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Comparative effectiveness of opioid replacement agents for neonatal opioid withdrawal syndrome: a systematic review and meta-analysis

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Abstract

Objective(s)—To compare short-term treatment outcomes of opioid pharmacotherapy for neonatal opioid withdrawal syndrome (NOWS).

Study design—PubMed/MEDLINE, Embase, PsycINFO, and The Cochrane Library were searched from inception through September 30, 2018. Primary outcome was treatment duration (LOT). Secondary outcomes included hospitalization duration (LOS) and rate of adjunct drug needed (RAD).

Results—Of 753 publications, 11 studies met inclusion criteria. There was no difference in LOT (WMD −1.39 [−5.79 to −3.01] days, I^2 82%) or LOS (WMD −1.48 [−5.75 to −2.79] days, I^2 92%) between morphine and methadone. RAD with morphine was higher (RR 1.51 [1.35–1.69], I^2 0%). Buprenorphine was associated with shorter LOT (WMD 7.70 [0.88–14.53] days, I^2 76%) and LOS (WMD 5.61 [−0.01 to 11.24] days, I^2 60%) compared with morphine, in addition to methadone according to two cohort studies.

Conclusions—Methadone had superior primary treatment success compared with morphine. Buprenorphine was associated with the shortest overall durations of treatment and hospitalization.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Introduction

Neonatal opioid withdrawal syndrome (NOWS) or neonatal abstinence syndrome (NAS) is a significant public health problem in the United States. The incidence of NOWS has risen dramatically with recent data citing an increase from 7 to 27 cases per 1000 neonatal intensive care (NICU) admissions between 2004 and 2013 [1]. Related health-care costs have risen accordingly to 2.5 billion dollars per year [2].

Nonpharmacologic care (e.g., rooming-in, swaddling, breastfeeding, etc.) is initially recommended for all opioid exposed neonates. This approach has resulted in significant reductions in the number of infants needing pharmacologic treatment [3]. However, many neonates are not completely responsive to these measures with a substantial number still requiring treatment with one of more drugs [1]. A meta-analysis published by the Cochrane Collaboration in 2010 demonstrated greater safety and efficacy of first-line opioids compared with alternate classes of drugs such as barbiturates, benzodiazepines, antipsychotics, and other sedatives [4, 5]. The use of older drug formulations, such as paregoric and diluted deodorized tincture of opium (DTO) was also discouraged due to the presence of toxic ingredients, high alcoholic content, and associated complications [4].

In fact, current American Academy of Pediatrics (AAP) treatment guidelines specifically recommend opioid replacement for NOWS as the first step in pharmacologic management [3, 6]. Morphine and methadone are the most commonly used opioids in the United States with buprenorphine recently being evaluated as an additional option [7]. While the implementation of a standardized treatment approach has been shown to improve outcomes, substantial variability in how NOWS is treated persists across North America [7–10]. Existing data has been conflicting and unclear as to which opioid should be used on a routine basis.

A recent network meta-analysis concluded buprenorphine to be the optimal treatment option [11]. However, this study included various non-opioid agents (e.g., phenobarbital, clonidine) and antiquated drugs (e.g., paregoric, DTO), which the AAP specifically advises against. In addition, this analysis included randomized controlled trials (RCTs) only, which remain scarce overall and may not fully capture the existing data. Therefore, there remains an important need to examine the NOWS literature with an in-depth focus on the comparative effectiveness of opioid pharmacotherapy in order to guide best practice.

We performed an up-to-date systematic review and meta-analyzed short-term treatment outcomes of first-line opioid pharmacotherapy with the most commonly used agents: morphine, methadone, and buprenorphine. Due to the limited number of prospective, multisite RCTs investigating these drugs, retrospective cohort and single site prospective studies were included in this analysis to maximize sample size and enhance our analyses. Non-opioid and older, potentially harmful drugs were excluded given existing treatment recommendations. The primary outcome was length of treatment (LOT), and secondary outcomes included length of hospitalization (LOS) and rate of adjunct drug use (RAD).

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used for reporting of methods and findings. Multiple databases were searched from their inception through September 30, 2018: PubMed/MEDLINE, Embase, PsycINFO, and The Cochrane Library. Human primary literature in the English language was searched and included RCTs and cohort studies for this review. All other study designs (case reports or series, review articles, meta-analyses, editorials) were excluded. We looked for gray references on clinicaltrials.gov to identify ongoing and completed trials with unpublished data related to NOWS. A snowballing technique of reviewing references of relevant studies was used as well as the Similar Articles feature in PubMed. See Table 1 for full search terms.

The present study compared short-term treatment outcomes of the most commonly used opioids (morphine, methadone, and buprenorphine) for the primary pharmacologic management of NOWS. Because opioids are recommended for pharmacotherapy of NOWS [3–6], the meta-analysis focused on opioids and did not include studies of non-opioids, such as antipsychotics (e.g., chlorpromazine) and other sedatives (e.g., phenobarbital, benzodiazepines). Older drug formulations like paregoric and DTO were excluded, as they are currently discouraged from clinical use due to significant safety concerns. In addition, studies of clonidine, a newer sedative undergoing investigation for potential use as primary pharmacologic treatment, were also excluded in the analysis due to the small number of studies.

The primary outcome was LOT with LOS and RAD as secondary outcomes. Reporting of at least one of the primary or secondary outcomes was required for the study to be considered for inclusion. Insufficient reporting of additional outcome measures precluded them from quantitative analysis.

The Covidence systematic review software was used to import studies and conduct all subsequent steps. Studies were initially screened from search results based on title and abstract by one author (JJL). Two independent reviewers (JJL and JC) assessed studies for eligibility by examining their full texts. They then independently performed quality assessments using the Cochrane Risk of Bias Tool for RCTs. Quality assessments for cohort studies were performed using the ROBINS-I Risk of Bias assessment tool for nonrandomized interventions. Studies were categorized as low, medium, or high risk. RCTs were considered low risk due to their rarity and importance. Cohort studies were rated as medium risk if both reviewers rated the study as either low risk or unclear risk of bias across all categories. Otherwise, they were rated as high risk. Data extraction was done using the templated forms through Covidence to collect critical study information. Discrepancies between the two reviewers were resolved at every step by consensus or adjudication with a third reviewer (LSS) when necessary.

RevMan software (version 5.3) was used to conduct the meta-analysis using a random-effect model. Meta-analysis was performed when at least three unique studies were available for evaluation. Weighted mean differences (WMD) and 95% confidence interval (CI) were used

to pool results for continuous outcomes. All continuous outcomes were analyzed as means and standard deviations (SD), and when necessary, the approximation method published by Wan et al. was used [12]. Risk ratios (RR) and 95% CI were used to pool results for dichotomous outcomes. Forest plots were generated for visual inspection of summary effect sizes. Groupings for heterogeneity were assessed using the I^2 statistic and a threshold of 50% was used to define meaningful heterogeneity. Sensitivity analyses were then performed in order to resolve heterogeneity and reanalyze outcomes based on results from the quality assessments.

Results

Search results

The search yielded 753 unique records. Of these, 7 were ongoing clinical trials identified on clinicaltrials.gov [13–19]. Of the remaining 746 records, 677 were excluded on the basis of title and abstract with 69 articles assessed for eligibility by full-text review. Twenty records [20–39] were selected for possible inclusion and further review after irrelevant records were excluded due to absent opioid exposure, wrong or absent pharmacologic intervention, and wrong or absent comparator drug.

Of these 20 articles, two studies required further inquiry via email communication with the primary authors in which unpublished data were queried for possible inclusion in the quantitative analyses: Patrick et al. [25] and Hall et al. [20]. Requested data were reported to be no longer available from Patrick et al., so this was excluded from the meta-analysis. Unpublished data were successfully obtained from Hall et al., which were then included in the meta-analysis.

Ultimately, 11 unique studies composed of 8989 total infants met full inclusion criteria. One cohort study (Hall et al.) [20] compared the effectiveness of morphine vs methadone vs buprenorphine; data from that particular study were extracted for all possible drug comparisons, which accounts for duplicate study numbers. Figure 1 depicts the study's PRISMA study selection flow diagram.

Characteristics of included studies are summarized in Table 2. The NOWS population was primarily identified through ICD-9 coding (NAS, 779.5) in conjunction with positive maternal and fetal toxicology results and/or maternal prenatal history when available. Opioid exposure was heterogeneous, comprising of illicit and prescription drugs and/or maternal maintenance therapy with methadone or buprenorphine. Polysubstance abuse was common. Neonates who were born preterm (<36 weeks of gestation) or with major congenital disease or complex medical issues were excluded. Withdrawal from postnatal opioid exposure was also excluded. All studies provided baseline comparisons of characteristics between the treatment arms. Universally examined characteristics included neonatal sex, gestational age, and anthropometric birth measures (e.g., birth weight, length, and head circumference). Opioid exposure type and dosage, polysubstance abuse profile, and the use of nonpharmacologic measures were examined when specifically delineated and compared between treatment groups.

Treatment regimens were comparable across the included studies. Pharmacologic therapy was initiated based on Finnegan, modified Finnegan, or MOTHER (Maternal Opioid Treatment: Human Experimental Research) Finnegan assessment scoring [40]. Medications were dosed by weight, typically as: morphine 0.2–0.4 mg/kg/day divided every 3–4 h, methadone 0.1 mg/kg/dose every 6–12 h, or buprenorphine 4–6 mcg/kg/dose sublingually every 8 h. Drugs were then titrated based on a score gradient and weaned when scores were stabilized for 12–48 h by 10% dosing decrements as tolerated. Phenobarbital was the most commonly used adjuvant drug when a predefined maximum opioid dose or score was met. A phenobarbital bolus dose of 10–30 mg/kg was initially given, followed by maintenance protocol of 5–6 mg/kg/day divided every 8–12 h. Studies that deviated significantly from this approach or had other methodologic differences were rated as high risk because their validity for comparative analysis was likely compromised. Follow-up sensitivity analyses removing these studies were conducted.

[1] Morphine vs methadone—Morphine and methadone are the two most commonly used opioids in the pharmacologic management of NOWS [7]. Morphine has a shorter half-life compared with methadone and is typically administered every 3–4 h according to either weight-based or less frequently, symptom-based regimens [41, 42]. While the longer half-life of methadone may allow for more consistent blood concentrations over time and allow for smoother weaning, the shorter half-life of morphine may facilitate easier dose adjustment and more rapid weaning [41].

There were eight total studies (two RCTs and six cohort studies, $n = 8876$ infants) comparing morphine and methadone that were eligible for quantitative analysis. There was no difference in LOT (Fig. 2; WMD -1.39 [-5.79 to 3.01] days, I^2 82%) or LOS (WMD -1.48 [-5.75 to 2.79] days, I^2 92%) between the morphine and methadone-treated groups. The use of adjunct drugs was significantly higher with the use of morphine (RR 1.51 [1.35 – 1.69], I^2 0%).

It was not feasible to perform a meta-analysis of the RCTs alone given the paucity of available studies. Qualitative summary of the two existing RCTs favored methadone over morphine in decreasing LOT (Davis et al. multisite: relative number of days adjusted for site and type of maternal opioid, 0.84 (0.73–0.97), $p = 0.02$; Brown et al. single site: 21 (15.8, 29.5) vs 14 (10, 20), $p = 0.008$) and LOS (Davis et al. multisite: relative number of days adjusted for site and type of maternal opioid, 0.86 (0.74–1.00), $p = 0.046$; LOS not measured in Brown et al.). The RAD use was less frequent in the methadone treatment groups (Davis et al. multisite: odds ratio adjusted for site and type of maternal opioid, 0.44 (0.18–1.09), $p = 0.07$; Brown et al. single site: 9/15 vs 6/15, $p = 0.64$), although this association was not statistically significant [22, 38].

Sensitivity analysis of the cohort studies alone produced comparable results to the meta-analysis of all studies. Although there was no significant difference in LOT (WMD -4.97 [-10.91 to 0.96] days, I^2 79%) and LOS (WMD -2.19 [-7.10 to 2.72] days, I^2 93%) between morphine and methadone treated infants, morphine was associated with a higher rate of adjuvant drug treatment (RR 1.51 [1.26 – 1.82], I^2 29%).

An additional sensitivity analysis was performed by removing the two cohort studies rated high risk for bias [23, 39]. These were judged to be high risk due to the absence of a specific treatment protocol. While this follow-up analysis reduced heterogeneity, it did not change the study results significantly (LOT WMD 0.34 [−2.92 to 3.60] days, I^2 70%), LOS WMD −1.01 [−3.57 to 1.54] days, I^2 48%, RAD RR 1.64 [1.32–2.04], I^2 0%).

[2] Morphine vs buprenorphine—Buprenorphine is a long-acting partial opioid agonist with a wide therapeutic index and low risk of respiratory depression that has received significant interest for the treatment of NOWS [43]. There were four total studies (three RCTs: two open-label safety and feasibility trials and one double-blinded, double dummy trial, and one cohort study, $n = 473$ infants) comparing treatment with morphine to buprenorphine. Although buprenorphine was associated with a shorter LOT (Fig. 3; WMD 7.70 [0.88–14.53] days, I^2 76%) and LOS (WMD 5.61 [−0.01 to 11.24] days, I^2 60%), there was no significant difference in the use of adjunct treatment (RR 1.04 [0.84–1.28], I^2 0%). Sensitivity analysis separating the RCTs from the cohort study did not significantly alter this finding (LOT WMD 10.68 [5.55–15.82] days, I^2 0%, LOS (WMD 8.84 [3.47–14.21] days, I^2 0%, RAD RR 0.76 [0.24–2.38], I^2 31%).

[3] Methadone vs buprenorphine—There were only two retrospective cohort studies ($n = 451$ infants) [20, 30] comparing methadone to buprenorphine, so meta-analysis was not feasible. Qualitative summary of these study findings suggested that buprenorphine was associated with a shorter LOT (Hall et al., 2016: 9.4 (7.1–11.7) vs 14.0 (12.6–15.4 days), $p < 0.001$; Hall et al., 2018: 7.4 (6.3–8.5) vs 10.4 (9.3–11.5) days, $p < 0.001$) and LOS (Hall et al., 2016: 16.3 (13.7–18.9) vs 20.7 (19.1–22.2) days, $p < 0.001$; Hall et al., 2018: 12.4 (11.3–13.6) vs 15.2 (14.1–16.4) days, $p < 0.001$). There were no significant differences in the need for adjunct therapy (Hall et al., 2016: 23.7 vs 25.8%, $p = 0.79$; Hall et al., 2018: 52.3 vs 46.2%, $p = 0.30$).

Discussion

This systematic review and meta-analysis of 11 studies (5 RCTs and 6 cohort studies) composed of 8989 infants found that the use of morphine or methadone did not differ in LOT or LOS. There was a 1.5-fold overall increase in the RAD use with morphine compared with methadone, which provides a compelling rationale to support the use of methadone for the pharmacologic management of NOWS. These findings suggest methadone therapy may be effective in minimizing deleterious polydrug exposure in these infants. For instance, phenobarbital, which is the most commonly used adjunct drug, has been associated with longer-term cognitive deficits in infants, with animal data suggestive of disruptions to synaptic development [44].

Fundamental differences exist between the effects of morphine and methadone on opioid and nonopioid receptors which may explain the better response seen with methadone therapy. Morphine and methadone have different opioid receptor affinities for each of the receptor sub-groups (μ , δ , and κ) [45]. In general, methadone has a broader opioid receptor action compared with morphine, which is more specific to the μ opioid receptor.

Moreover, methadone also possesses N-methyl-D-aspartate (NMDA) receptor antagonist effects [45].

These results favoring methadone were similar to those from the Davis and Brown RCTs [22, 38], which demonstrated that a lower percentage of infants needed rescue with adjuvant drugs in their methadone treatment arms, although their results were not significant. While both of these prospective trials demonstrated methadone to be associated with shorter LOT and LOS compared with morphine, this meta-analysis could not confirm these differences.

In contrast, a significant decrease in LOT and LOS durations was found with buprenorphine compared with morphine therapy, with an average reduction in LOT by 7 days and LOS by 5 days. Health-care costs have been reported to be more than three times greater in infants treated for NOWS compared with their nonaffected peers (US \$16,983 compared with \$5610 in 2012), largely owing to a prolonged hospitalization [46]. The magnitude of the results from this meta-analysis suggests that choice of pharmacotherapy could have significant influence on health care utilization and cost. In addition, the results from the present study comparing buprenorphine to methadone demonstrated a similar favorable outcome associated with buprenorphine. However, the existing literature was limited and thus, this particular effect could not be quantified due to the very small number of existing studies.

The mechanism by which buprenorphine may lead to a shorter duration of treatment is not entirely clear. One possible reason is that the long half-life of buprenorphine may produce consistent drug serum levels and allow for more gradual loss of agonist activity at the mu opioid receptor [27]. Buprenorphine also possesses mixed pharmacologic properties, acting as a partial agonist at the mu, delta, and opioid receptor-like (ORL1) receptors and an antagonist at the kappa receptors, which may ease the weaning process [27].

This meta-analysis is the first to examine treatment outcomes across various opioids with all of the most current available studies. A recent network meta-analysis of RCTs compared pharmacologic treatments in 1072 infants including various non-opioid agents (e.g., phenobarbital, clonidine) and outdated drugs (e.g., paregoric, DTO) [11]. In contrast, our analysis specifically focused on opioids in concordance with the most current AAP treatment recommendations and included both RCTs and cohort studies. This approach generated a more robust sample size of nearly 9000 infants with NOWS. Our findings were consistent with their conclusions in support of buprenorphine in decreasing LOT and LOS. In addition, this study revealed that methadone was associated with reduced primary treatment failure and need for adjuvant drug use compared with morphine.

Other strengths of this study include a strict adherence to PRISMA guidelines and a wide reaching search strategy. Multiple databases were searched across a broad timespan, and additional techniques were utilized to seek out unpublished data for inclusion. In addition, there was an in-depth examination of the methods to compare drugs that were clinically meaningful.

While the existing data comparing buprenorphine to other opioids favored buprenorphine, it is important to recognize that all the prospective RCTs to date comparing morphine to

buprenorphine were conducted at a single center (Thomas Jefferson University Hospital) and therefore results may not be generalizable to the public at large. In addition, buprenorphine is presently composed of a substantial amount of ethanol (30%), which may not be safe for neonates and could potentially impact outcome. Likewise, formulations of methadone also contain a significant amount of ethanol (8–15%), though lower than those of buprenorphine. It should be kept in mind that morphine is currently the only formulation that is preservative free. There is very limited data on longer-term neurodevelopmental follow-up which is essential prior to the recommendation of a specific agent for universal use. A large, multisite RCT comparing buprenorphine to morphine and methadone (i.e. a three arm trial with safer formulations) is needed to confirm which choice of opioid is optimal.

Limitations

The diagnosis of NOWS remains inconsistent, and this particular population is also inherently heterogeneous, most significantly in their exposure profiles. Study populations are small, limited to single institutions, and focused on full term, otherwise healthy infants. The number of high quality, double-blinded RCTs remains very low in the NOWS literature. Nonrandomized studies are therefore a critical part of the NOWS knowledge landscape and were included in this meta-analysis to maximize the total number of infants available for investigation. Despite the known limitations associated with cohort studies, the majority of included studies were judged to have a low risk of bias when evaluated with the ROBINS-I Risk of Bias assessment tool, which is a widely accepted, validated method to assess the quality of non-randomized studies.

Every effort was made to scrutinize treatment protocols closely to assure they were reasonably comparable. However, it was not possible to fully account for practice variations across different institutions in the real world and uniformity of adherence rates for treatments. Standardized approaches to NOWS clinical withdrawal such as the Finnegan scoring system with use of intra-observer reliability training programs are highly recommended, but were not universally utilized [6]. The use of different scoring systems (e.g., Finnegan, modified Finnegan, MOTHER Finnegan, and Lipsitz) may have influenced durations of treatment. Similarly, the implementation of nonpharmacologic interventions (e.g., rooming-in, breastfeeding, and soothing) was not consistently reported in the studies selected within the current meta-analysis, though they have been shown to substantially reduce LOS and the need for pharmacotherapy [47]. There may also be other unknown covariates that were not captured, but could confound the current study's outcome measures.

This sort of variability may be documented by examining the absolute measures of LOT and LOS, which varied significantly across the included studies (the “Results” column of Table 2) leading to high P statistic values. However, this heterogeneity was successfully resolved by performing sensitivity analyses that removed studies that were judged to be high risk for bias or to depart significantly from typical treatment protocols.

Future investigations

The investigation of outcomes in the NOWS literature has been limited primarily to LOT and LOS. This may be problematic since it is unclear whether less pharmacologic treatment,

earlier discharge, and shorter LOS are necessarily beneficial for these at-risk infants and mothers, or will result in improved neurodevelopmental outcome which is ultimately the most important outcome measure. There are certainly other measures of interest in the determination of optimal drug selection.

More robust data on the rate of adverse events, readmission, and long-term comorbidities are needed to further characterize drug safety. Holistic infant outcomes such as those related to neurodevelopment, behavior, and overall wellness are also desirable. As stated, most formulations of methadone and buprenorphine contain a significant amount of ethanol (8–15 and 30%, respectively), which could impact safety and longer-term outcomes. The most recent Davis RCT addressed this issue, as investigators developed an ethanol preservative-free methadone compound to use in their study [38]. In one paper, newborns with NOWS treated with morphine were found to have significantly higher scores in cognitive and gross motor domains compared with those treated with methadone [21]. Further studies are needed to elucidate the long-term outcomes of treatment in these infants.

Conclusions

In conclusion, determining optimal opioid selection for the treatment of NOWS remains challenging. Coordinated efforts to develop common definitions for exposure, intervention, and outcomes are critically needed. A large multisite, double-blinded RCT comparing morphine, methadone, and buprenorphine is necessary to make a definitive recommendation as to which opioid treatment is best. Moreover, safe formulations of buprenorphine and methadone must be developed prior to universally expanding their use in real clinical practice. According to this up-to-date meta-analysis, methadone and buprenorphine may confer better short-term treatment outcomes compared with morphine and warrant serious consideration for wider implementation.

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Fig. 1.

PRISMA Study Selection Flow Diagram. *Hall 2018 cohort study [20] compared treatment outcomes for morphine vs methadone vs buprenorphine therapies, which accounts for duplicate study numbers

A. Length of Treatment

B. Length of Hospitalization

C. Rate of Adjunct Drug Use

Fig. 2.

Morphine vs methadone on length of treatment, length of hospitalization, and rate of adjunct drug use

A. Length of Treatment

B. Length of Hospitalization

C. Rate of Adjunct Drug Use

Fig. 3.
 Morphine vs buprenorphine on length of treatment, length of hospitalization, and rate of adjunct drug use

Table 1

Search terms and databases

Search	Query	Items found
Queries in PubMed/MEDLINE		
#1	"Neonatal Abstinence Syndrome/drug therapy" [Mesh] OR "Neonatal Abstinence Syndrome/therapy" [Mesh] OR "Neonatal Abstinence Syndrome/rehabilitation" [Mesh] OR Neonatal Drug Withdrawal*[tiab] OR Neonatal Drug Withdrawal Syndrome*[tiab] OR Neonatal Opiate Withdrawal*[tiab] OR Neonatal Opiate Withdrawal Syndrome*[tiab] OR Neonatal Opioid Withdrawal*[tiab] OR Neonatal Opioid Withdrawal Syndrome*[tiab] OR Neonatal Substance Withdrawal*[tiab] OR Neonatal Substance Withdrawal Syndrome*[tiab]	777
#2	"Morphine/therapeutic use" [Mesh] OR "Methadone/therapeutic use" [Mesh] OR "Buprenorphine/therapeutic use" [Mesh] OR "Analgesics, Opioid/therapeutic use" [Mesh] OR "Opiate Substitution Treatment/therapeutic use" [Mesh] OR "Phenobarbital/therapeutic use" [Mesh] OR "Barbiturates/therapeutic use" [Mesh] OR "Clonidine/therapeutic use" [Mesh] OR "Diazepam/therapeutic use" [Mesh] OR "Anticonvulsants/therapeutic use" [Mesh] OR "Hypnotics and Sedatives/therapeutic use" [Mesh] OR "Treatment Outcome" [Mesh] OR Management*[tiab] OR Treatment*[tiab] OR Therapy*[tiab] OR Therapeutic*[tiab] OR Pharmacologic*[tiab]	6,496,772
#3	Search #1 and #2	542
Queries in Embase		
#1	Disease ("neonatal abstinence syndrome") and Disease Subheadings ("disease management" OR "drug therapy" OR rehabilitation OR "therapy")	112
Queries in PsycINFO		
#1	"neonatal abstinence syndrome" and "treat*"	156
Queries in The Cochrane Library		
#1	"neonatal abstinence syndrome" and "treat*"	94
Queries in Clinicaltrials.gov		
#1	"neonatal abstinence syndrome"	44 (11 included)

Table 2

Characteristics of studies included in the meta-analysis

Publication	Study design	Study size	Study setting	Exposure profile	Treatment criteria	Treatment drugs (protocol type)	Outcomes assessed	Superior drug	Results	Risk of bias
Morphine vs methadone										
Tolia [39]	CS	7667	343 U.S. NICUs	Heterogeneous	NOS	Morphine (NOS), methadone (NOS)	LOS, RAD	Methadone	LOS, median (IQR) 23 (16–33) vs 18 (11–30); RAD, % 26 vs 17	H
Davis [38]	RCT	116	8 U.S. hospitals	Methadone or buprenorphine, other opioids for chronic pain	FA 8 × 2, 12 × 1	Morphine (WB + SB), methadone (WB + SB)	LOT, LOS, RAD	Methadone	LOT, mean (SD) 16.6 (6.9) vs 14.7 (8.0); LOS, mean (SD) 23.2 (8.8) vs 21.8 (15.0); RAD, % 29.3 vs 17.2	L
Hall [20]	CS	360	1 community hospital (Kentucky)	Heterogeneous	Modified FA 8 × 3, 12 × 2	Morphine (WB), methadone (WB), buprenorphine (WB)	LOT, LOS, RAD	Buprenorphine	LOT, mean (SD) 9.6 (5.9) vs 12.6 (8.2) vs 8.1 (5.2); LOS, mean (SD) 14.6 (6.2) vs 18.1 (8.1) vs 13.4 (6.2); RAD, % 54.5 vs 34.2 vs 52.3	M
Burke [21]	CS	36	1 inpatient rehabilitation program (Rhode Island)	Heterogeneous	FA 8	Morphine (WB), methadone (WB)	LOT, LOS	No difference	LOT, mean (SD) 21 (10.33) vs 22.67 (14.54); LOS, mean (SD) 45.42 (12.22) vs 42.65 (10.95)	M
Brown [22]	RCT	78	1 NICU and multiple PTUs (Maine)	Methadone or buprenorphine	Modified FA 9 × 2, 13	Morphine (WB), methadone (WB)	LOT, RAD	Methadone	LOT, median (25th, 75th quartile) 21 (15.8, 29.5) vs 14 (10, 20); RAD, proportion 9/16 vs 6/15	L
Young [23]	CS	26	1 NICU (Ohio)	Heterogeneous	FA 8 × 2, NWI 8 × 2	Morphine (SB), methadone (NOS)	LOT, LOS, RAD	Morphine	LOT, mean (SD) 7.46 (4.88) vs 38.08 (27.38); LOS, mean (SD) 12.08 (4.63) vs 44.23 (27.95); RAD, proportion 3/13 vs 6/13	H
Hall [24]	CS	547	20 children's hospitals (Ohio)	Heterogeneous	FA NOS	Morphine (NOS), methadone (NOS)	LOT, LOS, RAD	No difference	LOT, mean (95% CI) 15.6 (13.0–18.1) vs 16.2 (12.7–19.6); LOS, mean (95% CI) 21.6 (19.9–23.4) vs 21.5 (19.2–23.8); RAD, % 39.5 vs 23.2	M
Lainwala [26]	CS	46	2 community hospitals (Boston)	Heterogeneous	FA > 8 × 3, 12 × 2	Morphine (WB), methadone (WB)	LOS	No difference	LOS, median (IQR) 36 (33–39) vs 40 (30–51)	M
Morphine vs buprenorphine										
Kraft [27]	RCT	63	1 university hospital (Philadelphia)	Heterogeneous	3 MOTHER FA 24, 12 × 1	Morphine (WB), buprenorphine (WB)	LOT, LOS, RAD	Buprenorphine	LOT, median (IQR) 28 (13–67) vs 15 (3–67); LOS, median	L

Publication	Study design	Study size	Study setting	Exposure profile	Treatment criteria	Treatment drugs (protocol type)	Outcomes assessed	Superior drug	Results	Risk of bias
Kraft [28]	RCT	24	1 university hospital (Philadelphia)	Heterogeneous	3 MOTHER FA 24, 12 × 1	Morphine (WB), buprenorphine (WB)	LOT, LOS, RAD	Buprenorphine	(IQR) 33 (18–70) vs 21 (7–71); RAD, % 23 vs 15 LOT, mean (SD) 38 (14) vs 23 (12); LOS, mean (SD) 42 (13) vs 32 (24); RAD, proportion 1/12 vs 3/12	L
Kraft [29]	RCT	26	1 university hospital (Philadelphia)	Heterogeneous	3 Modified FA 24	Morphine (WB), buprenorphine (WB)	LOT, LOS, RAD	Buprenorphine	LOT, mean (SD) 32 (16) vs 22 (11); LOS, mean (SD) 38 (16) vs 27 (11); RAD, proportion 1/13 vs 3/12	L

CS cohort study, *PIU* pediatric inpatient unit, *FA* Finnegan assessment score, *NOS* not otherwise specified, *WB* weight-based dosing, *SB* symptom-based dosing, *IQR* interquartile range, *H* high, *M* medium, *L* low