symptoms (Alroomi 1988; Brogly 2014; Coyle 2012; Doberczak 1991; Fricker 1978; Jones 2010; Kocherlakota 2014; Lam 1992; Maas 1990; Madden 1977; Olofsson 1983; Ostrea 1975). Although there is some evidence to correlate methadone dose and severity of withdrawal (Dashe 2002; Doberczak 1991; Harper 1977; Ostrea 1975), and clinically significant manifestations of NAS are uncommon when the dose is below 20 mg/day (Strauss 1976), the association between methadone dosage in pregnancy and subsequent development of NAS is inconsistent (Cleary 2010). There is some evidence that antenatal maintenance treatment with buprenorphine when compared to methadone may reduce the severity of NAS and length of hospital stay (Brogly 2014; Coyle 2012; Jones 2010; Kaltenbach 2012). However, multiple-drug use in pregnant women on maintenance buprenorphine has been reported to confound subsequent treatment of NAS in infants born to those women (Patel 2013).

The clinical presentation of NAS may involve central nervous system (CNS) signs including tremors, irritability, increased wakefulness, high-pitched crying, increased muscle tone, hyperactive deep tendon reflexes, exaggerated Moro reflex, seizures, frequent yawning and sneezing, poor feeding, uncoordinated and constant sucking; gastrointestinal signs including vomiting, diarrhoea, dehydration and poor weight gain; and autonomic signs including increased sweating, nasal stuffiness, fever, mottling and temperature instability (AAP 2012). Seizures occur in 2% to 11% of infants withdrawing from opioids (Doberczak 1991; Herzlinger 1977; Kandall 1977), and may be more common with methadone than heroin withdrawal (Herzlinger 1977). However, benign myoclonus is also common in infants with NAS from opioids and associated with a normal electroencephalogram (EEG) (Held-Egli 2009).

In human studies, exposure to in-utero opioids has been reported to reduce fetal growth parameters and lower birth weights (Finnegan 2005; Kandall 1976; Kennare 2005); reduce neuroanatomic volumes (Walhovd 2007); alter neuronal connective tracts on imaging studies (Walhovd 2012); reduce newborn head circumference (Visconti 2013); and increase the risk of stillbirth (Finnegan 2005; Kennare 2005), neonatal mortality (Hulse 1998), and sudden infant death syndrome (Kandall 1993). In older children, failure to thrive and short stature (Hunt 2008), visual disturbances including refractive errors and nystagmus (Spiteri Cornish 2013), psychobehavioural problems such as impulsivity and attention-deficit that may in turn lead to failure at school (Oei 2017; Sundelin Wahlsten 2013), have been associated with in-utero exposure to opioids and other drugs.

Description of the intervention

Intervention begins with identification of infants with NAS. A variety of scoring systems identify and document the severity of clinical manifestations associated with NAS including the Lipsitz tool (Lipsitz 1975), Neonatal Abstinence Scoring System (Finnegan 1975a), Neonatal Narcotic Withdrawal Index (Green 1981), Neonatal Withdrawal Inventory (Zahorodny 1998), and the MOTHER NAS Scale (Jones 2016). There are internal consistency, reliability and validity concerns with the use of scoring systems for NAS (Bagley 2014; Jones 2016; Wolff 2014), many of which relate to clinician competency in identifying symptoms of NAS and using the tool effectively (Orlando 2014), particularly where preterm infants are concerned (Allocco 2016). Despite these inadequacies, the Neonatal Abstinence Scoring System (NASS) (Finnegan 1975a), or modified versions remains the most commonly used method for assessing withdrawal symptoms and determining treatment (Kraft 2012; Kraft 2016). In general, pharmacological interventions are commenced once an infant scores more than 8 on the Neonatal Abstinence Scoring System (Kraft 2016).Treatment for NAS typically involves a combination of pharmacological and non-pharmacological interventions. Pharmacological interventions for NAS due to opioid withdrawal have included tincture of opium, paregoric, morphine, methadone and, more recently, buprenorphine. Sedatives used for opioid withdrawal have included clonidine, phenobarbital, diazepam and chlorpromazine (Kraft 2012; Siu 2014; Theis 1997). Non-pharmacological interventions have included reducing environmental stimuli, swaddling, settling, massage, relaxation baths, dummies (pacifiers) and waterbeds (Bagley 2014; Oro 1988). More recently, acupuncture (Boucher 2017; Raith 2015), together

with a much greater focus on promoting the mother–infant dyad through rooming-in programmes (Boucher 2017; Howard 2017; Newman 2015) and breastfeeding (Jansson 2016; Short 2016), have been shown to reduce the need for pharmacological intervention, decrease the severity of NAS symptoms and reduce hospital length of stay. However, as two reviews have shown, there are no high-quality clinical trials supporting efficacy of non-pharmacological treatment interventions (MacMillan 2018; Wachman 2018).

How the intervention might work

Following delivery, the abrupt cessation of opioid supply to the newborn results in a cascade of neurotransmitter activity, which involves an increase in the production of noradrenaline, acetylcholine and corticotrophin, as well as a decrease in the production of serotonin and dopamine (Kocherlakota 2014). Pharmacological interventions for NAS due to opioid withdrawal include opioid replacement therapies directed towards the μ-opioid receptor. These include tincture of opium (contains ethanol 19%, and opium alkaloids including morphine and codeine), paregoric (contains ethanol 44%, anhydrous morphine, camphor, anise oil, benzoic acid, glycerine and antispasmodics (papaverine and noscapine)), morphine (natural opioid), methadone (a synthetic μ-opioid receptor agonist) and more recently buprenorphine (a semi-synthetic partial μ-opioid receptor agonist and complete κ-opioid receptor antagonist). Sedatives used for opioid withdrawal have included clonidine (an α2 adrenergic receptor agonist that ameliorates
autonomic overactivity, such as tachycardia, hypertension, diaphoresis, restlessness and diarrhoea), phenobarbital and diazepam (gamma-aminobutyric acid (GABA) receptor agonists that bind to different sites on the receptor, are sedative and reduce excitability) and chlorpromazine (a dopamine antagonist that may also reduce autonomic overactivity) (Kraft 2012; Siu 2014; Theis 1997).

The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment. The goal of pharmacological treatment is achievement of the desired therapeutic effect by using the least amount of drugs at the lowest doses and for the shortest durations possible (AAP 2012). Treatment is usually initiated and titrated to NAS withdrawal scores. Once stabilised, treatment is withdrawn while continuing to monitor NAS withdrawal scores. In infants with predominant opioid dependency, opioid replacement therapy is usually titrated down gradually, whereas sedatives prescribed for relatively short periods can be titrated more rapidly allowing for shorter durations of treatment and earlier discharge of infants from hospital. However, although it is common for infants receiving pharmacological treatment for NAS to remain in hospital, there are increasing reports of safe discharge of infants receiving treatment (Kelly 2015; Middleton 2017).

Why it is important to do this review

Recommended first-line pharmacological treatment for newborns experiencing NAS from opioid withdrawal is generally with an opioid and may include adjunctive treatment with a sedative (AAP 2012). For sedative-hypnotic withdrawal, phenobarbital is recommended (AAP 2012). It may be that, by using a sedative, many infants will avoid further opioid exposure and duration of treatment will be reduced to the period of acute withdrawal. Non-pharmacological treatments directed at rooming-in, skin-to-skin and breastfeeding are also advantageous (MacMillan 2018; Wachman 2018), and may be challenging for clinicians to facilitate. The questions to be addressed by this review are:

1. what is the evidence, from randomised controlled trials (RCTs) and quasi-RCTs, that a sedative is better than control in the treatment of clinically significant NAS due to opioid withdrawal (control may be placebo, the usual management of the newborn infant or any form of non-pharmacological treatment designed to settle the infant and mother, establish feeding and facilitate mother–infant interactions)? and
2. what is the evidence for use of a specific sedative from trials comparing different types of sedatives?

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 in the infant; improve mother–infant interaction and reduce the incidence of infant mortality and abnormal neurodevelopment. This is an update of a previous review (Osborn 2002; Osborn 2005; Osborn 2010). A separate review, examines the evidence for the use of opioids in infants with NAS due to opioid withdrawal (Zankl 2021).

OBJECTIVES

To assess the effectiveness and safety of using a sedative versus control (placebo, usual treatment or non-pharmacological treatment) for NAS due to withdrawal from opioids and determine which type of sedative is most effective and safe for NAS due to withdrawal from opioids.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published and unpublished trials using random or quasi-random patient allocation. Cluster randomised trials where the unit of randomisation was a group of participants were eligible. We excluded cross-over trials.

Types of participants

We included infants in the neonatal period with NAS born to mothers with an opioid dependence. Withdrawal may have been 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. **Sedative versus placebo or no treatment/usual care:**
   a. phenobarbital versus placebo or no treatment/usual care;
   b. diazepam versus placebo or no treatment/usual care;
   c. chlorpromazine versus placebo or no treatment/usual care; or
   d. clonidine versus placebo or no treatment/usual care.

2. **Sedative versus other sedative –specific comparisons:**
   a. phenobarbital versus diazepam;
   b. phenobarbital versus chlorpromazine;
   c. phenobarbital versus clonidine;
   d. diazepam versus chlorpromazine;
   e. diazepam versus clonidine or
   f. chlorpromazine versus clonidine.
3. **Sedative versus sedative in opioid treated infants:**
   a. including any of the comparisons documented above in 2.
4. **Addition of a sedative in opioid treated infants.**
5. **Addition of an opioid versus other sedative in sedative treated infants:**
   a. including any of the comparisons documented above in 2.

Types of outcome measures

Outcomes are reported to discharge or latest time reported as appropriate.

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 (paroxysmal alterations in neurological function. This could have been behavioural, motor or autonomic (Volpe 2008). Neonatal seizures could have been clinical (with no EEG correlate), electroclinical (clinical associated with EEG findings) or electrographic (no clinical correlate) (Mizrahi 1987).)
3. Neonatal (latest time reported to discharge) and infant mortality.
4. Neurodevelopmental disability at 18 months' postnatal age or greater defined as a neurological abnormality including any one of the following:
   a. cerebral palsy on clinical examination;
   b. developmental delay more than two standard deviations (SDs) below population mean on a standardised test of development;
   c. blindness (visual acuity less than 6/60) or
   d. deafness (any hearing impairment requiring amplification) at any time after term corrected.

Secondary outcomes

1. Time to control of NAS (control of symptoms or reduction of NAS score to a clinically 'safe' level).
2. Days' admission to a newborn nursery.
3. Days' hospitalisation.
4. Days' pharmacological treatment of NAS.
5. Days to establishment of full sucking feeds.
6. Success of breastfeeding (exclusive breastfeeding; partial breastfeeding – at discharge; one, four and six months).
7. Postnatal growth failure (weight less than 10th percentile at discharge).
8. Infant growth: up to age one month; at latest time measured (definition = from one month to time of discharge); to follow-up beyond 12 months:
   a. weight gain (grams per kilogram per day);
   b. linear growth (centimetres per week);
   c. head circumference (centimetres per week).
9. Change of standardised growth: up to age one month; at latest time measured (definition = from one month to time of discharge); to follow-up beyond 12 months:
   a. change in weight z-score;
   b. change in length z-score;
   c. change in head circumference z-score.
10. Adverse effects occurring after commencement of therapy:
    a. apnoea;
    b. need for resuscitation;
    c. need for mechanical ventilation.
11. Disruption to the mother–infant relationship (e.g. separation of mother and infant, admission to a newborn nursery, failure to successfully breastfeed, maternal depression or parental dissatisfaction).
12. Out-of-home care (foster care; adoption).

Search methods for identification of studies

Electronic searches

We conducted a comprehensive updated search in September 2020, including: Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 9) in the Cochrane Library, and Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (2010 to 17 September 2020). We included the search strategies for each database in Appendix 1. We applied no language restrictions.

We searched clinical trial registries for ongoing or recently completed trials. We searched the WHO's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/), and the U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov), via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry (www.isrctn.com/), for any unique trials not found through the Cochrane CENTRAL search.

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as a *RCT* or as *Not an RCT*; and the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs.

For more information about Screen4Me and the evaluations that have been performed, see the Screen4Me webpage on the Cochrane Information Specialist's portal: community.cochrane.org/organizational-info/resources/resources-groups/information-specialists-portal/crs-videos-and-quick-reference-guides#Screen4Me. In addition, there is more detailed information regarding evaluations of the Screen4Me components in the following publications: Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

This is the third update of this review. Our previous search details are listed in Appendix 2.

Searching other resources

We included in our search strategy searches of citations of included studies for references to other trials; previous reviews including cross-references; abstracts and conferences and symposia proceedings of Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society of Paediatric Research to 2019) and Perinatal Society of Australia and New Zealand from 2010 to 2019. We attempted to contact the corresponding investigator for information if we identified any unpublished trials. We considered unpublished studies or studies only reported as abstracts as eligible for inclusion in the review if methods and data could be confirmed by the study author.

Data collection and analysis

We used the standard methods of Cochrane as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), and recommended by Cochrane Neonatal.

Selection of studies

Three review authors (AZ, JM, DO) independently assessed all potential studies identified as a result of the search strategy for inclusion. We resolved any differences of opinion through discussion.

Data extraction and management

For the 2021 review update, three review authors (AZ, JM, DO) independently extracted data using a specifically designed data extraction sheet to manage information. We resolved any differences in opinion through discussion with data then entered into Review Manager 5 (Review Manager 2020), and cross-checked for accuracy. One review author (DO) extracted data and requested additional data from the authors of three trials (Finnegan 1984a; Kaltenbach 1986; Khoo 1995), for the 2010 review update (Osborn 2010), which remains current for this review. Two review authors (DO and HJ) extracted data independently then compared data and resolved differences for the 2005 update (Osborn 2005), and 2002 review (Osborn 2002).

Assessment of risk of bias in included studies

Three review authors (AZ, JM, DO) independently assessed the risk of bias (low, high or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011):

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective reporting (reporting bias);
7. any other bias.

We resolved any disagreements by discussion. See Appendix 3 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We conducted statistical analyses using the statistical package in Review Manager 5 (Review Manager 2020). We summarised the data in a meta-analysis if they were sufficiently homogeneous, both clinically and statistically.

Dichotomous data

For dichotomous data, we presented results using risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB), or an additional harmful outcome (NNTH) with 95% CIs if there is a statistically significant change in RD.

Continuous data

For continuous data, we used the mean difference (MD) when outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as median and interquartile range (IQR) and data passed the test of skewness, we converted mean to median and estimated the SD as IQR/1.35.

Unit of analysis issues

The unit of randomisation was the intended unit of analysis. Cluster-RCTs were eligible.

Cluster-randomised trials

We intended to analyse cluster-randomised trials in the analyses along with individually randomised trials. We intended to analyse them using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible) or from another source. If ICCs from other sources were used, this was reported and a sensitivity analysis conducted to investigate the effect of variations in the ICC. Where cluster-randomised trials and individually randomised trials were identified, we synthesised relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between study designs, and if interaction between effect of the intervention and choice of randomisation unit unlikely.

Dealing with missing data

We obtained missing data from the study authors when possible. Where missing data could not be obtained, we examined the effect of excluding trials with substantial missing data (e.g. greater than 10% losses) in sensitivity analyses.

We attempted to overcome potential bias from missing data (greater than 10% losses) using one or more of the following approaches:

1. whenever possible, contacting the original investigators to request missing data;
2. performing sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made (e.g. the effect of excluding trials with substantial missing data (greater than 10% losses));
3. addressing the potential impact of missing data (greater than 10% losses) upon the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We used Review Manager 5 to assess the heterogeneity of treatment effects between trials (Review Manager 2020), using the two statistical methods described below.

1. The Chi^2 test, to assess whether observed variability in effect sizes between studies was greater than would be expected by chance. Since this test has low power when the number of studies included in the meta-analysis was small, we planned to set the probability at the 10% level of significance.
2. The I^2 statistic to ensure that pooling of data was valid. We considered a degree of heterogeneity less than 25% to represent no heterogeneity, 25% to 49% to represent minimal heterogeneity, 50% to 74% to represent moderate heterogeneity and 75% or greater to represent substantial or high heterogeneity.

We assessed the source of heterogeneity using sensitivity and subgroup analysis, looking for evidence of bias or methodological differences between trials where there was evidence of apparent or statistical heterogeneity.

Assessment of reporting biases

We assessed reporting bias by comparing the stated primary outcomes and secondary outcomes and reported outcomes of each study. Where study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias. We documented studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes in the Characteristics of included studies table. We used the funnel plots to screen for publication bias where there were sufficient numbers of studies (more than 10) reporting the same outcome. If publication bias was suggested by a significant asymmetry of the funnel plot on visual assessment, we planned to incorporate this in our assessment of the certainty of the evidence.

Data synthesis

We carried out statistical analysis using Review Manager 5 (Review Manager 2020). We used the fixed-effect model Mantel-Haenszel meta-analysis for dichotomous outcomes and fixed-effect model inverse variance meta-analysis for combining data where trials examined the same intervention and the populations and methods of the trials were similar. We intended to assess the possible source(s) of heterogeneity using subgroup and sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses included the following identified subcategories:

1. according to type of sedative used (e.g. clonidine, a benzodiazepine, barbiturate or neuroleptic agent);
2. according to type of non-pharmacological treatment used;
3. according to whether trials included mothers with only opioid dependence or with multiple drug use;
4. according to age of the infants at treatment (e.g. early versus delayed treatment) and duration of treatment (e.g. short versus long course).

All outcomes were eligible for inclusion in subgroup analysis.

Sensitivity analysis

We planned to undertake sensitivity analyses on the basis of methodological quality. Trials of good methodology had adequate randomisation and allocation concealment, blinding of treatment and greater than 90% follow-up on an intention-to-treat basis.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes:

1. treatment failure;
2. seizures;
3. neonatal and infant mortality;
4. neurodevelopmental disability;
5. days' hospitalisation;
6. days' pharmacological treatment of NAS;
7. adverse events.

Three review authors (AZ, JM, DO) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create six 'Summary of findings' tables to report the certainty of the evidence for each comparison.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

1. High certainty: further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low certainty: we are very uncertain about the estimate.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies tables.

Results of the search

The search was updated in September 2020 (Figure 1; Figure 2). We excluded 34 studies (34 reports) (see Characteristics of excluded studies table). Ten studies (21 reports) were eligible for inclusion (see Characteristics of included studies table). One study of clonidine as adjunct to morphine is ongoing (see Characteristics of ongoing studies table).

Figure 1. Screen4Me summary diagram. RCT: randomised controlled trial.

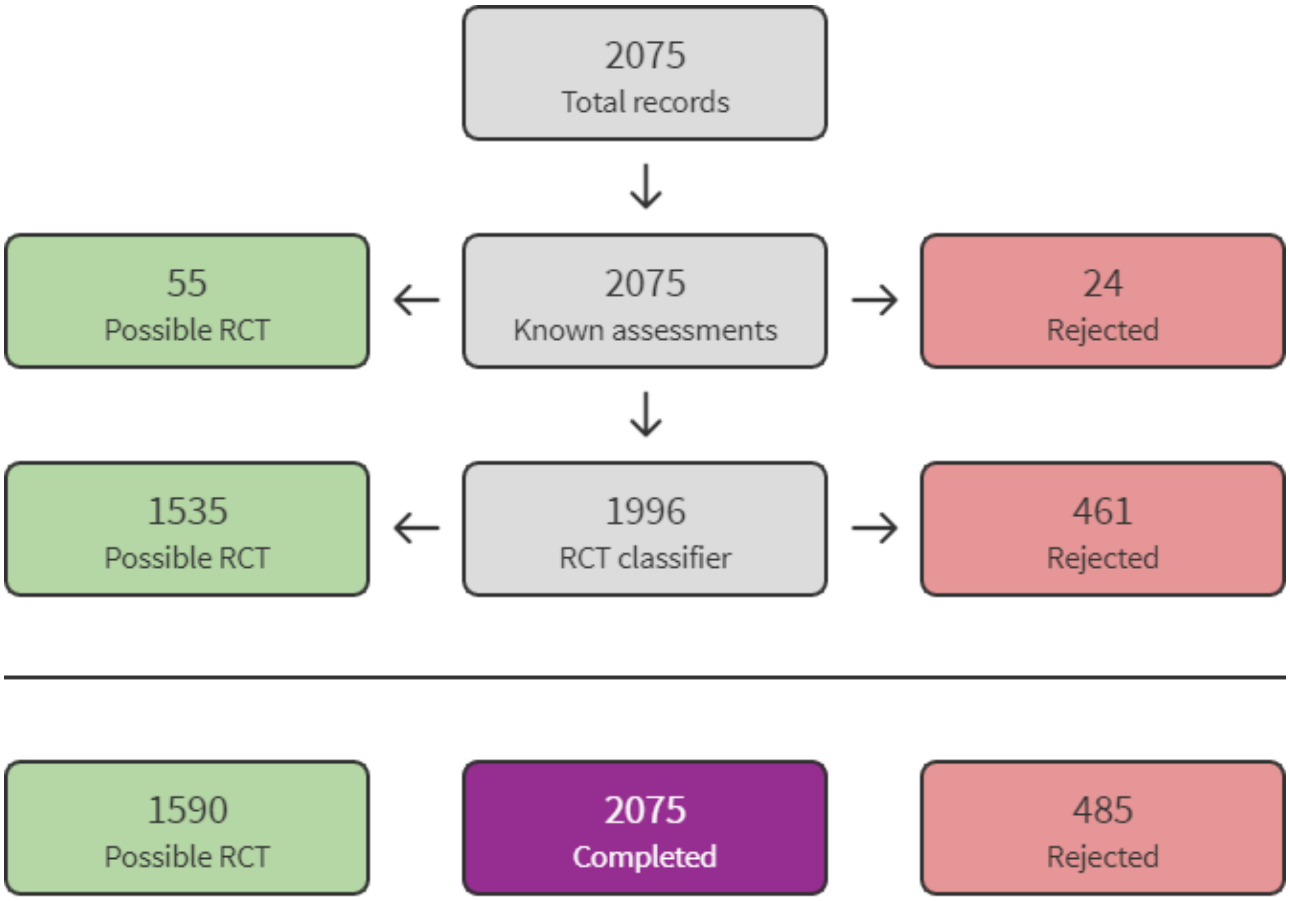


Figure 2. Study flow diagram: review update

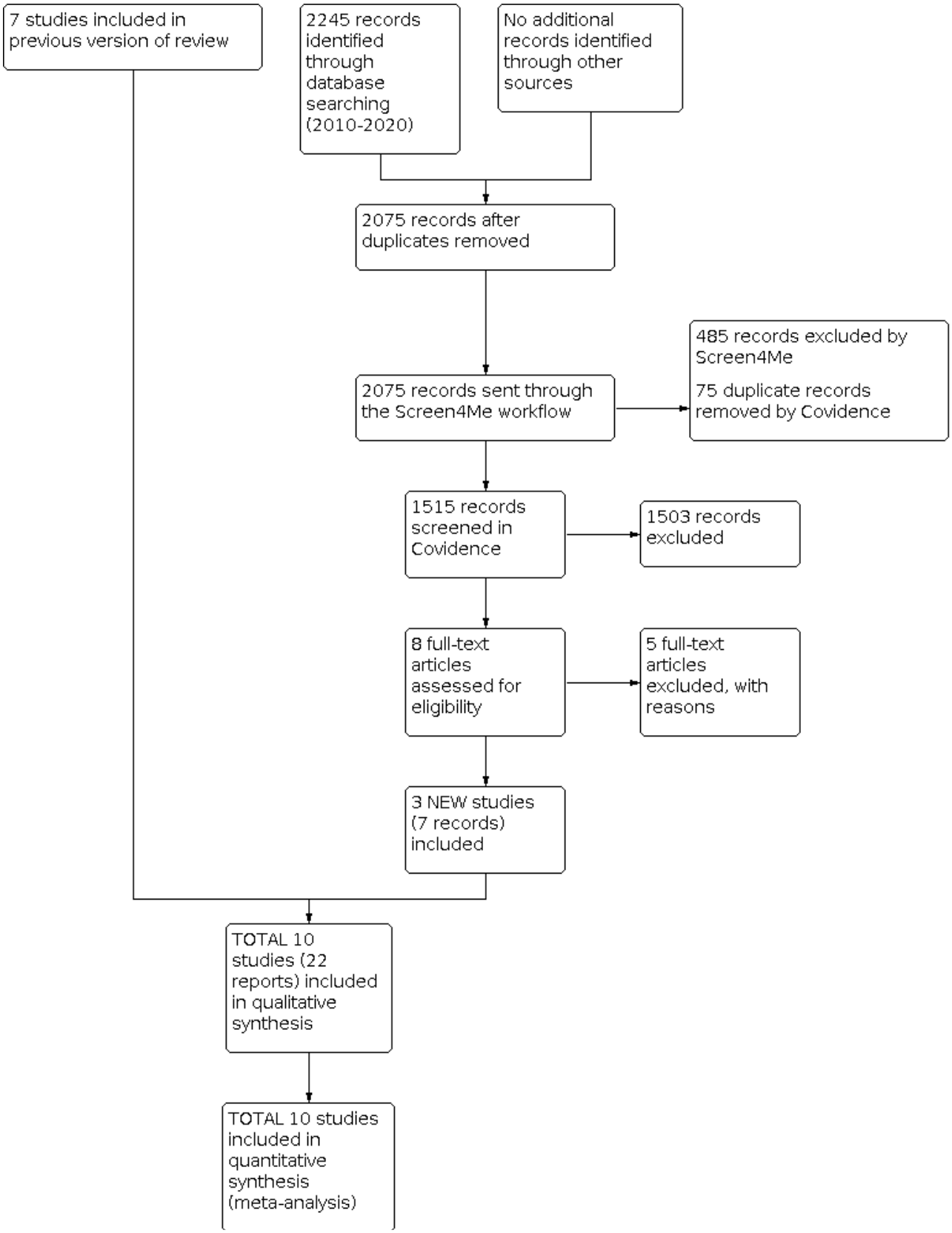
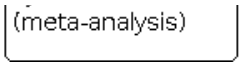


Figure 2. (Continued)



Included studies

We assessed 10 studies as eligible for inclusion (Agthe 2009; Brusseau 2020; Coyle 2002; Finnegan 1984a; Kahn 1969; Kaltenbach 1986; Khoo 1995; Madden 1977; Surran 2013; Zimmermann 2020). Two studies may be sequential reports in which some of the participants were the same (author communication) (Finnegan 1984a; Kaltenbach 1986). In view of this uncertainty, outcomes that are reported by Kaltenbach 1986 that were previously reported by Finnegan 1984a were not included in the meta-analyses tables, but were reported separately in the text (see Results).

Participants

One study was conducted in Australia (Khoo 1995), one in Switzerland (Zimmermann 2020), and the remainder in the USA. The 10 studies enrolled 581 infants. All studies enrolled infants experiencing NAS born to mothers using opioids and other drugs. One study reported infants of mothers using only opioids separately (Finnegan 1984a). One study excluded those infants born to mothers who disclosed using benzodiazepines (Surran 2013). Eight studies used the Neonatal Abstinence Scoring System (NASS) or a modification thereof with treatment generally commenced when the mean of three consecutive scores was 8 or greater or a single score was 12 or greater (Agthe 2009; Brusseau 2020; Coyle 2002; Finnegan 1984a; Kaltenbach 1986; Khoo 1995; Surran 2013; Zimmermann 2020). Two studies had modifications of criteria. Surran 2013 commenced treatment when two consecutive modified NASS scores were 8 or greater, and Zimmermann 2020 when two consecutive scores were greater than 9 or once scored greater than 14. Kahn 1969 used a scoring system based on a grading system for tremors and irritability. Madden 1977 reported using clinical decision to treat and did not use a scoring system.

Interventions

Six studies titrated the dosage of treatment interventions in both arms according to a nominated institutional NAS scoring system (Finnegan 1984a; Kahn 1969; Kaltenbach 1986; Khoo 1995; Surran 2013; Zimmermann 2020), or 'clinical assessment' for one study (Madden 1977). Agthe 2009 titrated the dose of dilute tincture of opium (DTO) in both groups to the modified NASS score and compared the addition of a fixed dose of clonidine versus placebo. Brusseau 2020 compared clonidine titrated to the NASS score versus phenobarbital adjusted to obtain a serum trough concentration of 25 µg/mL to 30 µg/mL. Coyle 2002 compared phenobarbital adjusted to obtain a serum trough level 20 µg/mL to 30 µg/mL to placebo. Five studies did not report adjunctive treatments used when allocated first treatment drug failed to control NAS (Agthe 2009; Coyle 2002; Finnegan 1984a; Kahn 1969; Madden 1977). Five studies used the alternative primary study treatment when allocated treatment failed (Brusseau 2020; Kaltenbach 1986; Khoo 1995; Surran 2013; Zimmermann 2020).

Sedative versus placebo or no treatment/usual care

Phenobarbital versus supportive care

Khoo 1995 compared phenobarbital 15 mg/kg (intramuscular loading dose) then 6 mg/kg/day orally in two divided doses, titrated to score up to maximum 10 mg/kg/day versus supportive care only.

Sedative versus other sedative

Phenobarbital versus diazepam

Finnegan 1984a compared phenobarbital with or without a loading dose of 20 mg/kg with maintenance 5 mg/kg/day to 10 mg/kg/day titrated against score, until control of NAS was obtained or serum concentration greater than 70 µg/mL or evidence of toxicity, versus diazepam (dose not reported).

Kaltenbach 1986 compared phenobarbital loading dose followed by maintenance titrated to score versus phenobarbital maintenance only (doses not reported but likely to be same at reported by Finnegan 1984a) versus diazepam (dose not reported).

Madden 1977 compared phenobarbital 5 mg/kg/day to 8 mg/kg/day (three divided doses) versus diazepam 0.5 mg to 2.0 mg eight hourly with doses "tailored day to day".

Phenobarbital versus chlorpromazine

Kahn 1969 compared phenobarbital short course 8.4 mg/kg/day (four divided doses) for four days then stopped versus phenobarbital long course 8.4 mg/kg/day (four divided doses) for 10 days then reduced by one third every second day and stopped day 16 versus chlorpromazine short course 2.8 mg/kg/day (four divided doses) for four days then stopped versus chlorpromazine long course 2.8 mg/kg/day (four divided doses) for 10 days then gradual reduction over next six days.

Zimmermann 2020 compared chlorpromazine starting dose 0.5 mg/kg four hourly to maximal 1 mg/kg four hourly (3 mg/kg/day to 6 mg/kg/day) versus phenobarbital loading dose 10 mg/kg then maintenance 0.83 mg/kg four hourly to maximum 1.66 mg/kg four hourly (5 mg/kg/day to 10 mg/kg/day), both titrations occurred if the NASS score was greater than 9.

Phenobarbital titration with loading dose versus phenobarbitone titration alone

Kaltenbach 1986 compared phenobarbital loading dose followed by maintenance titrated to score versus phenobarbital maintenance only (doses not reported).

Sedative versus sedative in opioid-treated infants

Clonidine and morphine versus phenobarbital and morphine

Brusseau 2020, in infants who failed morphine therapy (morphine dose greater than 0.16 mg every three hours or failed two weaning attempts), compared clonidine 6 µg/kg/day divided every three hours titrated to score in increments of 1.5 µg/kg/day every 24 hours up to maximum 12 µg/kg/day versus phenobarbital 20 mg/kg loading dose divided 12 hourly, then 2.5 mg/kg 12 hourly adjusted to obtain a trough 25 to 30 µg/mL.

Surran 2013, in infants treated with morphine 0.32 mg/kg/day to a maximum 0.8 mg/kg/day titrated to scores, compared clonidine 6 µg/kg/day to a maximum 12 µg/kg/day according to score, given every six hours in divided daily dose, versus phenobarbital 6 mg/kg/day to a maximum 12 mg/kg/day given every eight hours in divided daily dose titrated according to score.

Addition of a sedative in opioid-treated infants

DTO and clonidine versus DTO and placebo

Agthe 2009, in infants treated with DTO 0.48 mg/day titrated to maximum 2.88 mg/day, compared oral clonidine 1 µg/kg every four hours (6 µg/kg/day) versus placebo (no titration).

DTO and phenobarbitone versus DTO and placebo

Coyle 2002, in infants treated with DTO (morphine 0.4 mg/mL) 0.12 mg/kg/day to 0.16 mg/kg/day, compared phenobarbital loading dose 30 mg/kg (given as three oral doses every 12 hours) and maintenance 5 mg/kg/day, adjusted to maintain weekly serum level 20 mg/dL to 30 mg/dL, versus placebo.

Outcomes

See Characteristics of included studies table for details of outcome reporting for each study.

Primary outcomes

One study reported mortality after discharge (Agthe 2009), and one study reported mortality to discharge (Surran 2013). Kahn 1969 reported mortality but not according to allocated group. No study reported long-term neurodevelopmental outcomes according to treatment group as allocated. Kaltenbach 1986 reported the Bayley Scale of Mental Development at six months according to treatments received, not allocated. Coyle 2002 reported short-term neurodevelopmental and behavioural outcomes of a combined group of term and preterm infants in abstract form. The principal publication reported no neurodevelopmental data.

Seven studies, reporting treatment failure, used a standardised score to determine response to treatment (Agthe 2009; Brusseau 2020; Finnegan 1984a; Kaltenbach 1986; Khoo 1995; Surran 2013; Zimmermann 2020). Madden 1977 reported need for a second agent but did not use a standardised score. One study used a standardised score, with treatment failure taken as persistence of symptoms greater than four days (Kahn 1969). Agthe 2009 reported clinical seizures although criteria for seizures were not described. All infants received an EEG after administration of phenobarbital and no infant had an abnormal EEG. Coyle 2002 reported no infant in the study had seizures. Kahn 1969 reported myoclonic jerks that were not considered seizures by the attending clinician. These are not reported as seizures in this review. Khoo 1995 reported that infants developed myoclonic jerks with no infant being diagnosed with a clinical seizure or a seizure confirmed on EEG. Surran 2013 reported one infant with seizure later diagnosed as a benign familial seizure. Zimmermann 2020 reported no infant had a clinical seizure.

Secondary outcomes

Secondary outcomes were all incompletely reported. The most commonly reported outcomes were days' hospitalisation by eight studies (Agthe 2009; Brusseau 2020; Coyle 2002; Finnegan 1984a; Khoo 1995; Madden 1977; Surran 2013; Zimmermann 2020), days' pharmacological treatment by six studies (Agthe 2009; Brusseau 2020; Kahn 1969; Khoo 1995; Madden 1977; Surran 2013), and adverse events (treatment related) by four studies (Agthe 2009; Brusseau 2020; Surran 2013; Zimmermann 2020).

Excluded studies

We excluded 34 studies.

See Characteristics of excluded studies for details.

Ongoing studies

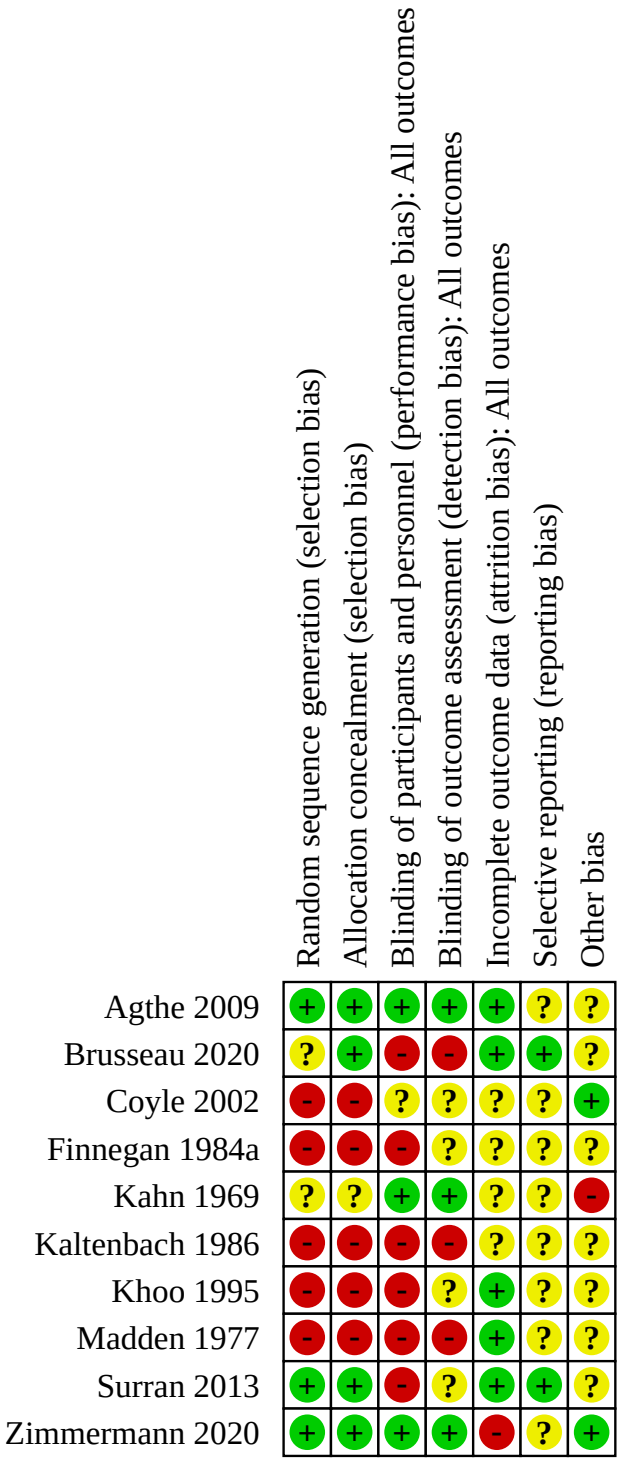
One study, comparing clonidine in addition to oral morphine versus placebo in addition to oral morphine is ongoing (NCT03762317).

See Characteristics of ongoing studies table for details.

Risk of bias in included studies

See Characteristics of included studies table for risk of bias assessments and risk of bias summary (Figure 3).

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



One study, with adequate randomisation and allocation concealment, blinding of treatment and greater than 90% follow-up on an intention-to-treat basis was at low risk of bias for all reported outcomes (Agthe 2009). Zimmermann 2020 was at low risk of bias for reporting of treatment failure, but high risk of bias for other outcomes due to incomplete outcome reporting.

Allocation

We assessed three studies at low risk of selection bias (Agthe 2009; Surran 2013; Zimmermann 2020). Brusseau 2020 was at low risk of allocation concealment but did not report method of sequence generation so overall risk of selection bias was unclear. Kahn 1969 did not report allocation methods so overall risk of selection bias was unclear. We assessed five studies at high risk of selection bias (Coyle 2002; Finnegan 1984a; Kaltenbach 1986; Khoo 1995; Madden 1977). Coyle 2002 prospectively matched treatment groups first by NASS score greater than 7; if there was no match then the infant was randomly assigned although the random method was not reported. Kahn 1969 reported random allocation to treatment but did not report method of random allocation. Finnegan 1984a 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. Madden 1977 reported random allocation but method was not reported and three infants were allocated at clinician's discretion so we assessed it at high risk. Several studies had sizeable and largely unexplained differences in the numbers of infants allocated to each group (Finnegan 1984a; Kaltenbach 1986; Khoo 1995). Finnegan 1984a communicated that an interim analysis found the diazepam group had excessive complications (somnolence and respiratory depression), so enrolment in this group was stopped. Therefore, patient allocation in the diazepam group was non-contemporaneous with the other groups so was at high risk of bias.

Blinding

Four studies reported blinding of treatment (Agthe 2009; Coyle 2002; Kahn 1969; Zimmermann 2020). Agthe 2009 reported use of a saline placebo, Kahn 1969 and Zimmermann 2020 used identical appearing solutions at a standard volume and frequency for dosing; these were at low risk of performance and detection bias. Coyle 2002 used a placebo and a standardised regimen for titrating doses, but weekly phenobarbital levels were revealed to the treating physician so the study was at unclear risk of performance and detection bias. Three studies did not blind treatment (Finnegan 1984a; Kaltenbach 1986; Madden 1977). No other study reported blinding of treatment and given the variable treatment regimens in each of the trials, it is unlikely this was possible.

Incomplete outcome data

Three studies accounted for all infants (Agthe 2009; Madden 1977; Surran 2013), although Agthe 2009 excluded one infant (clonidine group) who had a seizure from the analysis of treatment failure. Surran 2013 excluded two infants from the analysis in the clonidine group as one infant was exposed to a benzodiazepine in utero and the other infant experienced familial seizures requiring treatment with phenobarbital. Coyle 2002 reported one postrandomisation loss. In addition, the peer-reviewed publication did not report the preterm infants who were reported in the abstract publication. Finnegan 1984a did not report losses so attrition bias is unclear. Kahn 1969 reported deaths of two untreated infants, but it was unclear whether this occurred before or after randomisation. One study did not report numbers entered so that any losses were unknown (Kaltenbach 1986). Khoo 1995 excluded three infants from analysis (one in the phenobarbital and two in the supportive therapy groups) and seven infants had no data available for time to regain birthweight. Madden 1977 reported separately, for duration of treatment and hospital stay, one infant randomised to phenobarbital who received a second drug. Zimmermann 2020 reported need for a second drug for all infants, but 16% did not receive the allocated intervention and other outcomes only reported in infants receiving treatment.

Selective reporting

Two studies had available trial registrations and were at low risk (Brusseau 2020; Surran 2013). Eight studies were at unclear risk as trial registrations were not available, were retrospective, descriptions were unclear, or a combination of these.

Other potential sources of bias

Two studies had no other concerns including balanced groups at allocation and were at low risk of other bias (Coyle 2002; Zimmermann 2020). Agthe 2009 reported infants in the clonidine and DTO group had significantly lower mean birthweight and was at unclear risk. Two studies reported stopping enrolment in the diazepam arm early due to an interim analysis demonstrating the possibility of adverse effects and were at unclear risk (Finnegan 1984a; Kaltenbach 1986). Kahn 1969 had asymmetric group sizes after allocation and baseline characteristics were not reported. 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

See: **Summary of findings 1** Phenobarbital versus supportive care for opioid withdrawal in newborn infants; **Summary of findings 2** Phenobarbital versus diazepam for opioid withdrawal in newborn infants; **Summary of findings 3** Phenobarbital versus chlorpromazine for opioid withdrawal in newborn infants; **Summary of findings 4** Phenobarbital and opioid versus opioid alone for opioid withdrawal in newborn infants; **Summary of findings 5** Clonidine and opioid versus opioid alone for opioid withdrawal in newborn infants; **Summary of findings 6** Clonidine and opioid versus phenobarbital and opioid for opioid withdrawal in newborn infants

Comparison 1. Phenobarbital versus supportive care (all infants)

One study compared phenobarbital versus supportive care (Khoo 1995). See Summary of findings 1.

Primary outcomes

(Analysis 1.1; Analysis 1.2)

Khoo 1995 reported no evidence of a difference in treatment failure (RR 2.73, 95% CI 0.94 to 7.94; 62 participants; very low-certainty evidence). No infant had a clinical seizure (62 participants; very low-certainty evidence). The study did not report neonatal or infant mortality, or neurodevelopmental disability.

Secondary outcomes

(Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7)

Khoo 1995 reported the following for infants treated with phenobarbital compared to supportive care: an increase in days' hospitalisation (MD 20.80, 95% CI 13.64 to 27.96; 62 participants; very low-certainty evidence), days' treatment (MD 17.90, 95% CI 11.98 to 23.82; 62 participants; very low-certainty evidence), no evidence of a difference in time to regain birthweight (MD −1.40, 95% CI −4.07 to 1.27; 55 participants), increase in duration of stay in special care nursery (MD 23.13 days, 95% CI 15.87 to 30.39; 62 participants) and a reduction in duration of supportive care per day (MD −162.10 minutes, 95% CI −249.14 to −75.06; 62 participants). The study did not report adverse events.

Comparison 2. Phenobarbital versus diazepam (all infants)

Two studies compared phenobarbital versus diazepam (Finnegan 1984a; Madden 1977). See Summary of findings 2.

Primary outcomes

(Analysis 2.1)

Two studies found a reduction in treatment failure for infants treated with phenobarbital compared to diazepam (RR 0.39, 95% CI 0.24 to 0.62; 139 participants; I^2 = 52%; moderate heterogeneity; low-certainty evidence) (Finnegan 1984a; Madden 1977). The studies did not report neonatal or infant mortality, or neurodevelopmental disability.

Secondary outcomes

(Analysis 2.2; Analysis 2.3)

Madden 1977 reported no evidence of a difference in days' hospitalisation (MD 3.89, 95% CI −1.20 to 8.98; 32 participants; low-certainty evidence) or days' treatment (MD 4.30, 95% CI −0.73 to 9.33; 31 participants; low-certainty evidence). The study did not report adverse events.

Comparison 3. Phenobarbital versus diazepam (infants of mothers using only opioids)

One study comparing phenobarbital versus diazepam reported infants of mothers using only opioids separately (Finnegan 1984a).

Primary outcomes

(Analysis 3.1)

Finnegan 1984a reported a reduction in treatment failure for infants treated with phenobarbital compared to diazepam (RR 0.55, 95% CI 0.35 to 0.85; 31 participants). The study reported no other primary outcomes.

Secondary outcomes

The study reported no secondary outcomes.

Comparison 4. Phenobarbital versus diazepam (infants of mothers using opioids and other drugs)

One study comparing phenobarbital versus diazepam reported infants of mothers using opioids and other drugs separately (Finnegan 1984a).

Primary outcomes

(Analysis 4.1)

Finnegan 1984a reported a reduction in treatment failure for infants treated with phenobarbital compared to diazepam (RR 0.19, 95% CI 0.09 to 0.43; 76 participants). The study reported no other primary outcomes.

Secondary outcomes

The study reported no secondary outcomes.

Comparison 5. Phenobarbital versus chlorpromazine (all infants)

Two studies compared phenobarbital versus chlorpromazine (Kahn 1969; Zimmermann 2020. See Summary of findings 3.

Primary outcomes

(Analysis 5.1; Analysis 5.2; Analysis 5.3)

Data from two studies found a reduction in treatment failure favouring phenobarbital (RR 0.55, 95% CI 0.33 to 0.92; 138 participants; I^2 = 0%; very low-certainty evidence), and no infant had a seizure (140 participants; very low-certainty). Kahn 1969 reported no infant was treated with a second drug (38 participants). The studies did not report neonatal or infant mortality and neurodevelopmental disability.

Secondary outcomes

(Analysis 5.4; Analysis 5.5)

Zimmermann 2020 reported no evidence of a difference in days' hospitalisation (MD 7.00 days, 95% CI −3.46 to 17.46; 87 participants; low-certainty evidence) and none of 100 infants had an adverse event (low-certainty evidence).

Comparison 6. Phenobarbital titration with loading dose versus phenobarbital titration alone (all infants)

One study compared phenobarbital titration with loading dose versus phenobarbital titration alone (Kaltenbach 1986).

Primary outcomes

(Analysis 6.1)

Kaltenbach 1986 reported no evidence of a difference in treatment failure (RR 1.10, 95% CI 0.59 to 2.07; 36 participants). The study did not report neonatal or infant mortality, or neurodevelopmental disability.

Secondary outcomes

The study reported no secondary outcomes.

Comparison 7. Short versus long course of phenobarbital

One study compared short (four days) versus long (10 days) course of phenobarbital (Kahn 1969).

Primary outcomes

(Analysis 7.1)

Kahn 1969 reported no evidence of a difference in treatment failure (RR 0.58, 95% CI 0.04 to 7.94; 19 participants). The study reported no other primary outcomes.

Secondary outcomes

The study reported no secondary outcomes.

Comparison 8. Short versus long course of chlorpromazine

One study compared short (four days) versus long course (10 days) of chlorpromazine (Kahn 1969).

Primary outcomes

(Analysis 8.1)

Kahn 1969 reported no evidence of a difference in treatment failure between treatment regimens (RR 3.64, 95% CI 0.52 to 25.41; 19 participants). The study did not report neonatal or infant mortality, or neurodevelopmental disability.

Secondary outcomes

The study reported no secondary outcomes.

Comparison 9. Phenobarbital and opioid versus opioid alone

One study compared phenobarbital and DTO versus DTO alone (Coyle 2002). See Summary of findings 4.

Primary outcomes

(Analysis 9.1; Analysis 9.2)

Coyle 2002 reported no treatment failure or clinical seizure in either group (20 participants; very low-certainty evidence).

Secondary outcomes

(Analysis 9.3; Analysis 9.4)

Coyle 2002 reported a reduction in percent of time the NASS score was 8 or greater (MD –5.00, 95% CI –9.84 to –0.16; 20 participants) and days' hospitalisation (MD –43.50 days, 95% CI –59.18 to –27.82; 20 participants; low-certainty evidence). The study reported no other outcomes.

Comparison 10. Clonidine and opioid versus opioid alone

One study compared clonidine and DTO versus DTO alone (Agthe 2009). See Summary of findings 5.

Primary outcomes

(Analysis 10.1; Analysis 10.2; Analysis 10.3)

Agthe 2009 reported no evidence of a difference in treatment failure (RR 0.09, 95% CI 0.01 to 1.59; 80 participants; very low-certainty evidence), although all five infants with treatment failure were in the DTO alone group. There was no evidence of a difference in seizures (RR 0.14, 95% CI 0.01 to 2.68; 80 participants; very low-certainty evidence), although all three infants with seizures were in the DTO alone group. There was no evidence of a difference in mortality after discharge (RR 7.00, 95% CI 0.37 to 131.28; 80 participants; very low-certainty evidence), although all three infants who died were in the clonidine and DTO group. The causes of death confirmed by autopsy were myocarditis, sudden infant death syndrome and homicide (methadone overdose). The study did not report neurodevelopmental disability.

Secondary outcomes

(Analysis 10.4; Analysis 10.5; Analysis 10.6; Analysis 10.7)

Agthe 2009 reported no evidence of a difference in days' treatment (MD –4.00 days, 95% CI –8.33 to 0.33; 80 participants; very low-certainty evidence), maximum weight loss (MD –0.88%, 95% CI –2.33 to 0.57; 80 participants), one adverse event (supraventricular tachycardia) in the clonidine and opioid group (RR 3.00, 95% CI 0.13 to 71.51; 80 participants; very low-certainty evidence), and seven infants in the clonidine and opioid group with rebound NAS after stopping treatment (RR 15.00, 95% CI 0.89 to 254.13; RD 0.17, 95% CI 0.05 to 0.30; 80 participants).

Comparison 11. Clonidine and opioid versus phenobarbital and opioid

Two studies compared clonidine and opioid versus phenobarbital and opioid (Brusseau 2020; Surran 2013). Brusseau 2020 compared clonidine versus phenobarbitone in infants who had failed morphine treatment. Surran 2013 commenced treatment of infants with NAS with clonidine and morphine versus phenobarbital and morphine. See Summary of findings 6.

Primary outcomes

(Analysis 11.1; Analysis 11.2; Analysis 11.3)

Data from two studies found no evidence of a difference in treatment failure (RR 2.27, 95% CI 0.98 to 5.25; 93 participants; I^2 = 0%; very low-certainty evidence). Surran 2013 reported one infant in the clonidine and morphine group had a seizure (RR 3.00, 95% CI 0.13 to 71.15; 68 participants; very low-certainty evidence) and no infant died before discharge (68 participants; very low-certainty evidence). No studies reported neurodevelopmental disability.

Secondary outcomes

(Analysis 11.4; Analysis 11.5; Analysis 11.6)

Data from two studies found an increase in days' hospitalisation and days' treatment with phenobarbital and opioid versus clonidine and opioid (hospitalisation: MD 7.13, 95% CI 6.38 to 7.88; 91 participants; I^2 = 0%; low-certainty evidence; treatment: MD 7.57, 95% CI 3.97 to 11.17; 91 participants; I^2 = 0%; low-certainty evidence). There was no evidence of a difference in adverse events (RR 1.55, 95% CI 0.44 to 5.40; 93 participants; I^2 = 77%; high heterogeneity; very low-certainty evidence). Brusseau 2020 reported 6/14 infants in the clonidine and morphine group experienced adverse events including hypotension, rebound hypertension and rebound NAS. Surran 2013 reported 3/34 infants were oversedated in the phenobarbital and morphine group.

Other comparisons

There were no studies that compared diazepam and chlorpromazine.

Comparison 12. Sensitivity analysis

One study, with adequate randomisation and allocation concealment, blinding of treatment and greater than 90% follow-up on an intention-to-treat basis, was at low risk of bias for all

reported outcomes. Zimmermann 2020 was at low risk of bias for reporting of treatment failure, seizures and adverse events, but high risk of bias for other reported outcomes due to incomplete outcome reporting.

Prespecified summary of findings outcomes

1. Zimmermann 2020 compared phenobarbital versus chlorpromazine and reported no evidence of a difference in treatment failure (RR 0.61, 95% CI 0.35 to 1.06; 100 participants), and no infant had a seizure or an adverse event in either group (100 participants).
2. Agthe 2009 compared clonidine and DTO versus DTO alone and reported no evidence of a difference in treatment failure (RR 0.09, 95% CI 0.01 to 1.59; 80 participants), seizures (RR 0.14, 95% CI 0.01 to 2.68; 80 participants), mortality after discharge (RR 7.00, 95% CI 0.37 to 131.28; 80 participants), days' treatment (MD −4.00, 95% CI −8.33 to 0.33; 80 participants) or adverse events (RR 3.00, 95% CI 0.13 to 71.51; 80 participants).

DISCUSSION

Summary of main results

Phenobarbital versus supportive care

There was very low-certainty evidence from one study reporting outcomes of 62 infants of no difference in treatment failure from use of phenobarbital and supportive care versus supportive care alone. No infant had a clinical seizure. The study did not repot neonatal or infant mortality, neurodevelopmental disability and adverse events. There was very low certainty of evidence for a mean 21-day increase in hospitalisation and 18-day increase in treatment from use of phenobarbital compared to supportive care. There was no evidence of a difference in time to regain birthweight, but there was a mean 162-minute reduction in duration of supportive care per day for infants treated with phenobarbital compared to supportive care. We were unable to extract data for severity and duration of withdrawal.

Phenobarbital versus diazepam

There was low-certainty evidence from two studies reporting outcomes of 139 infants for a reduction in treatment failure from use of phenobarbital compared to diazepam (RD −0.29, 95% CI −0.45 to −0.14; NNTB 2 to 7). The studies did not report neonatal or infant mortality, neurodevelopmental disability and adverse events. There was low-certainty evidence from one study (32 infants) of no evidence of a difference in days' hospitalisation or days' treatment.

Phenobarbital versus chlorpromazine

Very low-certainty evidence from two studies reporting outcomes of 138 infants found a reduction in treatment failure (RD −0.19, 95% CI −0.34 to −0.03; NNTB 3 to 33) and no infant had a seizure in either group. The studies did not report neonatal or infant mortality and neurodevelopmental disability. Low-certainty evidence from one study (87 infants) reported no evidence of a difference in days' hospitalisation and none of the 100 infants had an adverse event.

Phenobarbital and opioid versus opioid alone

One study (20 infants) reported no treatment failures or clinical seizures in either group. The study did not report neonatal or infant mortality and neurodevelopmental disability. There was low-certainty evidence from one study for a reduction in percentage of time the NASS score was 8 or greater and a mean 44 days' reduction in hospitalisation for infants treated with phenobarbital and an opioid compared to an opioid alone. The study reported no other outcomes.

Clonidine and opioid versus opioid alone

Very low-certainty evidence from one study reporting outcomes of 80 infants found no evidence of a difference in treatment failure from clonidine and DTO versus DTO alone. However, all five infants with treatment failure were in the opioid alone group. There was very low-certainty evidence of no difference in seizures, although all three infants with seizures were in the DTO alone group. There was very low-certainty evidence of no difference in mortality after discharge, although all three infants who died were in the clonidine and DTO group. The causes of death were not attributed to treatment. The study did not report neurodevelopmental disability. There was very low-certainty evidence of no difference in days' treatment and maximum weight loss. One adverse event (supraventricular tachycardia) occurred in the clonidine and DTO group. Although there was no evidence of a difference in rebound neonatal abstinence syndrome after stopping treatment, all seven infants were in the clonidine and DTO group.

Clonidine and opioid versus phenobarbital and opioid

Very low-certainty evidence from two studies reporting 93 infants found no evidence of a difference in treatment failure. One study (68 infants) reported one infant in the clonidine and morphine group had a seizure and no infant died before discharge. The study did not report neurodevelopmental disability. Low-certainty evidence from two studies found a mean seven days' increase in hospitalisation and eight days' treatment with clonidine and an opioid compared to phenobarbital and opioid. There was very low-certainty evidence for no difference in adverse events. However, one study of clonidine versus phenobarbitone in infants who had failed morphine treatment reported 3/34 infants were oversedated in the phenobarbital and morphine group. One study of clonidine and opioid versus phenobarbital and opioid as initial treatment of neonatal abstinence syndrome reported 6/14 infants in the clonidine and morphine group experienced adverse events including hypotension, rebound hypertension and rebound NAS.

Phenobarbital dosing

One study (36 infants) compared phenobarbital titration with loading dose versus phenobarbital titration alone and reported no evidence of a difference in treatment failure. The same study (19 infants) compared a short (four days) versus long (10 days) course of phenobarbital and reported no evidence of a difference in treatment failure. The study did not report neonatal or infant mortality, neurodevelopmental disability and adverse events.

Chlorpromazine dosing

One study (19 infants) compared a short (four days) versus long (10 days) course of chlorpromazine and reported no evidence of a difference in treatment failure. The study did not report neonatal or infant mortality, neurodevelopmental disability and adverse events.

Overall completeness and applicability of evidence

This review should be considered in the context of the associated review 'Opioid treatment for opioid withdrawal in newborn infants' (Zankl 2021), which concluded "there is low certainty that the addition of an opioid increases duration of hospitalisation and treatment, but reduces days to regain birthweight and duration supportive care each day compared to supportive care alone. There is low to moderate certainty that use of an opioid reduces treatment failure compared to phenobarbital, diazepam or chlorpromazine, with low certainty of no effect on duration of hospitalisation or treatment. There is low to very low certainty for no difference in treatment failure according to type of opioid used. There is moderate certainty that buprenorphine reduces duration of hospitalisation and treatment compared to morphine. There are insufficient data to determine the effectiveness and safety of clonidine".

This review included 10 trials enrolling 581 infants with NAS secondary to maternal opioid use in pregnancy. All studies included infants of women using other drugs in addition to an opioid, although one study excluded infants exposed to benzodiazepines in utero. There were limited data differentiating infants exposed to opioid alone versus infants exposed to an opioid and another drug, so data are applicable to populations with high rates of multiple-drug use. All studies were conducted in high-income counties, one each in Australia and Switzerland, and the remainder in the USA. Eight studies used a validated neonatal abstinence syndrome score (NASS or modified NASS score) to determine pharmacological treatment. One study comparing short and long courses of phenobarbital and chlorpromazine used fixed-dosing schedules of each agent. Three studies monitored phenobarbital levels. Brusseau 2020 titrated phenobarbital dose to achieve a concentration of 25 µg/mL to 30 µg/mL, Coyle 2002 titrated phenobarbital dose to achieve a concentration of 20 µg/mL to 30 mg/dL, and Finnegan 1984a titrated phenobarbital dose to scores and limited increases to a level less than 70 µg/mL. All other studies titrated sedatives to NAS score without documented use of therapeutic monitoring.

Overall, outcomes were incompletely reported for all comparisons. No studies reported neurodevelopmental outcomes for any comparison. One study (62 infants) that compared phenobarbital and supportive care versus supportive care alone reported treatment failure and duration of hospitalisation and treatment, but did not report mortality and adverse events. Two studies (139 infants) compared phenobarbital versus diazepam and reported treatment failure. Only one study reported days' hospitalisation and days' treatment and no studies reported mortality, neurodevelopmental disability and adverse events. Two studies (138 infants) compared phenobarbital versus chlorpromazine and reported treatment failure and seizures, with only one study reporting days' hospitalisation, days' treatment and adverse events. Only one study assessed Only one study reported the addition of a sedative to an opioid versus an opioid alone when commencing pharmacological treatment for NAS; the studies used phenobarbital (20 infants) and clonidine (80 infants) with reporting more complete than for other outcomes. The one study of phenobarbital and DTO versus DTO alone reported treatment failure, seizures, mortality after discharge, days' treatment and adverse events. The one study of clonidine and morphine versus morphine alone reported treatment failure, seizures, mortality to discharge, days' hospitalisation, days' treatment and adverse events. Data for severity of withdrawal (percentage of time with a NASS score of 8 or greater) were from one study of phenobarbital and DTO versus DTO alone. There were no data for growth. One study of phenobarbital versus supportive care reported days to regain birthweight.

We prespecified the secondary outcome 'time to control of NAS (control of symptoms or reduction of NAS score to a clinically 'safe' level).' Although most studies used a NAS scoring system, severity of withdrawal from initiation of treatment was mostly unreported and no data were extractable for this outcome. Coyle 2002 reported a reduction in percentage of time with a NASS score of 8 or greater after commencement of treatment from use of DTO and phenobarbital versus DTO alone (Analysis 9.3). In this review, 'treatment failure' was a surrogate for control of NAS symptoms.

This review was limited to the comparisons stated. For comparisons of opioid versus sedative see the review 'Opioid treatment for opioid withdrawal in newborn infants' (Zankl 2021). We found no randomised trial of dexmedetomidine.

One study compared phenobarbital and supportive care versus supportive care alone. Supportive care included use of a dummy (pacifier), swaddling or close wrapping, small frequent feeds, close skin contact by carrying in sling and other methods. Other studies did not report specifics of usual or supportive care in sufficient detail to allow for subgroup analysis according to type(s) of non-pharmacological care as prespecified. For review of non-pharmacological care for opioid withdrawal in newborns, see Pahl 2020.

Apart from comparisons of addition of a loading dose of phenobarbital and long versus short course of phenobarbital or chlorpromazine, there were no comparisons of different dosage regimens of sedatives, and there were insufficient data to allow for subgroup analyses according to dosage used. Dosage regimens are reported in the Characteristics of included studies table.

Quality of the evidence

There was low or very low certainty of evidence for most comparisons and outcomes reported in this review with downgrading frequent for serious risk of bias and imprecision. The review was limited to 10 studies reporting 581 infants with NAS secondary to maternal opioid use in pregnancy across multiple comparisons of different sedatives and regimens, so analyses were largely underpowered to detect important differences, particularly for outcomes of lower incidence including seizures and treatment-related adverse effects. There were limited data for use in a sensitivity analysis of studies at low risk of bias (adequate randomisation and allocation concealment, blinding of treatment and greater than 90% follow-up on an intention-to-treat basis). Sensitivity analysis did not identify any statistically significant effects for treatment failure for single studies comparing phenobarbital versus chlorpromazine, and clonidine and DTO versus DTO alone for seizures, mortality after discharge, days' treatment and adverse events.

Potential biases in the review process

We performed an extensive search for published and unpublished studies to avoid publication bias, although searches of non-English databases were not performed. At least two review authors

independently assessed eligibility and risk of bias and performed data extraction. The review included studies using quasi-random participant allocation increasing the risk of selection bias in the studies included in the review. This was addressed using a sensitivity analysis. This review prespecified the primary outcomes and comparisons, with the exception of the comparisons between phenobarbital with or without a loading dose, and long and short course sedative regimens.

Agreements and disagreements with other studies or reviews

This review should be considered in the context of the associated review 'Opioid treatment for opioid withdrawal in newborn infants' (Zankl 2021).

Several reviews have assessed the evidence for different pharmacological and non-pharmacological treatments for infants with NAS (Disher 2019; Lee 2019; MacMillan 2018; Pahl 2020).

One systematic review and network meta-analysis of pharmacological treatments for neonatal abstinence syndrome included 18 trials with 1072 infants (Disher 2019). Sublingual buprenorphine was considered the optimal treatment for a reduction in the length of treatment and length of hospital stay, but not the need for adjuvant treatment. The results were robust to bias but sensitive to imprecision. The conclusion was the current evidence suggests that buprenorphine is the optimal treatment for NAS treatment, but limitations are considerable and wide-scale adoption requires a large multisite trial. Morphine, which is considered standard of care in most hospitals, was the lowest-ranked opioid for length of treatment and length of hospital stay. The findings of this systematic review and network meta-analysis are compatible with our review of an overview of direct comparisons. However, the conclusions of the review are strongly influenced by the network meta-analysis, which includes rankings derived from direct and indirect effects, and which is sensitive to imprecision due to the relatively small number of infants included in any comparison. In addition, outcomes were limited to surrogates of treatment effect including length of treatment, length of hospital stay, need for adjuvant treatment and discontinuation of treatment for adverse events. There are no comparisons of different sedatives.

One systematic review of RCTs and observational studies assessing the short-term treatment outcomes of opioid pharmacotherapy for neonatal opioid withdrawal syndrome found methadone increased treatment success compared with morphine, and buprenorphine was associated with the shortest overall durations of treatment and hospitalisation (Lee 2019). The conclusions should be treated with caution as the review was potentially biased by the inclusion of observational studies.

One systematic review of RCTs and observational studies reviewed the evidence for rooming-in for infants with NAS (MacMillan 2018). The review found no RCTs. Review of six before-after studies found opioid-exposed newborns rooming-in with mother or other family members appear to be significantly less likely to be treated with pharmacotherapy and have substantial reductions in length of hospital stay compared with those cared for in neonatal intensive care units. The conclusions should be treated with caution as the review is potentially biased by the inclusion of observational studies.

One Cochrane Review entitle 'Non-pharmacological care for opioid withdrawal in newborns' found six RCTs evaluating 353 infants, with four studies modifying environmental stimulation by comparing a study nursery to a regular nursery, non-oscillating waterbeds to conventional bassinets, rocking beds to standard beds, and prone sleep positioning to supine sleep positioning (Pahl 2020). One study evaluated feeding practices by comparing 24 kcal/oz formula to 20 kcal/oz formula, and one study evaluated support of the mother–infant dyad by comparing tailored breastfeeding support to standard Baby-Friendly Initiative care. The review concluded that the effect of non-pharmacological interventions reported in the studies was uncertain due to due to risk of bias inherent in the intervention, imprecision related to study size, and heterogeneity in study design, and many prespecified outcomes were not reported. There were no RCTs of the eat, sleep, console intervention found.

AUTHORS' CONCLUSIONS

Implications for practice

This review should be considered in the context of the associated review 'Opioid treatment for opioid withdrawal in newborn infants,' which found moderate-certainty evidence that use of an opioid reduces treatment failure compared to phenobarbital, and low-certainty evidence that use of an opioid reduces treatment failure compared to diazepam or chlorpromazine (Zankl 2021).

There are insufficient data to determine the effectiveness and safety of non-pharmacological interventions as an alternative to the addition of a pharmacological agent for neonatal abstinence syndrome (NAS) secondary to opioids. There is very low-certainty evidence that the addition of phenobarbital may increases duration of hospitalisation and treatment, but reduces days to regain birthweight and duration of supportive care each day compared to supportive care alone.

There is low-certainty evidence that phenobarbital may reduce treatment failure compared to diazepam and very low-certainty evidence that phenobarbital may reduce treatment failure compared to chlorpromazine.

There is low-certainty evidence of an increase in days' hospitalisation and days' treatment from use of clonidine and opioid compared to phenobarbital and opioid. There are insufficient data to determine the safety and incidence of adverse events of infants treated with combinations of opioids and sedatives including phenobarbital and clonidine.

Implications for research

Trials of non-pharmacological interventions (including the eat, sleep, console intervention) for reducing separation of mother and infant, admission to the nursery and pharmacological treatment of NAS are needed.

Adequately powered trials of the addition of phenobarbital to opioid therapy for NAS are needed to determine if severity and duration of NAS are reduced without adverse effects including oversedation.

Current trials of clonidine versus morphine (Bada 2015), adjunctive clonidine versus phenobarbital in infants who failed morphine treatment (Brusseau 2020), and adjunctive clonidine versus

phenobarbital in infants concomitantly treated with morphine (Surran 2013) have used clonidine doses 5 µg/kg/day or 6 µg/kg/day titrated to 12 µg/kg/day. One small trial of clonidine (titrated from 6 µg/kg/day to 12 µg/kg/day) versus placebo in morphine-treated infants is ongoing (NCT03762317). Trials to determine optimal dosing strategies (dose, timing and duration) of clonidine are needed. Dose-escalation studies should assess time to control of NAS (control of symptoms or reduction of NAS score to a clinically 'safe' level); severity and duration of withdrawal; infant feeding; weight loss and gain; and adverse effects including hypotension, rebound hypertension and rebound NAS after cessation of clonidine.

Future trials should measure the outcomes prespecified in this review, and be powered to detect important adverse events including seizures, oversedation, hypotension, rebound hypertension, rebound NAS and infant mortality. Trials are needed that measure psychosocial (mother–infant interaction, out-of-home care), growth and neurodevelopmental outcomes using validated scales of infant development.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agthe 2009

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial in USA March 2002 to December 2005
Participants	**Inclusion criteria** 1. Infants aged 0–14 days if they were exposed to opioids during the antenatal period and developed moderate-to-severe NAS (2 consecutive modified NASS scores ≥ 9) requiring pharmacotherapy **Exclusion criteria** 1. Gestational age < 35 weeks 2. Intrauterine growth retardation (birth weight < 5th percentile) 3. Congenital anomalies 4. Illness requiring oxygen, intravenous fluids or medications 5. Breastfeeding

Agthe 2009 *(Continued)*

	61% of infants were exposed to an opioid + cocaine in utero, 6/80 infants had positive benzodiazepine urine screens.
Interventions	**Intervention 1:** oral clonidine 1 µg/kg every 4 hours (6 µg/kg/day) and (clonidine/DTO) (n = 40) **Intervention 2:** DTO (placebo/DTO) (n = 40) DTO was given as a 1:25 dilution, 0.4 mg/mL (morphine equivalent). All infants started on 0.2 mL DTO (0.08 mg morphine equivalent) orally every 4 hours. NAS symptoms were uncontrolled if there were 2 consecutive MFSs ≥ 9. DTO was incrementally escalated to 0.3 mL, 0.4 mL and 0.5 mL every 4 hours, then to 0.5 mL, 0.7 mL and 0.9 mL every 3 hours, until withdrawal symptoms (MFS < 9) were controlled. (Dose range 0.48 mg/day titrated to maximum 2.88 mg/day.) Clonidine/placebo dose was based on weight (mL/kg) and maintained at that dose. When symptoms were controlled (mean daily MFS < 9), infants were continued on clonidine/placebo and DTO dose that controlled symptoms for ≥ 48 hours. Afterward, DTO was weaned by increments of 0.05 mL per dose, for each 24-hour period.
Outcomes	**Primary outcome** 1. Length of treatment for NAS **Secondary outcomes** 1. Amount of DTO required to treat the NAS (with or without clonidine) 2. Treatment failure (> 0.9 mL of diluted TO every 3 hours) 3. Seizures 4. Weight gain 5. BP, heart rate and haemoglobin saturation measured by pulse oximetry Diagnosis of seizures made by the clinical team; all infants received an electroencephalogram after phenobarbital was administered and no infant had an abnormal electroencephalogram.
Notes	Funded by a Thomas Wilson grant, an institutional research grant from JHH, General Clinical Research Center, and was supported by National Institute on Drug Abuse. ClinicalTrials.gov identifier NCT00510016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Infants were stratified according to hospital of birth and maternal methadone use before randomisation. After written parental consent it was reported that (quote): "eligible infants were randomly assigned by research pharmacist into 2 strata by a computerised random list in blocks of 4".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo (isotonic saline) used. Quote: "a clear, colourless, liquid formulation of clonidine was diluted".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators, parents, and caretakers were blinded to group allocations until the study was completed".

Agthe 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawn infant reported in intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	Retrospective trial registration. Only primary outcome documented in registration.
Other bias	Unclear risk	Reported that infants in the clonidine + DTO group had significantly lower mean birthweight.

Brusseau 2020

Study characteristics	
Methods	Randomised controlled trial in USA September 2018 to March 2019
Participants	**Inclusion criteria** 1. ≥ 35 weeks' gestation and failed first-line therapy with oral morphine. Infants considered to have failed morphine therapy were those whose morphine dose exceeded 0.16 mg every 3 hours or failed 2 weaning attempts after initial stabilisation. **Exclusion criteria** 1. Infants who developed NAS due to iatrogenic causes (analgesia or sedation), were unable to take oral medications at any point during treatment 2. In the custody of the department of child protective services with no legal guardian identified at the time of enrolment.
Interventions	**Intervention 1:** clonidine started at 6 µg/kg/day divided every 3 hours using a clonidine suspension 10 µg/mL. Clonidine dose increased by 1.5 µg/kg/day every 24 hours up to maximum 12 µg/kg/day to achieve control of symptoms. BP documented prior to each clonidine administration. The clonidine dose was held for a systolic BP < 60 mmHg. If > 2 clonidine doses were held in the previous 24 hours, the total daily dose was decreased by 1.5 µg/kg/day (n = 14) **Intervention 2:** phenobarbital 20 mg/kg loading dose divided every 12 hours, then 2.5 mg/kg every 12 hours using phenobarbital 4 mg/mL elixir (Qualitest). Phenobarbital trough levels were obtained on day 6 of therapy, then weekly thereafter. The phenobarbital dose was adjusted to obtain a trough 25–30 µg/mL. Infants with a trough < 25 µg/mL received an adjusted loading dose phenobarbital at 1 mg/kg for every 1 µg/mL increase from the obtained level to achieve the level of 25–30 µg/mL (n = 11) Infants with NASS score > 8 despite clonidine or phenobarbital dose continued morphine escalation per protocol. Infants unable to achieve control despite morphine dose > 0.16 mg and a maximum clonidine dose of 12 µg/kg/day or a phenobarbital level within the desired range were initiated on triple therapy with the alternative study medication.
Outcomes	**Primary outcome** 1. Length of morphine therapy **Secondary outcomes** 1. Time from initiation of adjunctive therapy until hospital discharge 2. Hospital LOS 3. Percentage of participants requiring triple therapy 4. Participant safety

Brusseau 2020 *(Continued)*

	5. 30-day readmission rates
Notes	Clinical trial registration NCT03670160 Sponsor: University of Tennessee Medical Center

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported.
Allocation concealment (selection bias)	Low risk	Eligibility and consent obtained before randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Blinding of assessment not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/24 infants withdrawn at parents' request.
Selective reporting (reporting bias)	Low risk	Trial registration available.
Other bias	Unclear risk	Estimated enrolment 50 participants. Study suspended with 24 infants enrolled. Reason not reported. Groups similar at baseline.

Coyle 2002

Study characteristics

Methods	Quasi-randomised study in USA March 1998 and May 2000
Participants	**Inclusion criteria** 1. Infants born to mothers with a history of heroin or methadone use, symptomatic of NAS with NASS score > 7. Criteria for starting medication same as recommendation of Finnegan. **Exclusion criteria** 1. None reported Incidence of non-opioid illicit drug use not reported. Reported the use of other illicit substances during pregnancy did not differ between groups.
Interventions	All infants treated with DTO (0.4 mg/mL morphine) 0.05 mL/kg 6–8 times per day. Dose increased if NASS score > 7, maintained if score 5–7 and reduced if score < 5 for 3 consecutive periods.

Coyle 2002 *(Continued)*

	Intervention 1: phenobarbital loading dose 30 mg/kg (given as 3 oral doses every 12 hours) and maintenance 5 mg/kg/day. Dose adjusted to maintain weekly serum level 20–30 mg/dL (n = 10) **Intervention 2:** placebo (n = 10)
Outcomes	**Primary outcomes** 1. Severity of withdrawal symptoms (using NASS score) 2. Duration of hospitalisation 3. Hospital cost **Other outcomes** 1. NICU Network Neurobehavioral Scale administered weekly for 3 weeks
Notes	35 infants (term and preterm) were reported in abstract form. The principal publication reported 21 term infants only. 32 infants reported in 2005 publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Infants prospectively matched by first NASS score. If no match then randomly assigned. Method of sequence generation not reported.
Allocation concealment (selection bias)	High risk	Allocation on basis of first NASS score predictable.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo used. Quote: "the study drug (phenobarbital or placebo) was similar in appearance". Comment: however, allocation may have been unblinded when phenobarbital levels reported to clinician.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Placebo used. Quote: "the study drug (phenobarbital or placebo) was similar in appearance". Comment: however, allocation may have been unblinded when phenobarbital levels reported to clinician.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	35 infants reported in abstract, 21 in primary publication, 32 in later publication. 1 excluded after consent as diagnosed with congenital heart disease and transferred to another facility.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	Groups similar at baseline.

Finnegan 1984a

Study characteristics	
Methods	Quasi-random study in the USA
Participants	**Inclusion criteria**

Finnegan 1984a *(Continued)*

	1. Infants born to mothers with: a. narcotic use only and b. narcotic and other drug use Finnegan NASS score determined need for treatment. **Exclusion criteria** 1. None reported Multiple-drug use: 71%. Reported separately
Interventions	**Intervention 1:** phenobarbital with or without loading dose (20 mg/kg) with maintenance 5–10 mg/kg/day titrated against score. Dose increased until control of NAS obtained, serum level > 70 µg/mL or evidence of toxicity (n = 87) **Intervention 2:** diazepam: dose not reported (n = 20) Also compared infants given paregoric
Outcomes	**Primary outcome** 1. Need for second pharmacological intervention **Other outcomes** 1. None Outcomes for loading dose and titration methods reported combined.
Notes	Additional information obtained from study 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 have included some of the infants as reported by Kaltenbach 1986. Randomisation not stratified according to type of antenatal drug used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-random, drug assignment from envelope designated according to first letter of last name (personal communication).
Allocation concealment (selection bias)	High risk	Method of sequence generation predictable.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different medications and regimens. Blinding not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Different medications and regimens. Blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Finnegan 1984a *(Continued)*

Other bias	Unclear risk	Asymmetric group sizes. Demographics not reported. Different proportions of infants in groups with antenatal exposures to multiple drugs.

Kahn 1969

Study characteristics	
Methods	Randomised controlled trial in USA October 1966 to September 1967
Participants	**Inclusion criteria** 1. Infants of mothers using heroin 2. Standardised scoring system 3. Infants with tremors or irritability > grade 1 on 3 grade score **Exclusion criteria** 1. Tremors and irritability ≤ grade 1 Multiple-drug use: 5 mothers used glutethimide, 4 amphetamines and 2 barbiturates.
Interventions	**Intervention 1:** phenobarbital short course: 8.4 mg/kg/day × 4 day (4 divided doses) then stopped (n = 12) **Intervention 2:** phenobarbital long course: 8.4 mg/kg/day (4 divided doses) × 10 days then reduced by one third every second day (stopped day 16) (n = 7) **Intervention 3:** chlorpromazine short course: 2.8 mg/kg/day (4 divided doses) × 4 days then stopped (n = 11) **Intervention 4:** chlorpromazine long course: 2.8 mg/kg/day (4 divided doses) × 10 days then gradual reduction over next 6 days (n = 8)
Outcomes	**Primary outcome** 1. None reported **Other outcomes** 1. Infant mortality 2. Severity and duration of withdrawal symptoms 3. Persistent symptoms > 4 days
Notes	Co-interventions: none reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random". Method not reported.
Allocation concealment (selection bias)	Unclear risk	Unclear allocation process.

Kahn 1969 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Used identical appearing syrup, volume and frequency of dosing.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Used identical appearing syrup, volume and frequency of dosing.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting detail.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	High risk	Asymmetric group sizes. Baseline characteristics not reported.

Kaltenbach 1986

Study characteristics	
Methods	Quasi-random trial in USA
Participants	**Inclusion criteria** 1. Infants of drug-dependant women maintained on methadone 2. Neonatal Abstinence Scoring System score averaging ≥ 8 for 3 consecutive scores **Exclusion criteria:** not reported Multiple-drug use: yes, incidence not reported
Interventions	**Intervention 1:** phenobarbital loading dose followed by titration: doses not reported (n = 20) **Intervention 2:** phenobarbital titration group: doses not reported (n = 16) **Intervention 3:** diazepam: dose not reported (n = 10) **Intervention 4:** paregoric
Outcomes	**Primary outcome** 1. Bayley Scale of Mental Development at 6 months (not reported by intention-to-treat) **Other outcomes** 1. Need for second agent to control symptoms.
Notes	Additional information obtained from authors. Group numbers not balanced. May have included some of the infants as reported by Finnegan 1984a. Randomisation not stratified according to type of antenatal drug use.
Risk of bias	

Bias	Authors' judgement	Support for judgement

Kaltenbach 1986 *(Continued)*

Random sequence generation (selection bias)	High risk	Quasi-random, drug assignment from envelope designated according to first letter of last name.
Allocation concealment (selection bias)	High risk	Allocation predictable.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different medications and regimens. Blinding not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different medications and regimens. Blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting detail to determine.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Asymmetric group sizes. Demographics not reported.

Khoo 1995

Study characteristics	
Methods	Quasi-randomised trial in Australia April 1991 to November 1994
Participants	**Inclusion criteria** 1. Infants of mothers with an opioid dependence who had NASS scores averaging ≥ 8 in 3 consecutive 4-hour periods. Urine drug screens performed during pregnancy. **Exclusion criteria** 1. Not reported. Multiple-drug use reported by 95% of mothers who had taken methadone. 76% of infants had been exposed to > 2 drugs in utero.
Interventions	**Intervention 1:** phenobarbital loading dose 15 mg/kg (intramuscular) then 6 mg/kg/day in 2 divided doses, titrated to score up to maximum 10 mg/kg/day; and supportive therapy (n = 29) **Intervention 2:** supportive therapy alone included dummy (pacifier), swaddling or close wrapping, small frequent feeds, close skin contact by carrying in sling and other methods (n = 36)
Outcomes	**Primary outcome** 1. Unclear **Other outcomes** 1. Need for second drug (failure to settle measured using NASS score) 2. Duration of supportive intervention

Khoo 1995 *(Continued)*

	3. Numbers of dose increments on therapy 4. Number of treatment days 5. Days in baby special care nursery 6. Days in hospital 7. 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-random, used last number of the participant's hospital number.
Allocation concealment (selection bias)	High risk	Allocation predictable.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Treatment regimens differed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported. Treatment regimens differed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 infant allocated phenobarbital and 2 supportive therapy excluded from analysis. Data available for days to regain birthweight from 27/29 infants on phenobarbital and 28/36 infants on supportive therapy.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Asymmetric group sizes. Some baseline demographic difference between groups.

Madden 1977

Study characteristics	
Methods	Randomised controlled trial in USA
Participants	**Inclusion criteria** 1. Infants of narcotic-addicted mothers. Clinical decision to treat. Abstinence score not used **Exclusion criteria** 1. None reported Multiple-drug use: non-opioid use reported in 15% of the baseline population of mothers
Interventions	**Intervention 1:** phenobarbital: 5–8 mg/kg/day (3 divided doses) (n = 16)

Madden 1977 *(Continued)*

	Intervention 2: diazepam: 0.5–2.0 mg every 8 hours (n = 16) Quote: doses "tailored day to day".
Outcomes	**Primary outcome** 1. None reported **Other outcomes** 1. Use of second drug 2. Duration of treatment 3. Day of hospital discharge
Notes	Duration of treatment and day of discharge not analysed according to original group of assignment. Co-interventions: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "randomly assigned except in three instances". Comment: method of sequence generation not reported. Judgement: high risk as some infants assigned at clinicians discretion.
Allocation concealment (selection bias)	High risk	Judgement: high risk as some infants assigned at clinicians discretion.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo. Different treatment regimens.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo. Different treatment regimens.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported. 1 infant given diazepam non-randomly excluded. 1 infant randomised to phenobarbital that received diazepam excluded from analysis for duration of treatment.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Unclear risk	Baseline characteristics of groups not reported.

Surran 2013

Study characteristics	
Methods	Randomised controlled trial in USA June 2010 to June 2012
Participants	**Inclusion criteria**

Surran 2013 *(Continued)*

1. Infants aged ≤ 15 days, with antenatal opioid exposure
2. Moderate-to-severe NAS defined as 2 consecutive MFS ≥ 8 and medically stable

Exclusion criteria

1. Infants < 35 weeks' gestational age
2. Intrauterine growth restriction (birthweight < 5th percentile for gestational age)
3. Congenital abnormalities
4. Known exposure to benzodiazepines in utero and medically unstable

Maternal multiple-drug use: 41%

Interventions	All infants (n = 68) were administered a standard morphine sulphate solution of 0.4 mg/mL titrated according to MFS. Scores 8–10 = 0.32 mg/kg/day, 11–13 = 0.43 mg/kg/day, 14–16 = 0.64 mg/kg/day, > 17 = 0.8 mg/kg/day given every 3 hours in divided daily dose. **Intervention 1:** clonidine suspension (10 µg/mL) titrated according to MFS. Scores of 8–10 = 6 µg/kg/day, 11–13 = 8 µg/kg/day, 14–16 = 10 µg/kg/day, ≥ 17 = 12 µg/kg/day given every 6 hours in divided daily dose (n = 34) **Intervention 2:** phenobarbital suspension (4 mg/mL) titrated according to MFS. Scores of 8–10 = 6 mg/kg/day, 11–13 = 8 mg/kg/day, 14–16 = 10 mg/kg/day, ≥ 17 = 12 mg/kg/day given every 8 hours in divided daily dose (n = 34) Infants were maintained on interventions for 48 hours once MFS < 8 for the preceding 24-hour period. Each infant then had morphine sulphate dose reduced once in 24 hours by 10% of absolute dose if the MFS remained < 8 and was discontinued at 0.12 mg/kg/day. Clonidine was weaned by 50% in a 2-step reduction every 24 hours until discontinued and infants stayed in hospital 36–48 hours after cessation for monitoring. Phenobarbital was weaned in outpatient setting using a standard hospital protocol for up to 8 months.
Outcomes	**Primary outcome** 1. Treatment days with morphine sulphate. **Secondary outcomes** 1. Mean total morphine sulphate dose 2. Outpatient phenobarbital days 3. Adverse events 4. Treatment failures
Notes	ClinicalTrials.gov identifier NCT01175668 Early termination of trial due to lack of efficacy at the interim analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Quote: "assignment was under equal allocation according to a computer-generated randomisation procedure in blocks of 4 or 6. Stratified according to maternal drug history to maintain balance between groups. Generated by the Epidemiology and Biostatistics Research Core within the institution". Clinical research team was blinded to randomisation.

Surran 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Different dosing intervals and additional clinical monitoring of the infants in the clonidine group prevented us from conducting a blinded study".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The PI remained blinded to treatment assignment in providing clinical oversight, and the interim statistical analysis was conducted in a blinded manner".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 infants in clonidine group discontinued intervention. 6 infants in phenobarbitone group lost to long-term follow-up.
Selective reporting (reporting bias)	Low risk	Trial registration available.
Other bias	Unclear risk	Terminated based on the planned interim analysis results at 50% recruitment, after the Institutional Review Board reviewed the results, further enrolment was stopped. Clonidine group had higher baseline NASS score and higher maternal oxycodone dose.

Zimmermann 2020

Study characteristics	
Methods	Multicentre, double-blind, parallel-group randomised controlled trial in Switzerland June 2001 to December 2007
Participants	**Inclusion criteria** 1. Late preterm and term infants (≥ 34 gestational weeks) who had withdrawal symptoms and were born to mothers who took opioids, including methadone, during pregnancy **Exclusion criteria** 1. Infants with diseases probably requiring a long hospitalisation
Interventions	NASS score every 8 hours. If an infant scored once > 14 or twice in a row > 9, and the parents had given written consent, the infant was randomised. **Intervention 1:** phenobarbital 10 mg/0.25 mL starting solution (loading dose) and 0.83 mg/0.25 mL maintenance solution: to maximum 1.66 mg/kg 4 hourly. Starting dose 0.25 mL/kg every 4 hours. Study drug was increased by 0.05 mL/kg until a maximum dose of 0.5 mL/kg if NASS score > 9 (n = 53) **Intervention 2:** chlorpromazine 0.5 mg/0.25 mL solution: starting dose 0.5 mg/kg 4 hourly to maximal 1 mg/kg 4 hourly (n = 47) Starting dose 0.25 mL/kg every 4 hours. Study drug was increased by 0.05 mL/kg until a maximum dose of 0.5 mL/kg if NASS score > 9. Maximal daily dosages: chlorpromazine 3 mg/kg and phenobarbital 10 mg/kg The second drug was predefined by allocation of the first drug and was blinded. If the first drug was phenobarbital or chlorpromazine, the second drug was morphine. If symptoms were controlled, the allocated drug or combination was administered at the same dose for 72 hours. When scores were < 8 for 24 hours, the drug was reduced by 10%. If 2 drugs had to be giv-

Zimmermann 2020 *(Continued)*

	en, the first drug was reduced first. If the infant needed no more drugs for 2 days, he/she could be discharged.
Outcomes	**Primary outcome** 1. Length of treatment based on the modified NASS score (medians and 95% CI). **Secondary outcomes** 1. Need for a second drug 2. Occurrence of seizures 3. Other adverse events
Notes	Morphine group reported in 'Opioid treatment for opioid withdrawal in newborn infants' review (Zankl 2021). Trial registration: NCT02810782. Retrospectively registered. 71% of mothers were multiple-drug users. Meconium analyses detected amphetamine (27.5%), barbiturate (15.8%), benzodiazepine (18.3%), cannabis (22.5%) and cocaine (23.3%). Bucher Hans Ulrich clarified data for denominators in each group and rates of treatment failure.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prepared in the pharmacy of Zurich University Hospital according to a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Quote: "If an infant scored once above 14 or twice in a row above 9, and the parents had given written consent, the infant was randomised to group A (morphine), B (chlorpromazine), or C (phenobarbital)".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To blind group allocation, water, ethanol, glycerine, and caramel colour (E150) were added to the active substance, and dosing regimen was standardised.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To blind group allocation, water, ethanol, glycerine, and caramel colour (E150) were added to the active substance, and dosing regimen was standardised.
Incomplete outcome data (attrition bias) All outcomes	High risk	All infants reported for need for a second drug. However, 16% did not receive allocated intervention as did not reach treatment threshold despite allocation and other outcomes only reported in infants receiving treatment.
Selective reporting (reporting bias)	Unclear risk	Retrospectively registered.
Other bias	Low risk	Groups similar at baseline.

BP: blood pressure; CI: confidence interval; DTO: diluted tincture of opium; LOS: length of stay; MFS: Modified NASS (Finnegan) Scores; n: number of participants; NAS: neonatal abstinence syndrome; NASS: Neonatal Abstinence Scoring System; NICU: neonatal intensive care unit.

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

Study	Reason for exclusion
Alroomi 1988	Observational study.
Autret 2004	Observational study.
Bada 2015	Randomised trial of morphine vs clonidine.
Calabrese 1985	Monograph review.
Carin 1983	Randomised trial of paregoric vs phenobarbital.
Dabek 2013	Retrospective study.
Daniel 2020	Aromatherapy not considered a sedative.
Doberczak 1991	Observational study.
Esmaeili 2010	Observational study – comparison of infants admitted to 2 different paediatric units treated with chloral hydrate or clonidine.
Finnegan 1975a	Observational study.
Finnegan 1975b	Observational study.
Finnegan 1979	Case series report.
Finnegan 1984b	Study comparing loading dose and titration approach to commencing phenobarbital therapy for neonatal abstinence syndrome. Method of treatment allocation not reported.
Harper 1977	Observational study.
Herzlinger 1977	Observational study.
Hoder 1981	Case report.
Hoder 1984	Non-randomised study of clonidine for neonatal narcotic abstinence. No controls.
Kaltenbach 1987	Observational study.
Kandall 1983	Randomised study of phenobarbital and paregoric for neonatal abstinence syndrome.
Kron 1975a	Observational study.
Kron 1975b	Observational study.
Kron 1976	Non-random allocation to treatment.
Leikin 2009	Case series in which clonidine was used for the prevention and management of patients with neonatal abstinence syndrome.
Mazurier 2008	Historical control study morphine vs chlorpromazine.
Nathenson 1971	Observational study of the use of diazepam in neonatal abstinence syndrome.

Study	Reason for exclusion
NCT01360450	Randomised trial of opioid/benzodiazepine administration combined with a placebo vs opioid/benzodiazepine combined with clonidine. Trial terminated due to low accrual rate (12 participants). No publication found.
Ostrea 1975	Infants randomised to experimental (noise and light reduced) and control nursery.
Ostrea 1976	Not a study of treatment.
Pacifico 1989	Compared morphine alone vs phenobarbital and diazepam vs phenobarbital and diazepam and morphine in infants of mothers using heroin. Did not report method of participant allocation. Authors unable to be contacted to-date.
Sutton 1990	Case report.
Tunis 1984	Control study of infants with neonatal abstinence syndrome given paregoric, phenobarbital or diazepam. Method of allocation not stated. No data given.
Wolman 1989	Monograph review.
Yaster 1996	Monograph review.
Zelson 1970	Letter documenting observations.

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

NCT03762317

Study name	Clonidine as adjunct to morphine for neonatal abstinence syndrome
Methods	Randomised double blind trial
Participants	**Inclusion criteria** 1. Requiring NICU admission for management of NAS 2. Gestational age ≥ 36 weeks 3. ≤ 48 hours of treatment with morphine for NAS **Exclusion criteria** 1. Presence of seizures 2. Congenital malformations, genetic syndromes or the presence of TORCH infections 3. Major medical problems 4. Heart rate or blood pressure (or both) instability
Interventions	**Intervention 1**: clonidine started at 6 µg/kg/day and increased to 12 µg/kg/day for duration of study + oral morphine **Intervention 2**: placebo + oral morphine
Outcomes	**Primary outcome** 1. Duration of pharmacotherapy for NAS **Secondary outcomes** 1. Duration of hospital stay

NCT03762317 *(Continued)*	2. Maximum dose of morphine used 3. Cumulative dose of oral morphine during hospital stay 4. Episodes of bradycardia, hypotension (blood pressure < 5th percentile for age) and hypertension (blood pressure > 95th percentile for age)
Starting date	30 April 2018
Contact information	Kunal Gupta and Vinay Sharma: Hennepin County Medical Center, Minneapolis, USA
Notes	32 participants

NAS: neonatal abstinence syndrome; NICU: neonatal intensive care unit; TORCH infections: toxoplasmosis, others (syphilis, hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex.

DATA AND ANALYSES

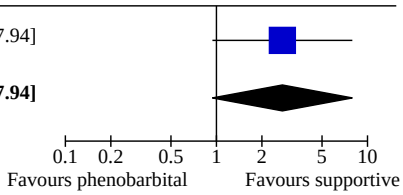
Comparison 1. Phenobarbital versus supportive care (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment failure	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.94, 7.94]
1.2 Seizures	1	62	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Days' hospitalisation	1	62	Mean Difference (IV, Fixed, 95% CI)	20.80 [13.64, 27.96]
1.4 Days' pharmacological treatment	1	62	Mean Difference (IV, Fixed, 95% CI)	17.90 [11.98, 23.82]
1.5 Time to regain birth weight (days)	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-4.07, 1.27]
1.6 Duration of stay in special care nursery (days)	1	62	Mean Difference (IV, Fixed, 95% CI)	23.13 [15.87, 30.39]
1.7 Duration of supportive care per day (minutes)	1	62	Mean Difference (IV, Fixed, 95% CI)	-162.10 [-249.14, -75.06]

Analysis 1.1. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Supportive therapy Events	Supportive therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khoo 1995	9	28	4	34	100.0%	2.73 [0.94 , 7.94]
Total (95% CI)		**28**		**34**	**100.0%**	**2.73 [0.94 , 7.94]**
Total events:	9		4			

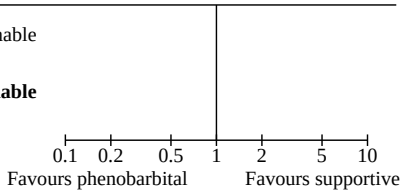
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 2: Seizures

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Supportive therapy Events	Supportive therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khoo 1995	0	28	0	34		Not estimable
Total (95% CI)		**28**		**34**		**Not estimable**
Total events:	0		0			

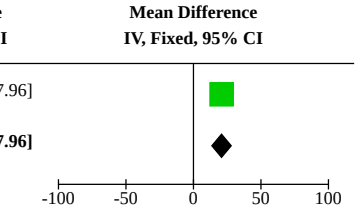
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 3: Days' hospitalisation

Study or Subgroup	Phenobarbital Mean	Phenobarbital SD	Phenobarbital Total	Supportive therapy Mean	Supportive therapy SD	Supportive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Khoo 1995	34.8	16.1	28	14	11.8	34	100.0%	20.80 [13.64 , 27.96]
Total (95% CI)			**28**			**34**	**100.0%**	**20.80 [13.64 , 27.96]**

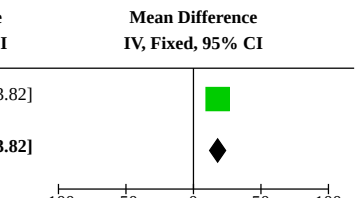
Heterogeneity: Not applicable
Test for overall effect: Z = 5.69 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 4: Days' pharmacological treatment

Study or Subgroup	Phenobarbital Mean	Phenobarbital SD	Phenobarbital Total	Supportive therapy Mean	Supportive therapy SD	Supportive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Khoo 1995	26.5	14	28	8.6	8.5	34	100.0%	17.90 [11.98 , 23.82]
Total (95% CI)			**28**			**34**	**100.0%**	**17.90 [11.98 , 23.82]**

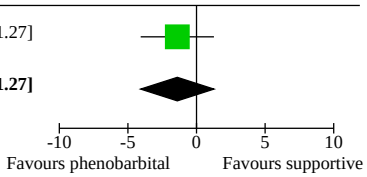
Heterogeneity: Not applicable
Test for overall effect: Z = 5.93 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 5: Time to regain birth weight (days)

Study or Subgroup	Phenobarbital Mean	SD	Total	Supportive therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Khoo 1995	13.6	4.2	27	15	5.8	28	100.0%	-1.40 [-4.07 , 1.27]
Total (95% CI)			**27**			**28**	**100.0%**	**-1.40 [-4.07 , 1.27]**

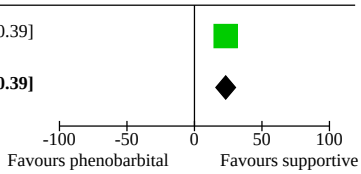
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 6: Duration of stay in special care nursery (days)

Study or Subgroup	Phenobarbital Mean	SD	Total	Supportive therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Khoo 1995	31.43	16.1	28	8.3	12.3	34	100.0%	23.13 [15.87 , 30.39]
Total (95% CI)			**28**			**34**	**100.0%**	**23.13 [15.87 , 30.39]**

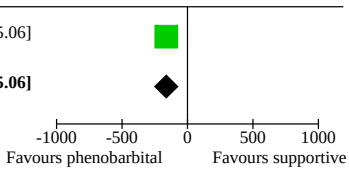
Heterogeneity: Not applicable
Test for overall effect: Z = 6.25 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Phenobarbital versus supportive care (all infants), Outcome 7: Duration of supportive care per day (minutes)

Study or Subgroup	Phenobarbital Mean	SD	Total	Supportive therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Khoo 1995	147.1	125.7	28	309.2	218.8	34	100.0%	-162.10 [-249.14 , -75.06]
Total (95% CI)			**28**			**34**	**100.0%**	**-162.10 [-249.14 , -75.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.65 (P = 0.0003)
Test for subgroup differences: Not applicable



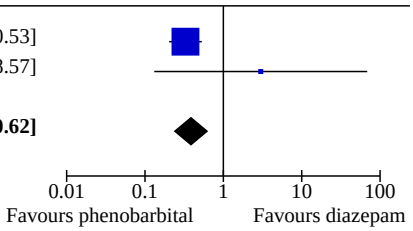
Comparison 2. Phenobarbital versus diazepam (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Treatment failure	2	139	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.24, 0.62]
2.2 Days' hospitalisation	1	32	Mean Difference (IV, Fixed, 95% CI)	3.89 [-1.20, 8.98]
2.3 Days' pharmacological treatment	1	31	Mean Difference (IV, Fixed, 95% CI)	4.30 [-0.73, 9.33]

Analysis 2.1. Comparison 2: Phenobarbital versus diazepam (all infants), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Diazepam Events	Diazepam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Finnegan 1984a	20	87	14	20	97.9%	0.33 [0.20 , 0.53]
Madden 1977	1	16	0	16	2.1%	3.00 [0.13 , 68.57]
Total (95% CI)		**103**		**36**	**100.0%**	**0.39 [0.24 , 0.62]**
Total events:	21		14			

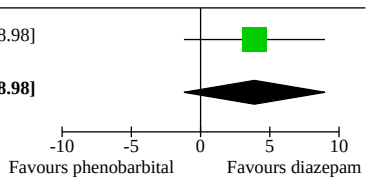
Heterogeneity: Chi² = 2.08, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 3.95 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Phenobarbital versus diazepam (all infants), Outcome 2: Days' hospitalisation

Study or Subgroup	Phenobarbital Mean	Phenobarbital SD	Phenobarbital Total	Diazepam Mean	Diazepam SD	Diazepam Total	Weight	Mean Difference IV, Fixed, 95% CI
Madden 1977	20.6906	9.2125	16	16.8	4.81	16	100.0%	3.89 [-1.20 , 8.98]
Total (95% CI)			**16**			**16**	**100.0%**	**3.89 [-1.20 , 8.98]**

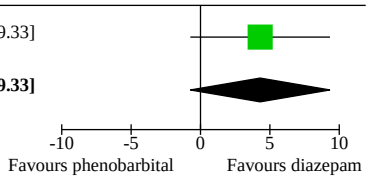
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Phenobarbital versus diazepam (all infants), Outcome 3: Days' pharmacological treatment

Study or Subgroup	Phenobarbital Mean	Phenobarbital SD	Phenobarbital Total	Diazepam Mean	Diazepam SD	Diazepam Total	Weight	Mean Difference IV, Fixed, 95% CI
Madden 1977	14.5	8.96	15	10.2	4.45	16	100.0%	4.30 [-0.73 , 9.33]
Total (95% CI)			**15**			**16**	**100.0%**	**4.30 [-0.73 , 9.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



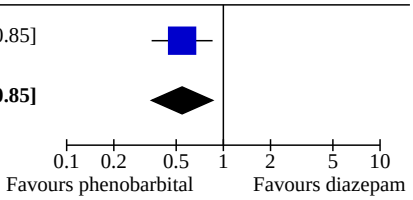
Comparison 3. Phenobarbital versus diazepam (infants of mothers using only opioids)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Treatment failure	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.35, 0.85]

Analysis 3.1. Comparison 3: Phenobarbital versus diazepam (infants of mothers using only opioids), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Diazepam Events	Diazepam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Finnegan 1984a	13	26	5	5	100.0%	0.55 [0.35 , 0.85]
Total (95% CI)		**26**		**5**	**100.0%**	**0.55 [0.35 , 0.85]**
Total events:	13		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable



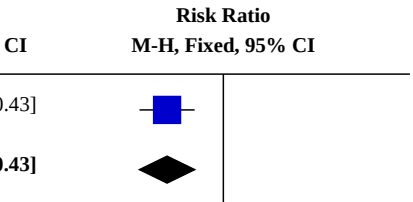
Comparison 4. Phenobarbital versus diazepam (infants of mothers using opioids and other drugs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Treatment failure	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.09, 0.43]

Analysis 4.1. Comparison 4: Phenobarbital versus diazepam (infants of mothers using opioids and other drugs), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Diazepam Events	Diazepam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Finnegan 1984a	7	61	9	15	100.0%	0.19 [0.09 , 0.43]
Total (95% CI)		**61**		**15**	**100.0%**	**0.19 [0.09 , 0.43]**
Total events:	7		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.00 (P < 0.0001)
Test for subgroup differences: Not applicable



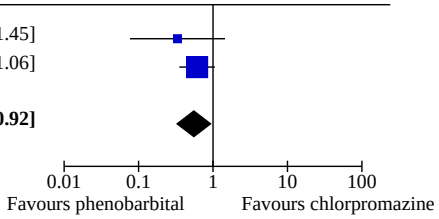
Comparison 5. Phenobarbital versus chlorpromazine (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Treatment failure	2	138	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.33, 0.92]
5.2 Need for second drug	1	38	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Seizures	2	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4 Days' hospitalisation	1	87	Mean Difference (IV, Fixed, 95% CI)	7.00 [-3.46, 17.46]
5.5 Adverse events	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 5.1. Comparison 5: Phenobarbital versus chlorpromazine (all infants), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Chlorpromazine Events	Chlorpromazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kahn 1969	2	19	6	19	21.0%	0.33 [0.08 , 1.45]
Zimmermann 2020	13	47	24	53	79.0%	0.61 [0.35 , 1.06]
Total (95% CI)		**66**		**72**	**100.0%**	**0.55 [0.33 , 0.92]**
Total events:	15		30			

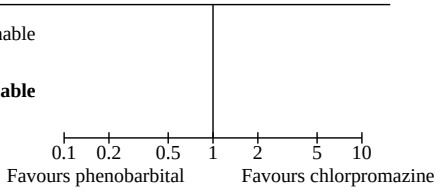
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Phenobarbital versus chlorpromazine (all infants), Outcome 2: Need for second drug

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Chlorpromazine Events	Chlorpromazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kahn 1969	0	19	0	19		Not estimable
Total (95% CI)		**19**		**19**		**Not estimable**
Total events:	0		0			

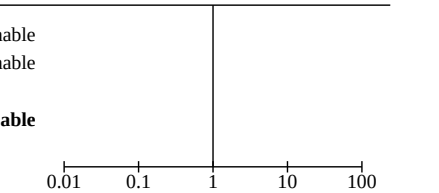
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Phenobarbital versus chlorpromazine (all infants), Outcome 3: Seizures

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Chlorpromazine Events	Chlorpromazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kahn 1969	0	19	0	21		Not estimable
Zimmermann 2020	0	47	0	53		Not estimable
Total (95% CI)		**66**		**74**		**Not estimable**
Total events:	0		0			

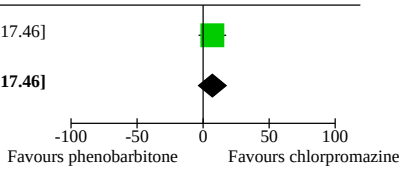
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Phenobarbital versus chlorpromazine (all infants), Outcome 4: Days' hospitalisation

Study or Subgroup	Phenobarbital Mean	Phenobarbital SD	Phenobarbital Total	Chlorpromazine Mean	Chlorpromazine SD	Chlorpromazine Total	Weight	Mean Difference IV, Fixed, 95% CI
Zimmermann 2020	32	19.735	43	25	29.2441	44	100.0%	7.00 [-3.46 , 17.46]
Total (95% CI)			**43**			**44**	**100.0%**	**7.00 [-3.46 , 17.46]**

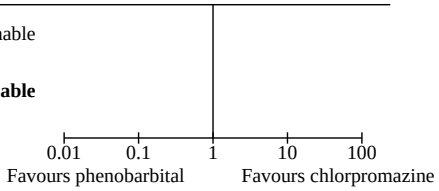
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Phenobarbital versus chlorpromazine (all infants), Outcome 5: Adverse events

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Chlorpromazine Events	Chlorpromazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zimmermann 2020	0	47	0	53		Not estimable
Total (95% CI)		**47**		**53**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



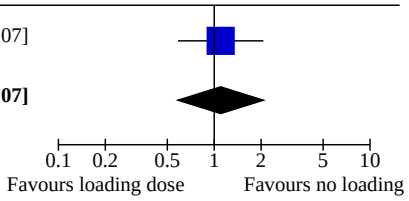
Comparison 6. Phenobarbital titration with loading dose versus phenobarbitone titration alone (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Treatment failure	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.07]

Analysis 6.1. Comparison 6: Phenobarbital titration with loading dose versus phenobarbitone titration alone (all infants), Outcome 1: Treatment failure

Study or Subgroup	Loading dose Events	Loading dose Total	No loading Events	No loading Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaltenbach 1986	11	20	8	16	100.0%	1.10 [0.59 , 2.07]
Total (95% CI)		**20**		**16**	**100.0%**	**1.10 [0.59 , 2.07]**
Total events:	11		8			

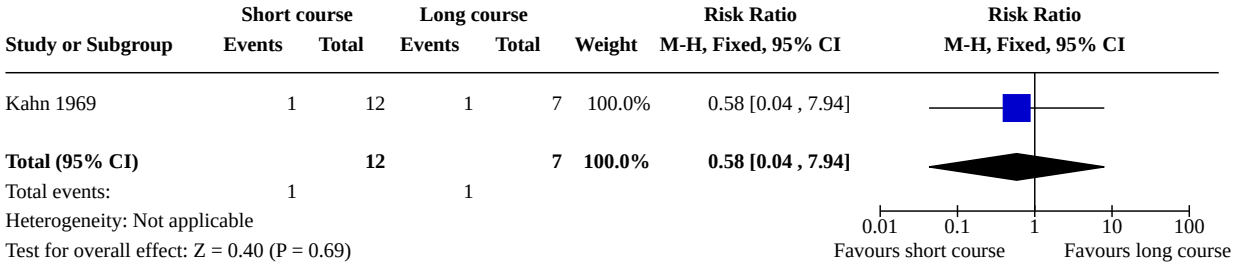
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Comparison 7. Short versus long course of phenobarbital (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Treatment failure	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.04, 7.94]

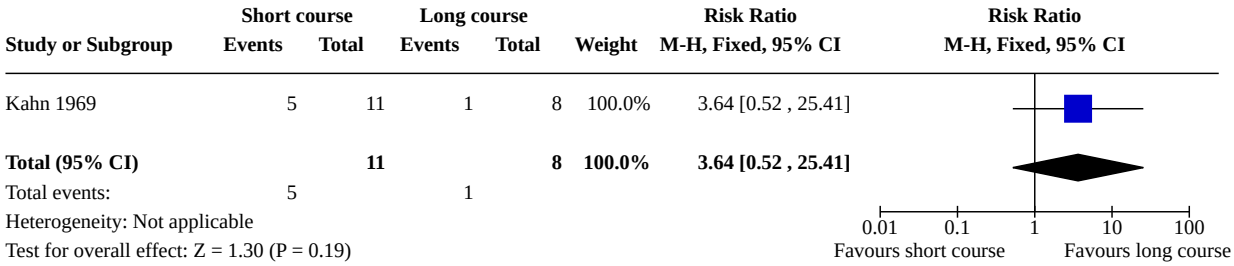
Analysis 7.1. Comparison 7: Short versus long course of phenobarbital (all infants), Outcome 1: Treatment failure



Comparison 8. Short versus long course of chlorpromazine (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Treatment failure	1	19	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.52, 25.41]

Analysis 8.1. Comparison 8: Short versus long course of chlorpromazine (all infants), Outcome 1: Treatment failure



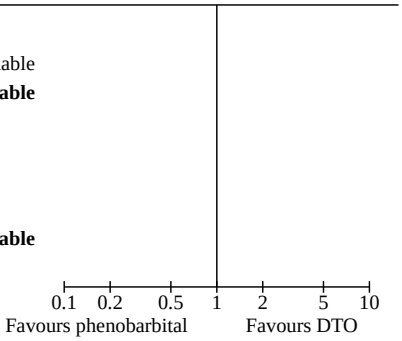
Comparison 9. Phenobarbital and opioid versus opioid alone (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Treatment failure	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1.1 Phenobarbital + dilute tincture of opium (DTO) vs DTO	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Seizures	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2.1 Phenobarbital + DTO vs DTO	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3 Percent time Finnegan score ≥ 8	1	20	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-9.84, -0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.1 Phenobarbital + DTO vs DTO	1	20	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-9.84, -0.16]
9.4 Days' hospitalisation	1	20	Mean Difference (IV, Fixed, 95% CI)	-43.50 [-59.18, -27.82]
9.4.1 Phenobarbital + DTO vs DTO	1	20	Mean Difference (IV, Fixed, 95% CI)	-43.50 [-59.18, -27.82]

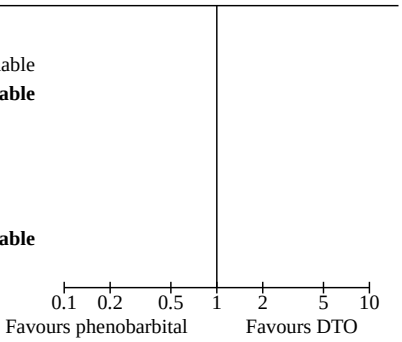
Analysis 9.1. Comparison 9: Phenobarbital and opioid versus opioid alone (all infants), Outcome 1: Treatment failure

Study or Subgroup	Phenobarbital + DTO Events	Total	DTO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Phenobarbital + dilute tincture of opium (DTO) vs DTO						
Coyle 2002	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

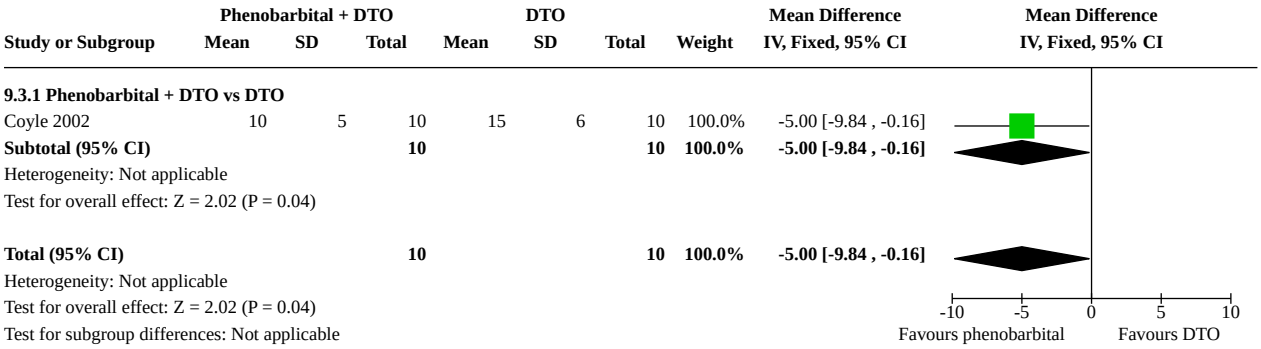


Analysis 9.2. Comparison 9: Phenobarbital and opioid versus opioid alone (all infants), Outcome 2: Seizures

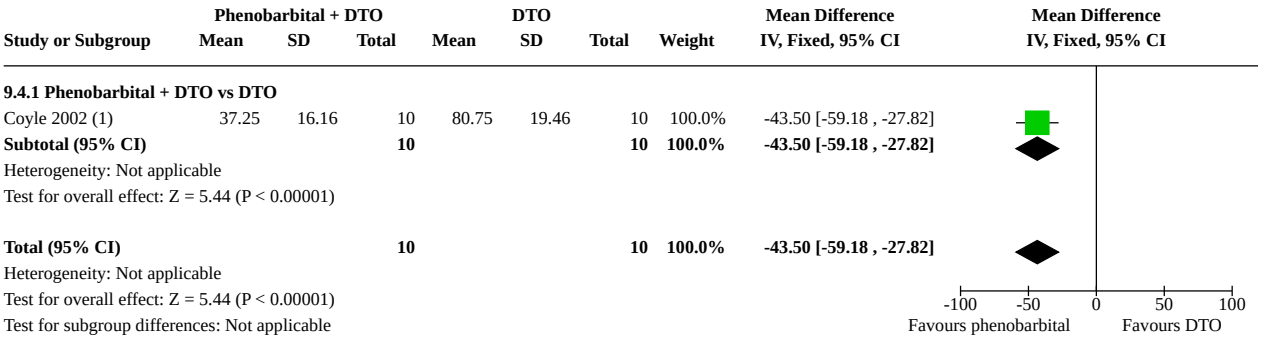
Study or Subgroup	Phenobarbital + DTO Events	Total	DTO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 Phenobarbital + DTO vs DTO						
Coyle 2002	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 9.3. Comparison 9: Phenobarbital and opioid versus opioid alone (all infants), Outcome 3: Percent time Finnegan score ≥ 8



Analysis 9.4. Comparison 9: Phenobarbital and opioid versus opioid alone (all infants), Outcome 4: Days' hospitalisation



Footnotes

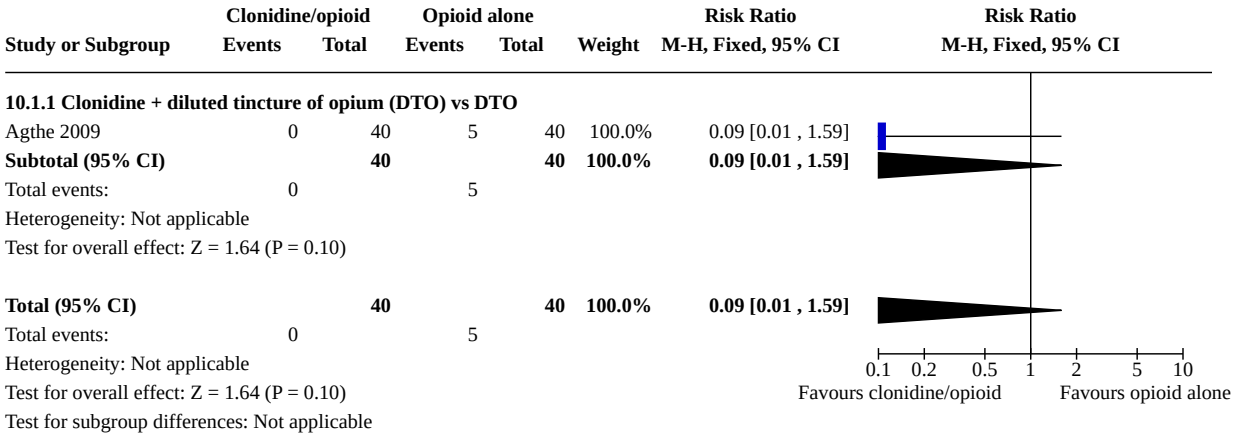
(1) Converted from non-parametric data

Comparison 10. Clonidine and opioid versus opioid alone (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Treatment failure	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.59]
10.1.1 Clonidine + diluted tincture of opium (DTO) vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.59]
10.2 Seizures	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
10.2.1 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
10.3 Mortality after discharge	1	80	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.37, 131.28]
10.3.1 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.37, 131.28]
10.4 Days' pharmacological treatment	1	80	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-8.33, 0.33]

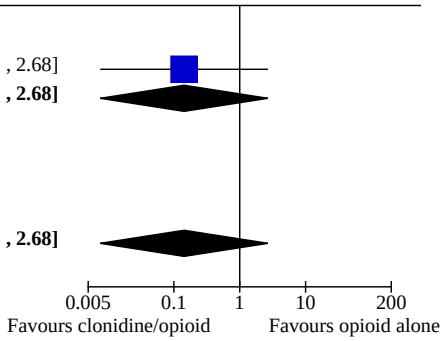
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.4.1 Clonidine + DTO vs DTO	1	80	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-8.33, 0.33]
10.5 Maximum weight loss (%)	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-2.33, 0.57]
10.5.1 Clonidine + DTO vs DTO	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-2.33, 0.57]
10.6 Adverse events (treatment-related)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.6.1 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 71.51]
10.7 Rebound neonatal abstinence syndrome after stopping treatment requiring retreatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.7.1 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	15.00 [0.89, 254.13]

Analysis 10.1. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 1: Treatment failure



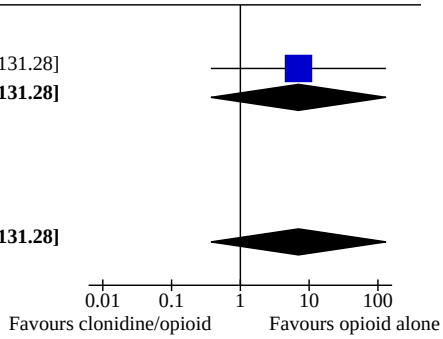
Analysis 10.2. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 2: Seizures

Study or Subgroup	Clonidine/opioid Events	Total	Opioid alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.2.1 Clonidine + DTO vs DTO						
Agthe 2009	0	40	3	40	100.0%	0.14 [0.01 , 2.68]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.14 [0.01 , 2.68]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**40**		**40**	**100.0%**	**0.14 [0.01 , 2.68]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						



Analysis 10.3. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 3: Mortality after discharge

Study or Subgroup	Clonidine/opioid Events	Total	Opioid alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 Clonidine + DTO vs DTO						
Agthe 2009 (1)	3	40	0	40	100.0%	7.00 [0.37 , 131.28]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**7.00 [0.37 , 131.28]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**40**		**40**	**100.0%**	**7.00 [0.37 , 131.28]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						

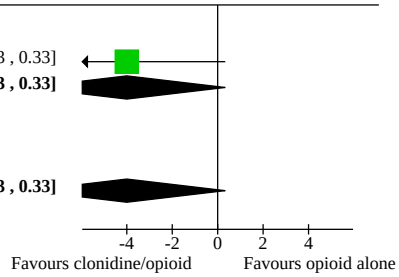


Footnotes

(1) The causes of death were myocarditis, SIDS, and homicide (methadone overdose), confirmed by autopsy.

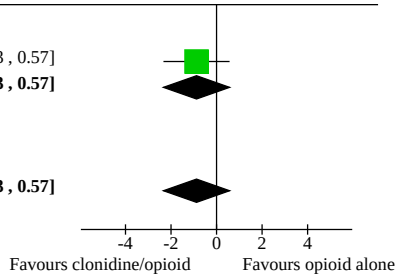
Analysis 10.4. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 4: Days' pharmacological treatment

Study or Subgroup	Clonidine/opioid Mean	SD	Total	Opioid alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.4.1 Clonidine + DTO vs DTO								
Agthe 2009	11	12.5072	40	15	6.2536	40	100.0%	-4.00 [-8.33 , 0.33]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**-4.00 [-8.33 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.81 (P = 0.07)								
Total (95% CI)			**40**			**40**	**100.0%**	**-4.00 [-8.33 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.81 (P = 0.07)								
Test for subgroup differences: Not applicable								



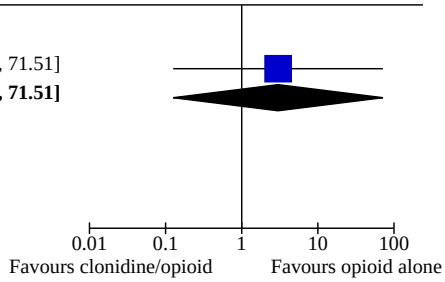
Analysis 10.5. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 5: Maximum weight loss (%)

Study or Subgroup	Clonidine/opioid Mean	SD	Total	Opioid alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.5.1 Clonidine + DTO vs DTO								
Agthe 2009	6.91	3	40	7.79	3.6	40	100.0%	-0.88 [-2.33 , 0.57]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**-0.88 [-2.33 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.23)								
Total (95% CI)			**40**			**40**	**100.0%**	**-0.88 [-2.33 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Not applicable								



Analysis 10.6. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 6: Adverse events (treatment-related)

Study or Subgroup	Clonidine/opioid Events	Total	Opioid alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.6.1 Clonidine + DTO vs DTO						
Agthe 2009 (1)	1	40	0	40	100.0%	3.00 [0.13 , 71.51]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**3.00 [0.13 , 71.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						

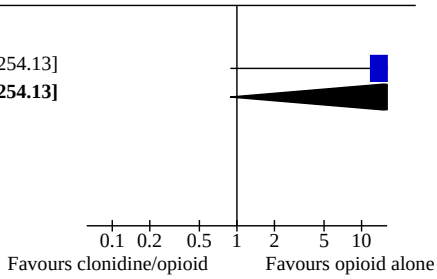


Footnotes

(1) One infant with SVT. No hypotension or rebound hypertension.

Analysis 10.7. Comparison 10: Clonidine and opioid versus opioid alone (all infants), Outcome 7: Rebound neonatal abstinence syndrome after stopping treatment requiring retreatment

Study or Subgroup	Clonidine/opioid Events	Total	Opioid alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.7.1 Clonidine + DTO vs DTO						
Agthe 2009	7	40	0	40	100.0%	15.00 [0.89 , 254.13]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**15.00 [0.89 , 254.13]**
Total events:	7		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						

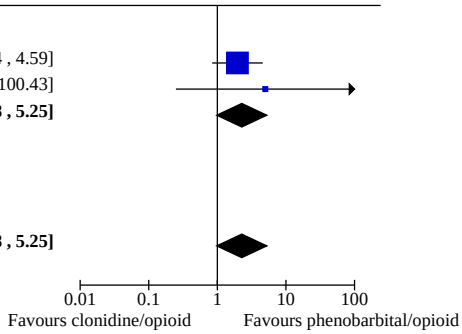


Comparison 11. Clonidine and opioid versus phenobarbital and opioid (all infants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Treatment failure	2	93	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.98, 5.25]
11.1.1 Clonidine + morphine vs phenobarbital + morphine	2	93	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.98, 5.25]
11.2 Seizures	1	68	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 71.15]
11.2.1 Clonidine + morphine vs phenobarbital + morphine	1	68	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 71.15]
11.3 Mortality to discharge	1	68	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3.1 Clonidine + morphine vs phenobarbital + morphine	1	68	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.4 Days' hospitalisation	2	91	Mean Difference (IV, Fixed, 95% CI)	7.13 [6.38, 7.88]
11.4.1 Clonidine + morphine vs phenobarbital + morphine	2	91	Mean Difference (IV, Fixed, 95% CI)	7.13 [6.38, 7.88]
11.5 Days' pharmacological treatment	2	91	Mean Difference (IV, Fixed, 95% CI)	7.57 [3.97, 11.17]
11.5.1 Clonidine + morphine vs phenobarbital + morphine	2	91	Mean Difference (IV, Fixed, 95% CI)	7.57 [3.97, 11.17]
11.6 Adverse events (treatment-related)	2	93	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.44, 5.40]
11.6.1 Clonidine + morphine vs phenobarbital + morphine	2	93	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.44, 5.40]

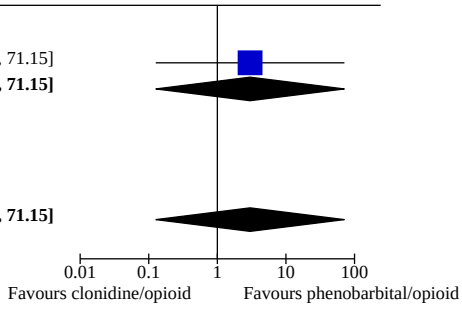
Analysis 11.1. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 1: Treatment failure

Study or Subgroup	Clonidine/opioid Events	Total	Phenobarbital/opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Clonidine + morphine vs phenobarbital + morphine						
Brusseau 2020	10	14	4	11	90.0%	1.96 [0.84 , 4.59]
Surran 2013	2	34	0	34	10.0%	5.00 [0.25 , 100.43]
Subtotal (95% CI)		**48**		**45**	**100.0%**	**2.27 [0.98 , 5.25]**
Total events:	12		4			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
Total (95% CI)		**48**		**45**	**100.0%**	**2.27 [0.98 , 5.25]**
Total events:	12		4			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
Test for subgroup differences: Not applicable						



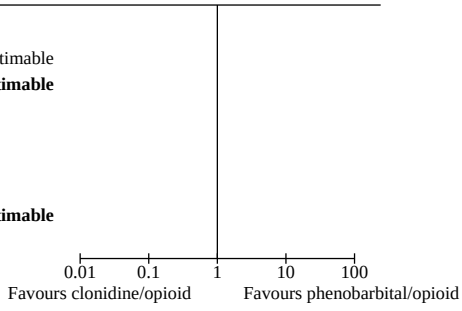
Analysis 11.2. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 2: Seizures

Study or Subgroup	Clonidine/opioid Events	Total	Phenobarbital/opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.2.1 Clonidine + morphine vs phenobarbital + morphine						
Surran 2013	1	34	0	34	100.0%	3.00 [0.13 , 71.15]
Subtotal (95% CI)		**34**		**34**	**100.0%**	**3.00 [0.13 , 71.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**34**		**34**	**100.0%**	**3.00 [0.13 , 71.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



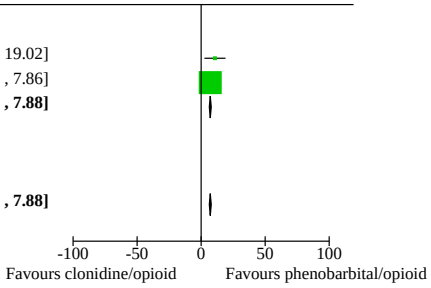
Analysis 11.3. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 3: Mortality to discharge

Study or Subgroup	Clonidine/opioid Events	Total	Phenobarbital/opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 Clonidine + morphine vs phenobarbital + morphine						
Surran 2013	0	34	0	34		Not estimable
Subtotal (95% CI)		**34**		**34**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**34**		**34**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



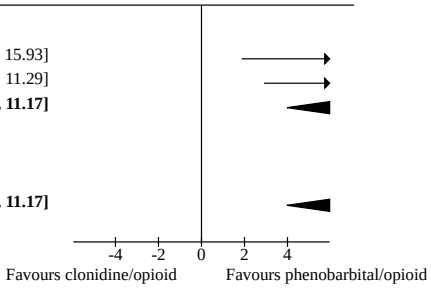
Analysis 11.4. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 4: Days' hospitalisation

Study or Subgroup	Clonidine/opioid Mean	SD	Total	Phenobarbital/opioid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
11.4.1 Clonidine + morphine vs phenobarbital + morphine								
Brusseau 2020	41.8	10.9	14	31	10	11	0.8%	10.80 [2.58 , 19.02]
Surran 2013	19.5	1.875	32	12.4	1.15	34	99.2%	7.10 [6.34 , 7.86]
Subtotal (95% CI)			**46**			**45**	**100.0%**	**7.13 [6.38 , 7.88]**
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 18.57 (P < 0.00001)								
Total (95% CI)			**46**			**45**	**100.0%**	**7.13 [6.38 , 7.88]**
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 18.57 (P < 0.00001)								
Test for subgroup differences: Not applicable								



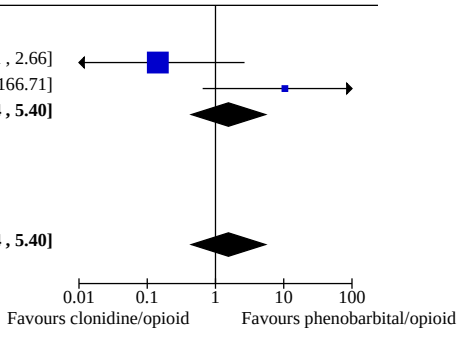
Analysis 11.5. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 5: Days' pharmacological treatment

Study or Subgroup	Clonidine/opioid Mean	SD	Total	Phenobarbital/opioid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
11.5.1 Clonidine + morphine vs phenobarbital + morphine								
Brusseau 2020	34.4	10.6	14	25.5	7.3	11	26.2%	8.90 [1.87 , 15.93]
Surran 2013	19.5	10.2624	32	12.4	6.5918	34	73.8%	7.10 [2.91 , 11.29]
Subtotal (95% CI)			**46**			**45**	**100.0%**	**7.57 [3.97 , 11.17]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 4.12 (P < 0.0001)								
Total (95% CI)			**46**			**45**	**100.0%**	**7.57 [3.97 , 11.17]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 4.12 (P < 0.0001)								
Test for subgroup differences: Not applicable								



Analysis 11.6. Comparison 11: Clonidine and opioid versus phenobarbital and opioid (all infants), Outcome 6: Adverse events (treatment-related)

Study or Subgroup	Clonidine/opioid Events	Total	Phenobarbital/opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.6.1 Clonidine + morphine vs phenobarbital + morphine						
Surran 2013 (1)	0	34	3	34	86.3%	0.14 [0.01 , 2.66]
Brusseau 2020 (2)	6	14	0	11	13.7%	10.40 [0.65 , 166.71]
Subtotal (95% CI)		**48**		**45**	**100.0%**	**1.55 [0.44 , 5.40]**
Total events:	6		3			
Heterogeneity: Chi² = 4.36, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**48**		**45**	**100.0%**	**1.55 [0.44 , 5.40]**
Total events:	6		3			
Heterogeneity: Chi² = 4.36, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Three infants were over sedated in the phenobarbital and morphine group

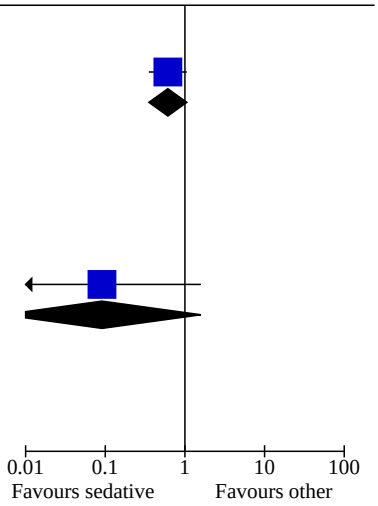
(2) Seven clonidine doses were withheld in three infants who developed hypotension during the treatment phase. One of these infants developed rebound hypertension and on

Comparison 12. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Treatment failure	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1.1 Phenobarbital vs chlorpromazine	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.35, 1.06]
12.1.2 Clonidine + diluted tincture of opium (DTO) vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.59]
12.2 Seizures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.2.1 Phenobarbital vs chlorpromazine	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2.2 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
12.3 Mortality after discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.3.1 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.37, 131.28]
12.4 Days' pharmacological treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.4.1 Clonidine + DTO vs DTO	1	80	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-8.33, 0.33]
12.5 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.5.1 Phenobarbital vs chlorpromazine	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.5.2 Clonidine + DTO vs DTO	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 71.51]

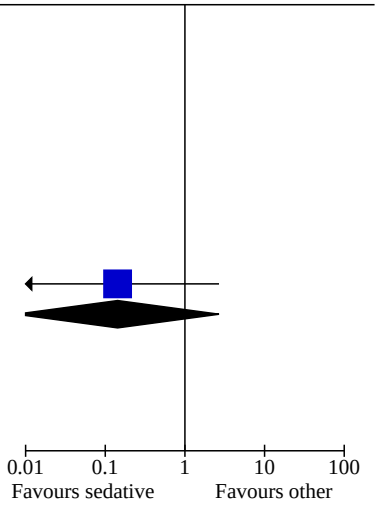
Analysis 12.1. Comparison 12: Sensitivity analyses, Outcome 1: Treatment failure

Study or Subgroup	Sedative Events	Sedative Total	Other Events	Other Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Phenobarbital vs chlorpromazine						
Zimmermann 2020	13	47	24	53	100.0%	0.61 [0.35 , 1.06]
Subtotal (95% CI)		**47**		**53**	**100.0%**	**0.61 [0.35 , 1.06]**
Total events:	13		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
12.1.2 Clonidine + diluted tincture of opium (DTO) vs DTO						
Agthe 2009	0	40	5	40	100.0%	0.09 [0.01 , 1.59]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.09 [0.01 , 1.59]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						



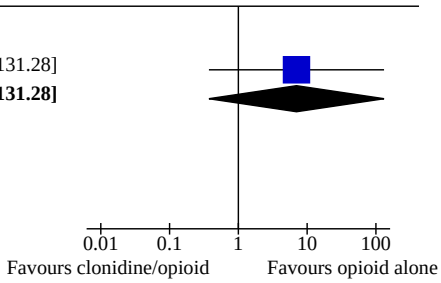
Analysis 12.2. Comparison 12: Sensitivity analyses, Outcome 2: Seizures

Study or Subgroup	Sedative Events	Sedative Total	Other Events	Other Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.2.1 Phenobarbital vs chlorpromazine						
Zimmermann 2020	0	47	0	53		Not estimable
Subtotal (95% CI)		**47**		**53**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.2.2 Clonidine + DTO vs DTO						
Agthe 2009	0	40	3	40	100.0%	0.14 [0.01 , 2.68]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.14 [0.01 , 2.68]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						



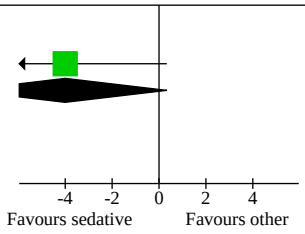
Analysis 12.3. Comparison 12: Sensitivity analyses, Outcome 3: Mortality after discharge

Study or Subgroup	Clonidine/opioid Events	Total	Opioid alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 Clonidine + DTO vs DTO						
Agthe 2009	3	40	0	40	100.0%	7.00 [0.37 , 131.28]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**7.00 [0.37 , 131.28]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						



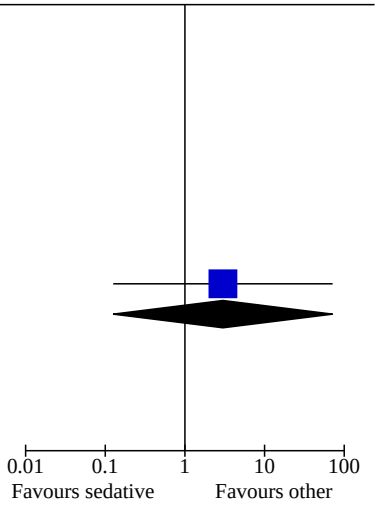
Analysis 12.4. Comparison 12: Sensitivity analyses, Outcome 4: Days' pharmacological treatment

Study or Subgroup	Sedative Mean	SD	Total	Other Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
12.4.1 Clonidine + DTO vs DTO								
Agthe 2009	11	12.5072	40	15	6.2536	40	100.0%	-4.00 [-8.33 , 0.33]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**-4.00 [-8.33 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.81 (P = 0.07)								



Analysis 12.5. Comparison 12: Sensitivity analyses, Outcome 5: Adverse events

Study or Subgroup	Sedative Events	Total	Other Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.5.1 Phenobarbital vs chlorpromazine						
Zimmermann 2020	0	47	0	53		Not estimable
Subtotal (95% CI)		**47**		**53**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.5.2 Clonidine + DTO vs DTO						
Agthe 2009	1	40	0	40	100.0%	3.00 [0.13 , 71.51]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**3.00 [0.13 , 71.51]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						



APPENDICES

Appendix 1. 2020 search strategies

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2020). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

CENTRAL via CRS Web

Date ranges: 1 January 2010 to 17 September 2020
Terms:
1 neonatal abstinence syndrome AND CENTRAL:TARGET
2 MESH DESCRIPTOR Neonatal Abstinence Syndrome EXPLODE ALL AND CENTRAL:TARGET
3 abstinence AND CENTRAL:TARGET
4 withdrawal AND CENTRAL:TARGET
5 MESH DESCRIPTOR Substance Withdrawal Syndrome EXPLODE ALL AND CENTRAL:TARGET
6 #1 OR #2 OR #3 OR #4 OR #5
7 MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET
8 infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET
9 #8 OR #7 AND CENTRAL:TARGET
10 #9 AND #6
11 2010 TO 2020:YR AND CENTRAL:TARGET
12 #11 AND #10

MEDLINE via Ovid

Date ranges: 1 January 2010 to 17 September 2020
Terms:
1. neonatal abstinence syndrome.mp. or exp Neonatal Abstinence Syndrome/
2. withdrawal.mp. or exp Substance Withdrawal Syndrome/
3. abstinence.mp.
4. 1 or 2 or 3
5. exp infant, newborn/
6. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.
7. 5 or 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. drug therapy.fs.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. or/8-15
17. exp animals/ not humans.sh.
18. 16 not 17
19. 7 and 18
20. randomi?ed.ti,ab.
21. randomly.ti,ab.
22. trial.ti,ab.
23. groups.ti,ab.
24. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.
25. placebo*.ti,ab.
26. 20 or 21 or 22 or 23 or 24 or 25
27. 6 and 26
28. limit 27 to yr="2019 -Current"
29. 19 or 28
30. 4 and 29
31. limit 30 to yr="2010 -Current"

ISRCTN:

Date ranges: 2010 to 17 September 2020
Terms:
“Neonatal Abstinence Syndrome” and AND (Participant age range: Neonate)
“Substance Withdrawal Syndrome” AND (Participant age range: Neonate)

Appendix 2. Previous search methodology

The standard search strategy of Cochrane Neonatal was used. See Review Group details for more information. This was supplemented by additional searches of the Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (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 conferences (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, hypnotics and sedatives, benzodiazepines, clonidine, diazepam, phenobarbital, antipsychotic agents] and [infant-newborn or pregnancy]") and text word searches (using terms including: "[withdrawal, abstinence, addiction, sedative, benzodiazepine, clonidine, diazepam, phenobarbital, phenobarbital] 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 (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 to 2005).

The search was updated in September 2010 by DO with additional searches of the Cochrane Central Register of Controlled Trials (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 2006 to 2010).

Appendix 3. Risk of bias tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

1. low risk (any truly random process, e.g. random number table; computer random number generator);
2. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
3. unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

1. low risk, high risk or unclear risk for participants; and
2. low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

1. low risk for outcome assessors;
2. high risk for outcome assessors or
3. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted 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 was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

1. low risk (less than 20% missing data);
2. high risk (20% or greater missing data) or
3. unclear risk.

6. Selective reporting bias. Were reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

1. low risk (where it was clear that all the study's prespecified outcomes and all expected outcomes of interest to the review had been reported);
2. high risk (where not all the study's prespecified outcomes had been reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or
3. unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

1. low risk;
2. high risk; or
3. unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
17 September 2020	New search has been performed	We updated the search on 17 September 2020.
17 September 2020	New citation required and conclusions have changed	This updates the review 'Sedatives for opiate withdrawal in newborn infants' published in Issue 10, 2010 of the Cochrane Database of Systematic Reviews (Osborn 2010). We included three additional studies (Brusseau 2020; Surran 2013; Zimmermann 2020). Conclusions are updated.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 3, 2002

Date	Event	Description
28 April 2010	New search has been performed	This updates the review "Sedatives for opiate withdrawal in newborn infants" published in Issue 3, 2005 of the Cochrane Database of Systematic Reviews (Osborn 2005). Search updated in March 2010. One new trial added (Agthe 2009). New outcomes included.
28 April 2010	New citation required and conclusions have changed	Conclusions updated.
16 October 2008	Amended	Converted to new review format.
31 March 2005	New citation required but conclusions have not changed	Substantive amendment
31 March 2005	New search has been performed	This is an update of the existing review "Sedatives for opiate withdrawal in newborn infants" published in The Cochrane Library, Issue 3, 2002 (Osborn 2002). One additional study included, which compared phenobarbitone versus placebo in infants treated with dilute tincture of opium for neonatal abstinence syndrome.

CONTRIBUTIONS OF AUTHORS

DO wrote the original protocol (Osborn 2000), and review (Osborn 2002). All review authors 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 reviews 2005 (Osborn 2005), and 2010 (Osborn 2010), DO searched for new studies, assessed eligibility, critically appraised studies and extracted data independently. In 2005, HJ critically appraised the new study and performed data extraction (Osborn 2005). In 2010, DO wrote the updated review (Osborn 2010).

For the updated review 2020, DO, AZ and JM independently assessed eligibility, critically appraised studies and extracted data. DO wrote the updated review. JD assessed eligibility, critically appraised studies and extracted data for studies published up to 2018.

DECLARATIONS OF INTEREST

AZ: none.

JM: none.

JGD: none.

DO: none.

SOURCES OF SUPPORT

Internal sources

- Australasian Satellite of Cochrane Neonatal, Australia

  Provided support for authors at all stages of the protocol and review.

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Updated to Review Manager 5 format. Methods for assessment of heterogeneity, unit of analysis issues and reporting bias added.
2. From previous version (Osborn 2010), intervention comparisons updated to include 'sedative versus sedative in opioid-treated infants'; 'addition of a sedative in opioid-treated infants'; and 'addition of an opioid versus other sedative in sedative-treated infants'. Specific sedative comparisons documented.
3. From previous version (Osborn 2010), specified or updated (or both) outcome definitions for seizures, neurodevelopmental disability and postnatal growth reporting.
4. From previous version (Osborn 2010), added outcomes 'Days pharmacological treatment of NAS' and 'Out of home care (foster care; adoption)'.
5. As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see 'How CENTRAL is created'; www.cochranelibrary.com/central/central-creation). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL.
6. Starting in July 2019, Cochrane Neonatal no longer searches for RCTs and CCTs on the following platforms: ClinicalTrials.gov or from The World Health Organization's International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/), as records from both platforms are added to CENTRAL on a monthly basis (see 'How CENTRAL is created'; www.cochranelibrary.com/central/central-creation). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN Registry (at www.isrctn.com/, formerly Controlled-trials.com), is searched separately.
7. Starting in September 2020, Cochrane Neonatal no longer searches for RCTs and quasi-RCTs from CINAHL, as records are identified and added to CENTRAL on a monthly basis through Cochrane's Centralised Search Service project (see 'How CENTRAL is created'; www.cochranelibrary.com/central/central-creation).
8. For the 2020 update, we ran searches in the following databases: CENTRAL via CRS Web and MEDLINE via Ovid. The search strategies are available in Appendix 1. The previous search methods are available in Appendix 2. We used Cochrane's Screen4Me workflow to help assess the search results.
9. We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol (Osborn 2000), or in previous publications of the review (Osborn 2002; Osborn 2005; Osborn 2010).

INDEX TERMS

Medical Subject Headings (MeSH)

Chlorpromazine [therapeutic use]; Clonidine [therapeutic use]; Diazepam [therapeutic use]; Hypnotics and Sedatives [*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; Infant, Newborn