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Pharmacological Treatments for Neonatal Abstinence Syndrome
A Systematic Review and Network Meta-analysis

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IMPORTANCE Incidence of neonatal abstinence syndrome is rising rapidly, and optimal pharmacotherapy may meaningfully reduce length of treatment.

OBJECTIVE To compare pharmacological therapies for neonatal abstinence syndrome.

DATA SOURCES Systematic review and network meta-analysis of Medline (1946-June 2018), Embase (1974-June 2018), Cochrane CENTRAL (1966-June 2018), Web of Science (1900-June 2018), and ClinicalTrials.gov (June 2018).

STUDY SELECTION Randomized clinical trials of pharmacological treatments for neonatal abstinence syndrome alone or in combination with adjuvant treatments. Abstract, title, and full-text screening were conducted independently by 2 reviewers (T.D. and C.G.).

DATA EXTRACTION AND SYNTHESIS Data extraction was conducted independently by 2 reviewers (T.D. and C.G.) according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)–Network Meta-Analyses guidelines. Quality was assessed with the Cochrane Risk of Bias tool and data were pooled with fixed-effect models as a result of the low number of trials that were included in the analysis.

MAIN OUTCOMES AND MEASURES The primary outcome was the length of treatment. The length of stay, need for adjuvant therapy, and adverse events were considered as secondary outcomes.

RESULTS Eighteen trials (N = 1072) were eligible for inclusion. The treatments that were included in the length of treatment analysis were buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Sublingual buprenorphine was considered the optimal treatment for a reduction in the length of treatment (days: mean difference vs morphine, −12.75 [95% CI, −17.97 to −7.58]; median rank, 1 [3-1]) and length of stay (days: mean difference vs morphine, −11.43 [95% CI, −16.95 to −5.82]; median rank, 1 [3-1]) but not the need for adjuvant treatment (odds ratio vs morphine, 1.23 [95% CI, 0.46-3.44]; median rank, 3 [5-1]). The results were robust to bias but sensitive to imprecision.

CONCLUSIONS AND RELEVANCE The current evidence suggests that buprenorphine is the optimal treatment for neonatal abstinence 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 stay.

Editorial

Supplemental content

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Neonatal abstinence syndrome (NAS) defines a constellation of symptoms that arise primarily in neonates who have been exposed to opioids during gestation.[1] Symptom onset typically occurs within 4 to 5 days and includes jitteriness, a high-pitched cry, diaphoresis, and diarrhea.[1] National data from a representative sample of hospital discharges in the United States suggest a more than 5-fold increase in incidence between 2004 to 2014 from 1.5 to 8.0 per 1000 live births among all payers.[2] In the Medicaid population, the inflation-adjusted total costs increased by a factor of 7 during the same period, from $65.4 million to $462 million (2014 US dollar), rising to 6.7% of all neonatal costs from an initial 1.6%.[2] Trends in Canada are similar, with a tripling of national incidence between 2003 and 2014 (1.8 CAD to 5.4 per 1000 live births) and an increase in total costs from $15.7 million to CAD $26.9 million.[3]

If initial nonpharmacologic treatments fail to control symptoms, guidelines suggest that pharmacological intervention should be initiated.[1] The choice of first-line treatment is variable across hospitals, with 53% of neonates with NAS in the Pediatric Health Information System receiving treatment with morphine, 36% receiving phenobarbital, and the remainder receiving a combination of treatments, methadone, or other treatments.[4] Additional treatments, including sublingual buprenorphine, have been investigated in randomized clinical trials (RCTs); however, to our knowledge, there is no current meta-analysis that provides estimates of the relative efficacy for all pharmacological interventions. The purpose of this network meta-analysis is to identify which treatment is the most effective at reducing the duration of pharmacotherapy.

Key Points

Question What is the most effective pharmacological treatment for neonatal abstinence syndrome?

Findings In this meta-analysis, buprenorphine was associated with the shortest length of treatment without additional adverse events. Morphine was consistently among the least effective treatments.

Meaning The choice of pharmacological agent may be associated with meaningful reductions in the length of treatment for infants with neonatal abstinence syndrome; however, there is a need for a large, multisite trial to assess the generalizability of the treatment benefits that are associated with buprenorphine.

Methods

Study Design and Search Strategy and Selection Criteria

This study was a systematic review with a Bayesian network meta-analysis and followed a prespecified protocol (PROSPERO 2017: CRD42017065394) (eAppendix 1 in the Supplement) and was Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-Network Meta-Analyses–compliant (eAppendix 2 in the Supplement). A database search was conducted in June 2018. The electronic search strategy was developed in partnership with an information specialist and included searches of the Cochrane Library Central Registry of Controlled Trials (1966-present), Ovid Medline (1946-present), Embase (1974-present), and the Web of Science Core Collection (1900-present) (eAppendix 3 in the Supplement). Forward and backward citation searching was conducted for all included studies. Ongoing trials were identified through ClinicalTrials.gov. No additional gray literature searching was conducted. The population of interest was neonates who were exposed to opioids in utero who required pharmacological treatment for symptoms of NAS. Eligible trials designs included RCTs that compared at least 2 pharmacological agents for treating NAS that were published in a peer-reviewed journal. The authors of published posters were contacted to confirm whether the research was subsequently published in a peer-reviewed format.

Study Selection and Data Extraction

Title and abstract screening, full-text screening, and data extraction were conducted independently by 2 reviewers (T.D. and C.G.) using Covidence (Cochrane).[5] All conflicts were resolved through consensus and, if necessary, consultation with a third reviewer. Data were extracted using standardized forms.

Primary and Secondary Outcomes

The primary outcome was the length of treatment, which was defined as the number of days that infants were receiving any pharmacological treatment for NAS (ie, opioids and/or other). Secondary outcomes included the length of stay in the hospital (days), the need for adjuvant treatment, and adverse events. If multiple adverse events were reported, the most serious was used for the analysis.

Quality Assessment and Risk of Bias

Critical appraisals were conducted using the Cochrane risk of bias tool for RCTs.[6] Two reviewers assessed each study, with conflicts resolved through consensus or, if required, consultation with a third reviewer. We planned to use funnel plots to investigate signs of publication bias.[6]

Statistical Analysis

Relevant clinical and study design characteristics were compared between eligible trials to assess the acceptability to synthesis (**Table**; eAppendix 4 in the Supplement). The analysis was restricted to trials conducted during 2000 or later because the clinical experts (M.C-Y. and B.S.) did not believe that the approach to treating infants before this point was consistent with the current standard of care, including an increase in using nonpharmacological interventions and movement away from the treatments used in earlier trials. The network structure was explored using network diagrams. The network meta-analysis was conducted using JAGS, version 4.3.1, and R, version 3.5 (R Foundation).[7] When at least 1 comparison contained 3 treatments, the applicability of a random-effects model was explored. Models properly accounted for correlations in multiarm trials, used a single heterogeneity parameter for the entire network, and placed vague priors on all of the parameters.[8] The absolute model fit was assessed through a comparison of residual deviance with the number

Table. Characteristics of Included Studies

Source	Treatments	No.	Nonpharmocological	Include Breastfed Infants	Assessment Scale	Gestational Age, wk	Birth Weight, g	Exposure, %	Included in Network Meta-analysis of Outcome		
									LoT	LoS	Adjuvant
Davis et al[9]	Morphine; methadone	117	Not described	Y	Finnegan	39.2	3157	Tobacco: 80.2; SSRI: 68.1; methadone: 62.9; buprenorphine: 33.7; illicit: 25	Y	Y	Y
Kraft et al[10]	Morphine; buprenorphine	63	Rooming in; promotion of breastfeeding; minimized stimulation; maternal engagement	Y	MOTHER NAS	38.7	3022.9	Tobacco: 88.9; methadone: 93.7; buprenorphine: 4.8; cocaine: 9.5; amphetamine: 1.6; illicit: 23.4	Y	Y	Y
Bada et al[11]	Morphine; clonidine	31	Swaddle; rocking; pacifier; reduced noise and light	Not described	Finnegan	37.8	2890	Tobacco: 38.7; methadone: 16.1; buprenorphine: 35.5; oxycodone: 71; benzodiazepine 23.2	Y	Y	N
Nayeri et al[12]	Morphine; phenobarbital (loading)	60	Not described	N	Finnegan	37.6	2750	Methadone: 6.7; heroin: 5; opium: 31.7; cocaine: 25; amphetamine: 3.3; polysubstance: 28.3	Y	N	Y
Brown et al[13]	Morphine; methadone	31	Not described	Y	Modified Finnegan	38.9	3143.1	Tobacco: 87.2; SSRI: 3.4; methadone: 41.9; buprenorphine: 58.1; cocaine: 35.5; amphetamine: 12.9; illicit: 32.3	Y	N	Y
Surran et al[14]	Morphine and phenobarbital; morphine and clonidine	66	Not described	Y	Modified Finnegan	38.9	3144.2	Tobacco: 56.1; methadone: 39.4; buprenorphine: 42.4; oxycodone: 24.2; polysubstance: 40.9	N	N	N
Kraft et al[15]	Morphine; buprenorphine	24	Not described	N	MOTHER NAS	39.2	2845	Methadone: 100	Y	Y	Y
Agthe et al[16]	DTO and placebo; DTO and clonidine	80	Not described	N	Modified Finnegan	38.7	2955.5	Tobacco: 88.75; methadone: 89; heroin: 68.8; cocaine: 61.3	Y	N	N
Kraft et al[17]	Morphine; buprenorphine	25	Not described	N	Modified Finnegan	39	3003	Methadone: 100	Y	Y	Y
Langenfeld et al[18]	Morphine; DTO	33	"Special gentle care"	Not described	Finnegan	38.9	2954.8	Methadone: 79; heroin: 39.9	Y	Y	N
Jackson et al[19]	Morphine; DTO and phenobarbital	75	Breastfeeding	Y	Lipsitz	39.5	2878.4	Methadone: 100; benzodiazepine: 32; illicit: 15.9	Y	N	Y

(continued)

Table. Characteristics of Included Studies (continued)

Source	Treatments	No.	Nonpharmacological	Include Breastfed Infants	Assessment Scale	Gestational Age, wk	Birth Weight, g	Exposure, %	Included in Network Meta-analysis of Outcome		
									LoT	LoS	Adjuvant
Kaltenbach et al[20]	Paregoric; phenobarbital (loading); phenobarbital (titration); diazepam	69	Not described	Not described	Neonatal abstinence scoring system	NA	NA	Methadone: 100	N	N	N
Finnegan et al[21] 1984a	Paregoric; phenobarbital (loading dose); diazepam	139	Swaddling; infrequent handling; demand feeding	Not described	Finnegan	NA	NA	Polysubstance: 67.7; illicit: 32.3	N	N	N
Finnegan et al[22]	Phenobarbital (titration); phenobarbital (loading)	30	Swaddling; infrequent handling; demand feeding	Not described	Finnegan	NA	NA	NA	N	N	N
Carin et al[23]	Paregoric; phenobarbital	31	Not described	Not described	Finnegan	38	2776.1	Methadone: 100; heroin: 12.9; cocaine: 9.8; benzodiazepine: 19.4	N	N	N
Kandall et al[24]	Paregoric; phenobarbital	111	Not described	Not described	Modified Lipsitz	39.3	2815.3	Methadone: 100; polysubstance: 56	N	N	N
Madden et al[25]	Diazepam; phenobarbital; methadone	48	Not described	Not described	Symptoms	NA	NA	NA	N	N	N
Kahn et al[26]	Phenobarbital (short course); phenobarbital (long course); chlorpromazine (short course); chlorpromazine (long course)	40	Not described	Not described	Unvalidated checklist	NA	NA	Heroin: 100	N	N	N

Abbreviations: DTO, diluted tincture of opium; LoS, length of stay; LoT, length of treatment; N, no; NA, not applicable; SSRI, selective serotonin reuptake inhibit; Y, yes.
MOTHER-NAS, Maternal Opioid Treatment: Human Experimental Research Neonatal Abstinence Syndrome scale;

of unconstrained data points, and the relative differences between models fit to the same data were assessed with deviance information criteria.[8] When a treatment comparison has no direct evidence (ie, the treatments have never been compared in a head-to-head trial), the network meta-analysis (NMA) estimates an indirect treatment effect. When both direct and indirect evidence exists for a treatment, the NMA estimates a mixed effect, which is generally more precise than the direct effect alone. Network meta-analyses rely on the assumption of transitivity to estimate indirect treatment effects. This requires trials to be considered comparable in terms of the distribution of effect modifiers. For example, if a treatment was more effective in infants who were born at younger gestational ages than older gestational ages, then gestational age could be considered an effect modifier. After data extraction and before formal synthesis, clinical experts (M.C-Y. and B.S.) assessed whether differences in trial protocols, cotreatments, and patient characteristics could be expected to act as effect modifiers. This process was conducted by using tables of trial characteristics and visualizations (Table; eAppendix 4 in the Supplement).[9-26] We planned to explore differences quantitatively, but no nodes had sufficient data for a meta-regression to be feasible. We planned to formally assess inconsistencies, which are the statistical manifestation of intransitivity, using unrelated mean-effects models. A sensitivity analysis was performed to assess the implications of the risk of bias and uncertainty using threshold plots outlined by Phillippo et al.[27] These methods identify the smallest bias adjustment that would lead to a change in treatment recommendations. All analyses were run on 4 chains with 20 000 iterations per chain, including a burn-in period of 1000 runs. Convergence was monitored using the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if they were consistent with a visual inspection of convergence and time series plots.[28,29] When medians were reported, the mean and standard deviation were imputed using standard methods.[30] The results of continuous outcomes were expressed in mean differences and accompanied with their 95% credible intervals. Adverse events were expressed as odds ratios. Treatment rankings were summarized using the median rank with its 95% credible interval.[31]

Results

Search Results and Study Characteristics

The database search returned 2149 citations after removing duplicates, of which 18 studies[9-26] met all the inclusion criteria (N = 1072) (eAppendix 3 in the Supplement). Studies ranged in size from 25[15] to 139[21] participants with a median sample size of 54 (interquartile range, 42.5) (Table). Ten studies were published since 2000, with the remainder published from 1977 to 1986. For 2 studies,[21,22] it was unclear whether a formal treatment protocol was followed. All other studies followed a formal treatment protocol. The most common tool used to assess symptom severity and guide treatment was the Finnegan tool,[9,11,12,18,21,23] followed by modified Finnegan tool,[13,14,16,17] the Maternal Opioid Treatment: Human Experimental Research NAS scale,[10,15] and 2 versions of the Lipsitz scale.[32,33] Older trials relied on clinical judgement[25] or informal checklists.[26] The use of nonpharmacological interventions was generally poorly reported (Table). The indication for initiation varied between trials, as did indication for dose increases, weaning, the definition of thresholds before an adjuvant drug was added, and the indication for treatment discontinuation (eAppendix 4 in the Supplement). Clinical leaders on the review team (M.C-Y. and B.S.) determined that while these differences may be prognostic for treatment length and the length of stay, they were not expected to interact with comparator treatments to modify their effect relative to morphine. Further, it was judged that treatment protocols were not likely to meaningfully bias one treatment over another within trials.

Risk of Bias Within Studies

Few included studies were considered to be at low risk of bias on all components.[10,11,13,16,18] Eleven trials either made no effort to mask treatments or did not provide sufficient information to judge the risk of bias related to blinding (eAppendix 4 in the Supplement).

Publication Bias and Ongoing Trials

No comparisons included a sufficient number of studies to assess publication bias using quantitative methods. Three posters were identified that were never published, although all 3 examined treatments that are not currently used. No registries were identified indicating the existence of other unpublished trials or trials that were terminated for a lack of effects or adverse events.

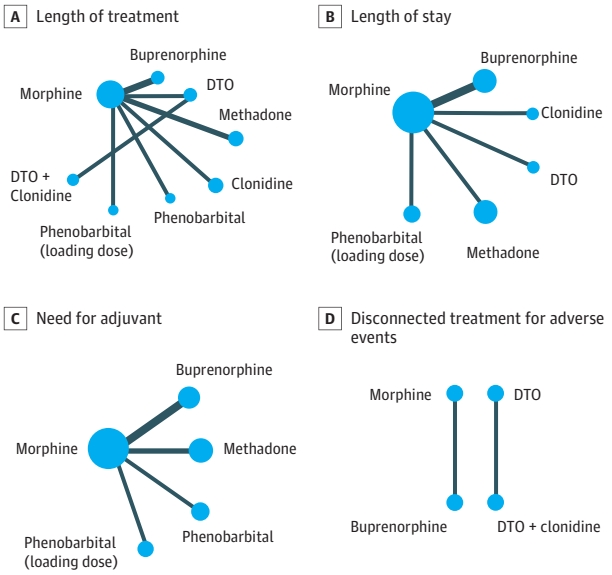
Ongoing Trials

Five ongoing trials were identified in the ClinicalTrials.gov database. Four assessed the efficacy of clonidine (NCT03092011 vs morphine, anticipated N = 90; NCT03396588 vs morphine, anticipated N = 200) and methadone (NCT02851303 vs morphine, anticipated N = 60) and 1 assessed buprenorphine (NCT01708707 vs morphine, anticipated N = 64).

Primary Outcome

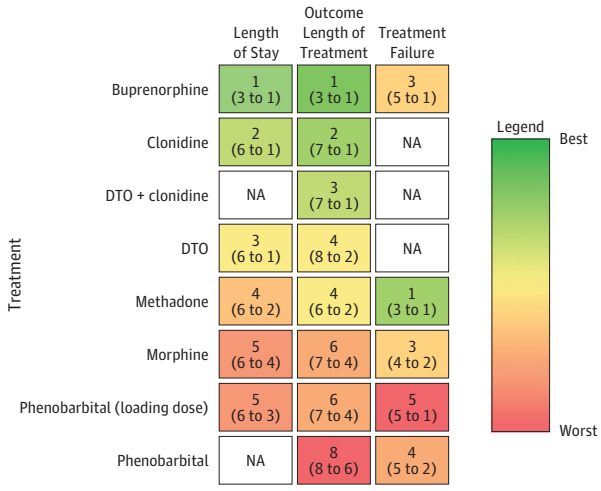
The connected network for length of treatment included 8 interventions assessed in 10 studies[9-13,15-19] (N = 538; **Figure 1**; eAppendix 5 in the Supplement). Based on a lack of multistudy comparisons, a fixed-effects model was used and was a good fit to the data (residual deviance, 19.64 on 20 data points). Three studies included treatments that are not typically used in contemporary North American practice. Agthe et al[16] compared diluted tincture of opium (DTO) monotherapy with concomitant DTO and clonidine and was included because of its influence on clinical practice (albeit replacing DTO with morphine). Langenfeld et al[18] compared morphine and DTO monotherapies and was included to allow concomitant DTO and clonidine to be connected to the network (Figure 1). Nayeri et al[12] compared morphine against phenobarbital monotherapy and was included to maintain relevance to global practice. Median ranks suggest buprenorphine as the best treatment, but the ranks for most treatments are imprecise (**Figure 2**). The NMA estimates that buprenorphine is associated with a reduction of length of treatment of 2.19 days (95% CI, −16.64 to 12.19) vs clonidine (indirect evi-

Figure 1. Network Graphs



Nodes indicate treatments and edges indicate comparisons from a single study for length of treatment (A), length of stay (B), the need for adjuvant (C), and disconnected treatment for adverse events (D). The size of the nodes indicates the relative sample size in a comparison, and the width of the edges represents the number of studies. DTO indicates diluted tincture of opium.

Figure 2. Heat Plot for All Outcomes Based on Median Rank



Median rank with 95% credible interval for each treatment and outcome combination with data. Lower ranks indicate that treatments are better. The tile color indicates where treatments are placed from worst (red) to best (green) within an outcome. NA indicates no information for a treatment; DTO, diluted tincture of opium.

dence only) and 12.75 days (95% CI, −17.97 to −7.58) vs morphine (**Figure 3**; eAppendix 6 in the Supplement). There were no loops of evidence that allowed for an assessment of inconsistency. Assessments of the threshold plots by study (eAppendix 7 in the Supplement) suggested that the analysis is robust to feasible adjustments of bias, although contrast plots indicated that the analysis was sensitive to imprecision (eAppendix 7 in the Supplement). This means that the credible intervals for treatment comparisons were wide enough that they included values that would change the treatment ranking from the analysis. Four trials were published before 2000[22,23,25,33] and excluded (N = 163).

Secondary Outcomes

Length of Stay

Seven studies (N = 352; eAppendix 5 in the Supplement) assessed the effect of 6 interventions on the length of hospital stays (Figure 1). A fixed-effects model offered a satisfactory fit to the data (residual deviance, 12 on 14 data points). The NMA estimates that buprenorphine is associated with a reduction of length of stay of 5.35 days (95% CI, −14.15 to 3.53) vs clonidine (indirect evidence only) and 11.43 days (95% CI, −16.95 to −5.82) vs morphine (Figure 3; eAppendix 6 in the Supplement). Threshold plots indicate that the analysis was robust to feasible adjustments for risk of bias, but sensitive to imprecision in the estimates of treatment effects at the contrast level (eAppendix 7 in the Supplement). The treatment rankings were consistent with those observed for the length of treatment (Figure 2). One trial was excluded from the analysis for being conducted before 2000.[25]

Need for Adjuvant

Seven studies (N = 394; eAppendix 5 in the Supplement) reported the number of infants who required adjuvant treatment. Three were excluded from analysis for being conducted before 2000.[20,21,25] Two studies could not be connected to the network.[14,16] A fixed-effects model had a satisfactory fit (residual deviance, 14.8 on 14 data points) and found no statistically significant differences between treatments; however, the treatment rankings differ meaningfully from other outcomes (Figures 2 and 3; eAppendix 6 in the Supplement). The interpretation of threshold plots was similar to other outcomes (eAppendix 7 in the Supplement). Agthe et al[16] found that no infants in the concomitant DTO and clonidine arm required additional therapy, whereas 5 in the DTO only arm did. Surran et al[14] found that 2 of 32 infants (6.25%) failed weaning attempts in the concomitant morphine and clonidine group, whereas none of the 34 infants in the morphine and phenobarbital group did (P = .23).

Adverse Events

No connected network could be formed (Figure 1). One of 12 infants (8.3%) receiving buprenorphine in the 2008 Kraft et al[17] study had a seizure, but this did not appear associated with treatment. Agthe et al[16] found that 3 infants experienced seizures in the DTO only arm compared with 0 who received concomitant clonidine. Three infants who received concomitant phenobarbital and morphine were assessed as oversedated by Surran et al.[14] Two remaining studies were conducted before 2000.[26,34]

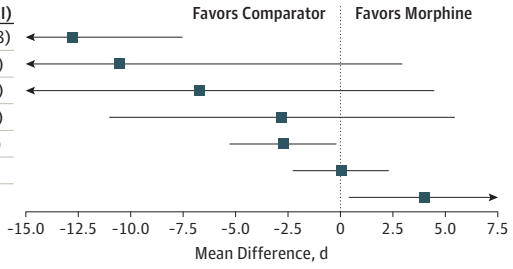
Discussion

Based on the current direct and indirect evidence from RCTs, buprenorphine has the highest probability of being the opti-

Figure 3. Forest Plot of Network Meta-analysis Estimates vs Placebo

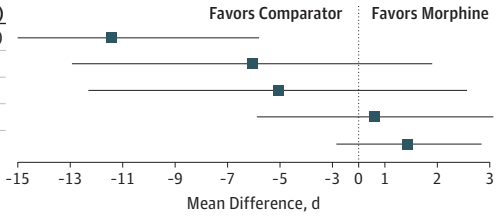
A Length of treatment vs morphine

Treatment	Mean Difference (95% CI)
Buprenorphine	-12.75 (-17.97 to -7.58)
Clonidine	-10.52 (-24.05 to 2.92)
DTO + clonidine	-6.76 (-18.06 to 4.43)
DTO	-2.84 (-11.01 to 5.42)
Methadone	-2.72 (-5.25 to -0.20)
Phenobarbital (loading dose)	0.00 (-2.29 to 2.28)
Phenobarbital	3.98 (0.39 to 7.63)



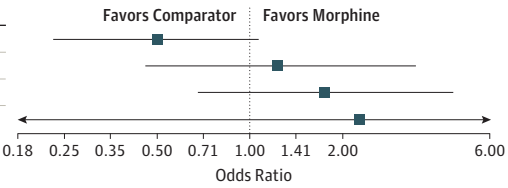
B Length of stay vs morphine

Treatment	Mean Difference (95% CI)
Buprenorphine	-11.43 (-16.95 to -5.82)
Clonidine	-6.09 (-12.93 to 0.79)
DTO	-5.04 (-12.29 to 2.10)
Methadone	-1.39 (-5.86 to 3.11)
Phenobarbital (loading dose)	-0.10 (-2.84 to 2.66)



C Treatment failure vs morphine

Treatment	Odds Ratio (95% CI)
Methadone	0.50 (0.23 to 1.07)
Buprenorphine	1.23 (0.46 to 3.45)
Phenobarbital	1.74 (0.68 to 4.54)
Phenobarbital (loading dose)	2.27 (0.15 to 100.00)



Treatments effects are reported based on a fixed-effects model in comparison with morphine monotherapy for length of treatment (A), length of stay (B), and treatment failure (C). Smaller values favor the treatment being compared with morphine. DTO indicates diluted tincture of opium.

mal treatment for reducing the length of pharmacotherapy and length of stay in neonates with NAS, although the treatment rankings for best treatments were imprecise. The worst treatments in terms of relative effects and rankings were morphine and phenobarbital monotherapies. These findings are of particular interest within the existing observational literature, which finds that morphine and phenobarbital are the most frequently used pharmacological approaches in the United States[4,35] and Canada.[3] The American Academy of Pediatrics[1] highlights that phenobarbital is most commonly used only as adjuvant therapy, raising additional concerns regarding the rationale used by centers that use phenobarbital monotherapy as a first-line treatment.

The rationale for why different pharmacological treatments affect the length of treatment is underdeveloped. The initial justification for buprenorphine focused on the ease of its dosing schedule and a potentially improved safety profile as a result of the drug's longer half-life and increased μ-opioid receptor activity.[17] This explanation was subsequently elaborated on by suggesting that the prolonged half-life could prevent a sudden appearance in withdrawal symptoms. Additional hypotheses included the suggestion that the dosing regimen of buprenorphine allowed a more rapid uptitration and that buprenorphine dosing and cessation guidelines favored shorter lengths of treatment.[15] Explanations in the most recent buprenorphine trial return to arguments based on half-life and receptor activity, although the differences in treatment protocols were broadly similar.[10] A further elucidation of possible mechanisms may be provided by a recent observational trial of a pharmacokinetically optimized methadone weaning schedule[36] that resulted in a 3-day reduction in the length of treatment when compared with a retrospective sample. These results question how much of the observed improvement in buprenorphine may be attributable to the differences in optimization of the treatment and weaning protocols. Further uncertainty in the effect of buprenorphine relative to morphine comes from its published use being restricted to a single center. A recent observational trial offers some evidence that observed improvements may generalize to other settings. Hall et al compared 174 infants who received buprenorphine and 186 who were treated with either morphine and methadone and found a 3-day (30%) reduction in the length of treatment.[36]

Recent research argues for an emphasis on providing shared rooms for families and infants (ie, rooming in) and nonpharmacological interventions to reduce the overall need for pharmacological treatment in addition to the use of standardized treatment protocols to reduce the associated length of stay when treatment is required. A recent review of rooming in included 6 nonrandomized studies (N = 549) and found a considerable reduction in the need for pharmacotherapy (relative risk, 0.37; 95% CI, 0.19-0.71) and the length of stay (mean difference, -10.41 days; 95% CI, 16.84 to −3.98).[37] Breastfeeding is associated with modest reductions in the length of stay

(mean, 3-7 days) and reductions in the need for pharmacotherapy (7%-44%).[38] Even with the use of nonpharmacological interventions, up to 70% of neonates with NAS will require pharmacological treatment.[39] Pharmacological treatment is associated with a doubling of the average length of stay (22 vs 10.9 days) and treatment costs ($44 720 vs $20 708, 2016 US dollars). Beyond costs, it is feasible to wonder whether long hospital stays may have small but meaningful effects on the quality of life of family members and their infants, although these outcomes were not measured in any included studies. Findings from this NMA emphasize that choice pharmacological treatments can make small to large improvements in the length of treatment required when both treatments are provided according to a stringent protocol. Thus, continued efforts to identify the optimal pharmacological agents are justified.

Limitations

Despite the trials forming the complete evidence base being found to be generally at a high risk of bias, most trials included in the meta-analysis were at low risk of bias and their conclusions appear robust to feasibly large treatment biases based on clinical judgement and the meta-epidemiological literature.[40] For example, for treatment rankings for the length of treatment to change, it would be necessary to estimate that the bias adjustment of the 2008 and 2011 Kraft buprenorphine trials[15,17] would reduce their point estimates to −1.10 (90% reduction) or −6.53 (57% reduction), respectively. Similarly, the results of Davis et al[9] showed an imbalance in the numbers of infants who were exclusively formula fed that may have favored methadone; however, no feasible amount of bias would lead to a change in the optimal treatment. However, treatment decisions are sensitive to imprecision in estimates, pointing toward a need to prioritize sufficiently powered comparisons of treatments. This is further complicated by poor reporting related to nonpharmacologic care, which can substantially reduce the length of treatment required with any opioid and could affect the generalizability of mean differences. Small, single-center trials and single-study connections increase the risk that the underlying assumptions of meta-analyses and network meta-analyses (eg, transitivity) are violated by chance and may limit generalizability to new locations.[41,42] The lack of loops of direct and indirect evidence means that there were no opportunities to test whether these sources of evidence were consistent. The current point estimates and their uncertainty should thus be interpreted with caution, particularly if used to inform future trials and practice change. The sparseness of the network also meant that it was impossible to quantitatively assess the potential effect of different assessment scales, treatment protocols, or nonpharmacological cointerventions on estimated treatment effects. We attempted to address this through engaging with our clinical expert team members (M.C-Y and B.S.), but it is possible that others may disagree with those assessments or that unmeasured effect modifiers were present. We encourage individuals to use the threshold plots in the Supplement to assess whether a feasible hypothetical bias adjustment (eg, a meta-regression on nonpharmacological strategies) would change the conclusions of the review.

Strengths

To our knowledge, this is the first comprehensive synthesis pharmacological treatment for NAS that allows estimates of head-to-head comparisons for all contemporary modalities. By combining all RCT evidence in a single review with common methods, clinicians and researchers are provided with a single source of reference and the ability to assess strengths and weaknesses across the entire body of evidence. The use of threshold plots allowed for the identification of imprecision to be a more feasible threat to the validity of results than risk of bias, which allowed for a clearer focus on aspects of interventions that are important for future research.

Implications for Research

It is unlikely that the current evidence base is sufficient to recommend specific, large-scale changes in treatment away from the current standard of care. There is a need to complement ongoing trials with a sufficiently large, pragmatic multisite trial that will allow an estimation of the effectiveness of buprenorphine (and potentially clonidine) vs morphine and identify the magnitude and causes of between-site heterogeneity. Efforts should be made to identify and eliminate differences in treatment protocols that may explain differences in lengths of treatment.

There is concern that using opioids and sedatives during the postnatal period may have deleterious long-term effects. Some preclinical and observational research suggests that exposure to opioids and sedatives in the neonatal period may result in poorer neurodevelopmental outcomes (eg, standardized developmental scales).[43] Buprenorphine currently lacks long-term outcome data, although preclinical studies suggest that it causes less demyelination of the immature brain than methadone.[43] Clonidine monotherapy has been suggested as a nonopioid alternative treatment based on preclinical rational and preliminary findings that suggest an improved score on the neonatal intensive care unit Network Neurobehavioral Score[44] for infants who were randomized to receive clonidine alone. If researchers believed that these effects could be expected to translate to longer-term developmental outcomes, future consideration of clonidine monotherapy may be warranted, although the sample sizes required to detect an effect amidst the complex home environment of many neonates born with NAS may make these efforts infeasible.[1]

Conclusions

The NMA showed a significant reduction in the length of stay and length of treatment with the use of buprenorphine for treatment of NAS as compared with morphine and other medications. We did not find any significant adverse events with the use of buprenorphine. Morphine, considered standard of care in most hospitals, was the lowest-ranked opioid for length of treatment and length of stay; however, it is impossible to provide strong recommendations for any alternative when the limitations of the evidence are considered. There is a need for a large multisite pragmatic trial that compares buprenorphine with other treatments before it can be universally accepted as a standard of care for treating NAS.

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