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REVIEW ARTICLE

Therapeutic approaches for neonatal abstinence syndrome: a systematic review of randomized clinical trials

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Abstract

Neonatal abstinence syndrome (NAS) which is observed in 55–94% of the newborns from opioids-taking mothers produces deleterious neurological symptoms. Various pharmacological therapies have been investigated in neonates with NAS. This article reviews all studies on NAS treatment to analyze the duration of treatment, length of hospitalization and possible drug adverse effects. The search was limited to the randomized clinical trials which examined the treatments of neonates with NAS. Scientific databases including PubMed, Cochrane Library, ISI Web of Science, Embase and Scopus were systematically searched. Retrieved articles were reviewed by two researchers and evaluated using the JADAD scoring system. Finally, the treatment duration, hospitalization length and drug side-effects were extracted. Methadone, buprenorphine and clonidine were found more effective than morphine. Diluted tincture of opium (DTO) in combination with phenobarbital or clonidine was significantly more effective than DTO alone. Clonidine was a significantly better adjunctive therapy than phenobarbital in reducing morphine treatment days. No significant difference was observed between morphine and DTO effectiveness. Deciding the optimal regimen to manage symptomatic NAS, as a single or an adjunct therapy is not possible based on the literature, due to the low quality, small size and short-term treatment considered in the published studies.

Keywords Neonatal abstinence syndrome · Neonatal withdrawal syndrome · Neonatal passive addiction · Opioid · Opium · Methadone · Morphine · Clonidine · Withdrawal

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Highlights
- Although Neonatal abstinence syndrome (NAS) produces deleterious neurological symptoms with considerable emotional and economic burden to the society, no definite approach has been suggested for its treatment.
- The effectiveness of methadone, buprenorphine and clonidine was found to be superior to that of morphine in the treatment of NAS.
- Diluted tincture of opium (DTO) in combination with either phenobarbital or clonidine was significantly more effective than administered alone.
- There were conflicting findings regarding the comparative effectiveness of phenobarbital versus morphine to treat NAS.
- Clonidine was significantly better than phenobarbital as adjunctive therapy in reducing morphine treatment days in NAS.
- No significant difference was observed between morphine and DTO effectiveness.

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Introduction

The prevalence of nonmedical use of opioids is increasing. In the US, it is estimated that nearly 1% of the pregnant women actually use opioids during pregnancy [1]. Neonatal abstinence syndrome (NAS) is defined as "*sudden discontinuation of fetal exposure to chemicals/drugs used/abused by the mother during pregnancy*". This syndrome is observed in 55–94% of infants born from opioid-dependent mothers [2]. Infants with NAS may present deleterious and even life-threatening features including neurological hyperexcitability (insomnia, irritability, hypertonia, hyperreflexia, tremors, and seizures), gastrointestinal symptoms (vomiting, diarrhea, and feeding disturbances) and sympathetic/parasympathetic deregulation (sweating, fever, tachypnea, and congestion) [2]. The time of NAS symptom onset is variable ranging from hours to 8 days post-delivery [3]. NAS is also associated with costly hospitalizations [4].

The majority of symptomatic newborns require pharmacological support for safe opioid weaning [3]. Nevertheless, no

single drug has been evidenced as the most appropriate therapy to treat NAS. Although the American Academy of Pediatrics (AAP) has indicated opioids as first-line treatment of NAS, their use remains controversial in the neonate [1]. Alternative therapies include sedative drugs and/or centrally acting α2-agonists such as clonidine. The present article reviews all major studies published in the medical literature on NAS treatment aiming to analyze the duration of treatment, the length of hospitalization and the possible drug adverse effects.

Methods

Search strategy

The search was limited to the randomized clinical trials which examined the treatments of neonates with NAS. Scientific databases including PubMed, Cochrane Library, ISI Web of Science, Embase and Scopus were systematically searched for articles published until 29 August 2018, using combinations of the following keywords: ("Neonatal Abstinence Syndrome" OR "Neonatal Withdrawal Syndrome" OR "Neonatal Passive Addiction" OR "Opioid" OR "Opiates" OR "Heroin" OR "Hydromorphone" OR "oxycodone" OR "Opium" OR "Methadone" OR "Morphine" OR "Tramadol") AND ("Management" OR "Therapy" OR "Therapeutics" OR "Treatment" OR "Detoxification). The reference lists of the retrieved publications were thoroughly checked to complete the search.

Inclusion/exclusion criteria

Randomized Clinical trials that investigated the drug effects on NAS were included in this systematic review. There was no limitation for the control group. Duplicate and non-English articles were excluded.

Data extraction

The articles were reviewed by two researchers. First, related articles were identified based on the title and abstract. Then, full-text articles were downloaded and evaluated independently by two researchers. The references cited in the retrieved articles as well as the review articles published in this field were reviewed to find relevant studies.

Outcome measures

Outcome measures were the "type of treatment", "duration of treatment", "length of hospitalization" and "drug side-effects".

Quality assessment

To evaluate the quality of the trials, the Jadad scale which examines three important items [5] namely, randomization (description and adjustment), blinding (description and adjustment), report of withdrawals and the cause of loss to follow up, was used. Total score of Jadad ranges from 3 to 5 points. In the present work, two reviewers independently assessed the articles and calculated Jadad score. Any disagreements were resolved via consensus or by consulting with a third party. Intention-to-treat analysis was also reviewed and reported.

Data analysis

Due to the heterogeneity of the studies, it was not possible to perform meta-analysis and retrieved data were reported using a qualitative approach.

Results

We identified 1961 publications in our preliminary search. After excluding duplicate studies, 1011 articles remained. Of them, 963 articles were excluded based on the title and abstract and finally 48 full texts were reviewed. Here, 13 original articles were included in the final review. The PRISMA flow chart of this systematic review is presented in Fig. 1. The quality assessment of these articles is presented in Table 1. Their characteristics including the author's name, time of study, design (with details), type of opioid exposure in utero, the intervention and control groups, assessment tool of NAS

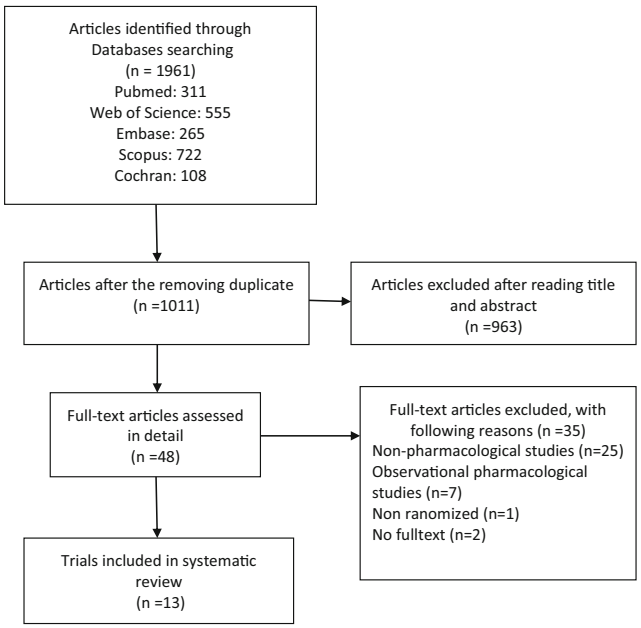

Fig. 1 Process of selecting trials included in the present systematic review

Table 1 The quality assessment of included studies in this systematic review

First author, year	Registration site/ code	Randomization			Blinding			Report of loss to follow up	Intention-to-treat analysis
		Mention randomization	appropriate Method	Inappropriate Method	Mention blinding	appropriate Method	Inappropriate Method		
Davis, 2018 [6]	ClinicalTrials.gov NCT01958476	+	+	–	+	+	–	+	+
Kraft, 2017 [7]	ClinicalTrials.gov NCT01452789	+	–	–	+	+	–	+	+
Nayeri, 2015 [8]	IRCT.ir IRCT201406239568N8	+	+	–	–	–	–	+	?
Bada, 2015 [1]	ClinicalTrials.gov NCT01734551	+	+	–	+	+	–	+	?
Brown, 2014 [9]	–	+	+	–	+	+	–	+	+
Surran, 2013 [10]	–	+	+	–	–	–	–	+	?
Kraft, 2011 [11]	ClinicalTrials.gov NCT00521248	+	+	–	–	–	–	+	+
Agthe, 2009 [2]	ClinicalTrials.gov NCT00510016	+	+	–	+	+	–	+	+
Kraft, 2008 [12]	ClinicalTrials.gov NCT00521248	+	+	–	–	–	–	+	?
Langenfeld,2005 [13]	–	+	+	–	+	+	–	+	?
Coyle, 2005 [14]	–	+	–	–	+	+	–	+	?
Jackson,2004 [15]	–	+	+	–	+	+	–	+	?
Coyle, 2002 []	–	+	–	–	+	+	–	+	?

+: Present; −: Absent;?: Intention-to-treat not reported

severity and the study primary outcome of are shown in Table 2.

Methadone vs. morphine

Treatment with methadone was associated with 14% reduction in the mean number of hospitalization days ($p = 0.046$) and 16% reduction in the length of treatment ($p = 0.02$) in comparison to morphine [6]. In another study, methadone-compared to morphine-treated newborns had significantly shorter duration of treatment ($p = 0.008$) [9].

Phenobarbital vs. morphine

No significant differences between oral phenobarbital and morphine were reported in one study regarding the treatment duration ($p = 0.9$) and hospital length of stay ($p = 0.7$) [8]. Conversely, shorter treatment duration following oral morphine versus phenobarbital ($p = 0.02$) was reported in a second study [15]. Interestingly, in both studies, no significant differences in terms of need for adjuvant therapy were observed between the two groups.

Morphine vs. diluted tincture of opium (DTO)

No significant differences in the treatment duration and hospitalization length were reported between the newborns treated with DTO vs. morphine [13].

Buprenorphine vs. morphine

The outcomes of buprenorphine vs. morphine were compared showing significantly shorter length of treatment ($p < 0.001$) and hospital stay ($p < 0.001$) in the buprenorphine-treated newborns [7]. Moreover, 15% versus 23% of the newborns in the buprenorphine and morphine groups required supplemental phenobarbital, respectively; nonetheless, this difference was not significant ($p = 0.36$). In another study comparing the same treatments, the durations of treatment ($p = 0.01$) and hospital stay l ($p = 0.05$) were significantly shorter in the buprenorphine vs. the morphine group [11]. Besides, 25% vs. 8.3% of the newborns in the buprenorphine and morphine groups required phenobarbital, respectively. No statistical comparisons between the groups were performed.

Buprenorphine vs. opium solution

Sublingual buprenorphine and DTO treatment did not result in significantly different effects on the length of treatment ($p = 0.077$) and hospital stay ($p = 0.068$) [12].

Clonidine vs. morphine

The duration of treatment ($p = 0.02$) and post-discharge treatment ($p = 0.005$) significantly decreased in the clonidine-compared to the morphine-treated newborns; nevertheless, the length of hospital stay did not vary significantly between the groups [1].

Clonidine /morphine vs. phenobarbital/morphine

Clonidine was compared with phenobarbital when co-administered as adjuvant therapy along with morphine to reduce NAS treatment days [10]. Significantly longer duration of treatment ($p = 0.037$) was observed in the clonidine (18.2 days) compared to phenobarbital group (13.6 days).

Clonidine/ DTO vs. placebo/DTO

NAS newborns orally received DTO before being randomized to two groups to receive clonidine vs. placebo as adjuvant therapy. In the clonidine group, the median duration of treatment was reduced by 27% compared to the placebo group ($p = 0.02$). Importantly, 12.5% of treatment failure was seen in the placebo group while no treatment failure was observed in the clonidine group ($p = 0.05$) [2].

DTO vs. DTO/phenobarbital

About 48% decrease in the length of hospital stay ($p < 0.001$) was reported with DTO/phenobarbital as compared to DTO alone to treat NAS [16]. Additionally, DTO/phenobarbital-treated newborns spent less time presenting severe withdrawal ($p < 0.04$). In another study, treatment with DTO alone significantly improved orientation and resulted in smoother movements in comparison to DTO/phenobarbital treatment ($p < 0.05$) [14]. The newborns were significantly more interactive. Additionally, length of hospital stay was significantly shorter in the DTO/phenobarbital-treated newborns compared to those who received DTO alone ($p < 0.01$).

With respect to the serious adverse effects observed following administration of the above-noted treatments, methadone could induce apnea, lethargy and hypothermia [6]; morphine could induce inguinal hernia [7]; buprenorphine caused supraglottoplasty, reflux/poor feeding (probably not related) [11], and generalized seizures [12]; and clonidine/DTO induced supraventricular tachycardia (SVT). Furthermore, three clonidine/DTO-treated infants died within 2 months after being discharged from the hospital. Deaths were reported to be due to myocarditis, sudden infant death syndrome (SIDS), and methadone overdose; nevertheless, according to the FDA, deaths were not likely caused by clonidine [12].

Table 2 Systematic review of the randomized studies regarding the neonatal abstinence syndrome

Author, year	Study design	No. of patients (Int. /Cont.)	Type of Opioid exposure in uterus	Intervention	Control	Drop out (%) (Int. /Cont.)	Assessment tool	Primary outcome	Results
Davis, 2018 [6]	Multi centric, randomized, double-blind, clinical trial	**59/59**	Buprenorphine/Methadone/ opioids for pain decreasing in pregnancy	methadone	Morphine	1.7/0	Finnegan	LOS	methadone was associated with decreased mean number of days for LOS by 14% ($P = .046$)
Kraft, 2017 [7]	single-site, randomized, double-blind, clinical trial	33/30	Methadone/ buprenorphine	sublingual buprenorphine	oral morphine	9/6.7	MOTHER NAS scale	Median length of treatment	shorter duration in Int. group vs. Cont. group [15 d vs. 28 d($p < 0.001$)]
Nayeri, 2015 [8]	Multi centric randomized, open-label, clinical trial	30/30	Opium/heroin/methadone/ cocaine/methamphetamine	Phenobarbital	Oral Morphine	0/0	Finnegan	Mean length of treatment	Non Sig. difference for the duration of treatment between Int. group (8.5 ± 4 d) vs. Cont. (8.5 ± 5 d) (P = 0.9)
Bada, 2015 [1]	randomized, double-blind clinical trial	15/16	Methadone, Buprenorphine, Oxycodone, hydrocodone Benzodiazepines	morphine	clonidine	0/0	Finnegan	Median length of Treatment	Longer duration of treatment in Int. group (39 d) Vs. Cont. (28 d) (p = 0.02)
Brown, 2014 [9]	single-site, randomized, double-blind clinical trial	15/16	Methadone/ buprenorphine	methadone	morphine	0/0	modified Finnegan	Median length of opioid treatment	shorter duration in Int. group vs. Cont. group [14 d vs. 21 d (p = 0.008)]
Surran, 2013 [10]	single site, open-label, randomized clinical trial	34/34	Methadone/ Buprenorphine/ Oxycodone	Clonidine+ morphine	Phenobarbital +morphine	6/0	Modified Finnegan	Median length of morphine treatment	Longer duration of treatment in clonidine Vs. Phenobarbital group [18.2 d Vs. 13.6 d, $p = 0.037$)]
Kraft, 2011 [11]	single site, open-label, Randomized, clinical trial	12/12	Buprenorphine/ Methadone	Sublingual buprenorphine	Morphine	0/0	MOTHER NAS score	Mean length of treatment	shorter duration in Int. group vs. Cont. group [23 ± 12 d vs. 38 ± 14 d, (p = 0.01)]
Agthe, 2009 [2]	Multi centric, double-blind, randomized, clinical trial	40/40	Methadone/ Heroin/ Cocaine	oral clonidine/ DTO*	placebo/DTO*	0/0	modified Finnegan	median length of treatment	shorter duration in Int. group vs. Cont. group [11 d vs. 15 d ($p = 0.02$)]
Kraft, 2008 [12]	open-label, randomized, clinical trial	13/13	opioids	sublingual buprenorphine	Opium solution	8/0	modified Finnegan	safety, tolerability,	Length of treatment (22d Vs. 32d), length of stay (27d Vs. 38d) were not significantly different
Langenfeld, 2005 [13]	Randomized double-blind clinical trial	16/17	Morphine/ Methadone	tincture of opium	Morphine	0/0	Finnegan	1.Length of treatment 2.total dose of tincture of opium needed	Length of treatment wasn't different significantly (26.9 d Vs.29.8 d)
Coyle, 2005 [14]	partially Randomized, clinical trial	17/15	methadone	phenobarbital/ DTO*	placebo/ DTO*	0/0	Finnegan	infant neurobehaviour during the first three weeks of life. LOS	improved orientation, quality of movement, lower total stress/ abstinence score ($p < 0.05$) Shorter duration in Int. group Vs. control [39.6 ± 25 d Vs. 69.8 ± 31 d ($p < 0.01$)]
Jackson, 2004 [15]	Double blind, randomized clinical trial	41/34	opioids	morphine	phenobarbital	0/0	Lipsitz	Median length of treatment	Shorter duration in Int. group Vs. control [8 d vs. 12 d (p = 0.02)]
Coyle 2002, [16]		10/10	Methadone/ heroin		Placebo/ DTO*	0/0	Finnegan		

Table 2 (continued)

Author, year	Study design	No. of patients (Int. /Cont.)	Type of Opioid exposure in uterus	Intervention	Control	Drop out (%) (Int. /Cont.)	Assessment tool	Primary outcome	Results
	partially randomized, clinical trial			Phenobarbital/ DTO*				duration of hospitalization	Shorter duration in Int. group Vs. control [38 d vs. 79 d ($P < 0.001$)]

LOS length of stay, *Int.* Intervention, *Cont.* Control, *vs.* versus, *d* day, *DTO* Diluted tincture of opium

*DTO: 0.4 mg/mL morphine

Non-serious adverse reactions of treatments used against NAS reported by the clinical trials discussed in this systematic review, are shown in Table 3.

Discussion

In 2005, an estimate of 250,000–300,000 females were reported to be intravenous drug abusers in the US and 75–90% of these abusers were of child bearing ages [14]. It was also estimated that almost 1% of the pregnant women take opioids [1]. Interestingly, fetal exposure to methadone during pregnancy poses a 60–80% risk of NAS development [14]. However, despite the increasing number of NAS in neonates, no optimal therapeutic approach has been established.

NAS pathophysiology is complex. The mesolimbic dopaminergic pathway is crucially involved in the development of physical dependency to opioids. In this regard, it was shown that in morphine abstinence syndrome, decrease in serotonin and mesolimbic dopamine lead to continued physical symptoms [17]. Following fetal exposure to opioids, the inhibitory effect of opioids on the noradrenergic neuronal pathways is suddenly abolished at birth, thus augmenting the noradrenergic activities [1].

In the present review article, we found that the efficacy of methadone, buprenorphine and clonidine for NAS treatment was higher than that of morphine. Also, a combination of diluted tincture of opium (DTO) and phenobarbital or clonidine was significantly more effective than DTO alone. Clonidine was a significantly better adjunctive therapy than phenobarbital in reducing morphine treatment days. Nevertheless, no significant difference was observed between morphine and DTO effectiveness.

Opioid use to treat NAS remains controversial, although recommended as first-line agents by the AAP due to their ability to rapidly control withdrawal symptoms [15]. The effectiveness of four different opioids namely buprenorphine, methadone, morphine and DTO as well as clonidine and phenobarbital, used in trials investigating NAS treatment has been discussed in our study.

Buprenorphine is a partial opioid receptor agonist responsible for ceiling effects. High affinity and slow dissociation from opioid-receptors enable buprenorphine to block the effects of other opioids taken after buprenorphine, characteristics that may explain its higher effectiveness in NAS as compared to short-acting opioids [7, 18]. The bioavailability of buprenorphine is around 48 and 31% following intranasal and sublingual administrations, respectively. Its oral bioavailability is very low [19]. Observed half-time ranges from 2.2 h following IV administration to 37 h following sublingual administration [20]. Its partial effects on opioid receptors causes less respiratory depression, sedation, withdrawal syndrome, and arrhythmia compared to methadone [21]. However,

Table 3 The side-effects of the drugs reported in the articles of this systematic review

Drug	Adverse effects	Ref	Drug	Adverse effects	Ref
Methadone	Shallow breathing	[6]	Buprenorphine	Anemia	[7]
	Bradycardia			Skin condition	
	Oxygen desaturation			Gastro-intestinal condition	
	Lethargy			Cough	
	Poor feeding			Tachycardia	
	Hypothermia			Umbilical granuloma	
	Emesis			CMV infection*	[11]
Morphine	Shallow breathing	[6]		Aminoaciduria*	
	Bradycardia			Clavicle fracture*	
	Oxygen desaturation			Elevated transaminases *	
	Lethargy			mild fungal paronychia *	[11]
	Poor feeding				[12]
	Hypothermia		Phenobarbital	poor feeding	[10]
	Emesis			mild respiratory depression	
			Clonidine/DTO	–	
			Opium solution	–	
			DTO	–	
	Skin condition	[7]			
	Gastro-intestinal condition				
	Respiratory infection				
	Urinary tract infection				
	Oral thrush*				
	conjunctivitis*				
	reflux*				

*probably unrelated in to intervention; Ref, Reference number; CMV, Cytomegalovirus; DTO, Tincture of opium

buprenorphine side-effects include hyperthermia, tachycardia, blood pressure increment [18], constipation, headache, nausea, urinary retention, and sedation [22]; rarely, it may induce idiosyncratic hepatotoxic reactions [23]. Similarly to buprenorphine, treatment of NAS with methadone reduced the mean number of hospitalization and treatment days in comparison to morphine. Methadone is a fat-soluble opioid rapidly absorbed by oral route. Methadone binds and activates the opioid receptors leading to analgesia, euphoria, constipation, sedation, respiratory depression, nausea, and miosis. Methadone oral bioavailability differs widely among patients with different genetic background; however, its average oral bioavailability is approximately 60–70%, nearly two times higher than that of buprenorphine. The half-life of methadone ranges from 15 to 55 h [24]. Besides constipation, respiratory depression, nausea, miosis, and impaired judgment, heart failure, and cardiac arrhythmias [21] have been reported as rare side-effects of long-term methadone administration.

Morphine is a full opioid receptor agonist. It also binds and inhibits GABA inhibitory interneurons. Morphine presents a variety of effects such as analgesia, anxiolysis, euphoria, sedation, constipation, nausea, vomiting, respiratory depression, and gastrointestinal system smooth muscle contraction [25, 26].

Hyperalgesia [27] and rhabdomyolysis-induced acute renal failure [28] were rarely reported after morphine administration, especially following high-dose opioid therapy. The bioavailability of morphine is approximately 30% and it has a half-life of about 2–4 h [26].

There has been a growing tendency towards the administration of non-opioid drugs due to the concerns of potential deleterious consequences of prolonged opioid exposure in the newborns who are in the early stages of their brain development [1]. Clonidine and phenobarbital have been regularly used as adjunct drugs. Phenobarbital, which causes sedation by activation of gamma-amino butyric acid (GABA) receptors in the central nervous system, has been used to treat NAS due to the frequent combination of benzodiazepine and opioid abuse [22]. Phenobarbital binds GABA-receptors and increases synaptic inhibition resulting in elevation of seizure threshold. Phenobarbital also inhibits calcium channels and reduces the excitatory neurotransmitter release. The sedative and hypnotic effects of phenobarbital are attributed to calcium channel inhibition in the midbrain [29]. The side-effects of phenobarbital include incoordination, impaired balance, and drowsiness. The bioavailability of phenobarbital is approximately 95% [30] and its half-life decreases by increasing age as it has a half-life of 79 h in adults but 110 h in children [31].

Similarly, clonidine was shown to be a satisfactory alternative for morphine. Clonidine is a α2-adrenergic agent which suppresses noradrenergic activity and alleviates opiate withdrawal signs and symptoms. In this context, stimulation of α2-receptors by clonidine inhibits the secretion of noradrenaline leading to reduction in sympathetic tone, blood pressure and heart rate [32]. The bioavailability of clonidine is 75–95% and 60–70% for oral and transdermal administration, respectively [33]. The half-life is around 6–20 h in subjects with normal renal function. However, in those with impaired renal function the elimination half-time increases to 18–41 h. The elimination half-life is also dose-dependent and increases at higher doses [32]. Both hypo- and hypertension, bradycardia, hypothermia, arrhythmia, coma, and death were reported following clonidine abuse [34]. Long-term exposure to opioids increases opioid receptors in the locus coeruleus which includes groups of noradrenergic cells. Opioid exposure inhibits adenylate cyclase activity which reduces cyclic adenosine monophosphate concentration. This reduction augments the potassium efflux in parallel with reductions in calcium influx, both inhibiting brain noradrenergic activities [1]. Clonidine is able to suppress the increase in noradrenergic activity when opioid exposure is terminated [1]. Although the co-administration of clonidine with opioids to NAS newborns decreases the duration of therapy, concerns with postnatal exposure to opioids remain [1].

Drug combination was also highly suggested to improve the results in NAS newborn, due to their multiple drug exposure in utero. The active ingredient of DTO is morphine, with 1 mg DTO containing 0.04 mg morphine [35]. Addition of phenobarbital to DTO resulted in shorter hospital stay and therefore decreased hospital charges per patient, compared to DTO alone [23]. In comparison to the newborns treated with only DTO, those treated with the two agents showed more marked improvements, higher levels of movements and less anxiety during the first three weeks after delivery. Though both groups improved over time, newborns getting the two-drug treatment more rapidly exhibited improvement in their neurobehavioral conditions [14].

NAS newborns frequently require dose increase to reach the control of their symptoms [9]. Therefore, evaluation of drug exposure in pregnancy based on the individual characteristics is mandatory to optimize drug response in NAS. Considering the side-effects of the conventional approaches used to treat NAS, future researches should be oriented on the assessment of new pharmacological therapies.

Our analysis clearly showed that studies investigating the pharmacological management of NAS have been performed on small sample sizes with single-center designs, thus limiting their power and external validity. Almost all included studies had not reported intention-to-treatment analysis. Additionally, some studies did not exclude preterm neonates and/or were based on rather low-quality methods.

In conclusion, it is difficult to acknowledge which therapy is optimal to treat NAS newborns based on the available literature. High-quality studies with large sample sizes are urgently required to improve the management of these neonates and limit further morbidities.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

References

1. Bada HS, Sithisarn T, Gibson J, Garlitz K, Caldwell R, Capilouto G, et al. Morphine versus clonidine for neonatal abstinence syndrome. Pediatrics. 2015;135(2):e383–91.
2. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics. 2009;123(5):e849–56.
3. Schwartz L, Xiao R, Brown ER, Sommers E. Auricular acupressure augmentation of standard medical management of the neonatal narcotic abstinence syndrome. Med Acupunct. 2011;23(3):175–86.
4. Winhusen T, Wilder C, Wexelblatt SL, Theobald J, Hall ES, Lewis D, et al. Design considerations for point-of-care clinical trials comparing methadone and buprenorphine treatment for opioid dependence in pregnancy and for neonatal abstinence syndrome. Contemp Clin Trials. 2014;39(1):158–65.
5. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
6. Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. JAMA Pediatr. 2018;172(8):741–8.
7. Kraft WK, Adeniyi-Jones SC, Chervoneva I, Greenspan JS, Abatemarco D, Kaltenbach K, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. N Engl J Med. 2017;376:2341–8.
8. Nayeri F, Sheikh M, Kalani M, Niknafs P, Shariat M, Dalili H, et al. Phenobarbital versus morphine in the management of neonatal abstinence syndrome, a randomized control trial. BMC Pediatr. 2015;15(1):15.
9. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. J Perinatol. 2014;35(4):278–83.
10. Surran B, Visintainer P, Chamberlain S, Kopcza K, Shah B, Singh R. Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome. A prospective randomized clinical trial. J Perinatol. 2013;33(12):954–9.
11. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. J Addict. 2011;106(3):574–80.
12. Kraft WK, Gibson E, Dysart K, Damle VS, Larusso JL, Greenspan JS, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. Pediatrics. 2008;122(3):601–7.
13. Langenfeld S, Birkenfeld L, Herkenrath P, Müller C, Hellmich M, Theisohn M. Therapy of the neonatal abstinence syndrome with

tincture of opium or morphine drops. Drug Alcohol Depend. 2005;77(1):31–6.
14. Coyle MG, Ferguson A, Lagasse L, Liu J, Lester B. Neurobehavioral effects of treatment for opiate withdrawal. Arch Dis Child Fetal Neonatal Ed. 2005;1(90):73–4.
15. Jackson L, Ting A, McKay S, Galea P, Skeoch C. A randomized controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome. Arch Dis Child Fetal Neonatal Ed. 2004;89(4):300–4.
16. Coyle MG, Ferguson A, Lagasse L, Oh W, Lester B. Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. J.Pediatr. 2002;140(5):561–4.
17. Diana M, Muntoni AL, Pistis M, Melis M, Gessa GL. Lasting reduction in mesolimbic dopamine neuronal activity after morphine withdrawal. Eur J Neurosci. 1999;11(3):1037–41.
18. Ilbäck N-G, Siller M, Stålhandske T. Effects of buprenorphine on body temperature, locomotor activity and cardiovascular function when assessed by telemetric monitoring in rats. Lab Anim. 2008;42(2):149–60.
19. Welsh C, Valadez-Meltzer A. Buprenorphine: a (relatively) new treatment for opioid dependence. Psychiatry (Edgmont). 2005;2(12):29.
20. National Center for Biotechnology Information. PubChem Compound Database; CID=644073, https://pubchem.ncbi.nlm.nih.gov/compound/644073. Accessed 1 Nov 2018.
21. Behzadi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: a literature review. Med Princ Pract. 2018;27(5):401–14.
22. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone metabolism and drug-drug interactions: in vitro and in vivo literature review. J Pharm Sci. 2018;107(12):2983–91.
23. Bogenschutz MP, Abbott PJ, Kushner R, Tonigan JS, Woody GE. Effects of buprenorphine and hepatitis C on liver enzymes in adolescents and young adults. J Addict Med. 2010;4(4):211–6.
24. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J. 2004;80(949):654–9.
25. Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg. 2008;107(4):1384–9.
26. National Center for Biotechnology Information. PubChem Compound Database; CID=5288826, https://pubchem.ncbi.nlm.nih.gov/compound/5288826.. Accessed 1 Nov 2018.
27. Wilson GR, Reisfield GM. Morphine hyperalgesia: a case report. Am J Hosp Palliat Care. 2003;20(6):459–61.
28. Shen C, Hung C, Wu C, Huang H, Ho W. Rhabdomyolysis-induced acute renal failure after morphine overdose–a case report. Acta Anaesthesiol Sin. 1999;37(3):159–62.
29. Lewis CB, Adams N. Phenobarbital. [Updated 2018 Oct 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan 2018. Available at https://www.ncbi.nlm.nih.gov/books/NBK532277. Accessed 1 Nov 2018.
30. Nelson E, Powell JR, Conrad K, Likes K, Byers J, Baker S, et al. Phenobarbital pharmacokinetics and bioavailability in adults. J Clin Pharmacol. 1982;22(2–3):141–8.
31. National Center for Biotechnology Information. PubChem Compound Database; CID=4763, https://pubchem.ncbi.nlm.nih.gov/compound/4763. Accessed 1 Nov 2018.
32. National Center for Biotechnology Information. PubChem Compound Database; CID=2803, https://pubchem.ncbi.nlm.nih.gov/compound/2803. Accessed 1 Nov 2018.
33. Lowenthal D, Matzek K, MacGregor T. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet. 1988;14(5):287–310.
34. Chiu S, Campbell K. Clonidine for the treatment of psychiatric conditions and symptoms: a review of clinical effectiveness, safety, and guidelines [internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Feb 21. Available at https://www.ncbi.nlm.nih.gov/books/NBK531717. Accessed 1 Nov 2018.
35. Liu T, Lewis T, Gauda E, Gobburu J, Ivaturi V. Mechanistic population pharmacokinetics of morphine in neonates with abstinence syndrome after oral administration of diluted tincture of opium. J Clin Pharmacol. 2016;56(8):1009–18.

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