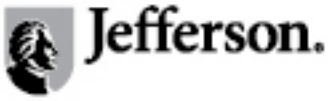

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Pharmacological and Non-pharmacological treatments for the Neonatal Abstinence Syndrome (NAS)

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Abbreviations:

Neonatal Abstinence Syndrome	-NAS
Neonatal Intensive Care Unit	-NICU
Randomized Control Trial	-RCT

ABSTRACT

Neonatal abstinence syndrome is defined by signs and symptoms of withdrawal that infants develop after intrauterine maternal drug exposure. All infants with documents in utero opioid exposure, or a high pre-test probability of exposure should have monitoring with a standard assessment instrument such as a Finnegan Score. A Finnegan score of >8 is highly correlated with opioid exposure, even in the absence of declared use during pregnancy. At least half of infants in most locales can be treated without the use of pharmacologic means. For this reason, symptom scores will drive the decision for pharmacologic therapy. However, all infants, regardless of initial manifestations, should be treated with non-pharmacologic approaches. Non-pharmacologic approaches should not be considered an alternative to drug therapy, but instead the base upon which all patients are treated. Those who continue to have symptoms should have addition of pharmacologic treatment.

Introduction

Neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome is defined by signs and symptoms of withdrawal that infants develop after intrauterine maternal drug exposure [1]. Following the cessation of umbilical drug transfer, presentations include mild and transient withdraw symptoms (nicotine, SSRIs) or toxidromes from direct drug effect (cocaine) [2]. In contrast, prolonged in utero exposure to opioids is associated with a more specific and often severe withdrawal syndrome [2]. The etiologic link has led to a proposed name of neonatal opioid withdrawal syndrome (NOWS) rather than the more non-specific NAS [2]. As polydrug exposure, particularly with concomitant benzodiazepines, is frequent and often leads to more symptomatology, the term NAS remains more common in clinical practice [3]. The maternal dose of methadone only weakly predicts severity of NAS symptoms [3]. The other clinical covariates of NAS severity are similarly not particularly predictive, and actionable decisions are based primarily on symptom presentation. Conceptually, the disease "NAS" captures a spectrum of severity. Imprecision of descriptions often conflate a diagnosis of NAS only with a neonatal opioid withdrawal that requires pharmacologic treatment. In fact, a more accurate approach is to define NAS as cardinal symptoms of withdrawal in the setting of known or highly suspected opioid exposure. NAS in whom pharmacologic therapy is used represent more severe disease. Most newborns will develop withdrawal symptoms within 24-48 hours after birth, however, delayed presentations of 5-10 days after birth are seen [4]. Severity and length of NAS might vary based on gestational age, type of illicit drug, and when the substance was used last. Withdrawal symptoms are graded using a standard instrument. The most commonly used are modifications of the Finnegan Score, which was developed as a research tool in the 1970's (Figure 1 for one variant

known as MOTHER NAS score) [5], and once a certain Finnegan Score threshold is exceeded newborns are treated [6, 7].

In the last 15 years, there has been a fivefold increase in NAS, which is associated with the rise of opioid use during pregnancy [8]. The incidence of NAS in 2012 was estimated to be 6.0 per 1000 live US births - a 5-fold increase since 2000. Since 2012, the incidence has continued to increase, with data in 2016 from 23 hospitals in the US Pediatric Health Information System showing an incidence of 20 per 1000 live births [9]. This puts a heavy burden on health resources since these newborns require prolonged medical treatment and longer hospital admission [10].

Treatment Approaches

All infants with documents in utero opioid exposure, or a high pre-test probability of exposure should have monitoring with a standard assessment instrument such as a Finnegan Score. A Finnegan score of >8 is highly correlated with opioid exposure, even in the absence of declared use during pregnancy [11]. At least half of infants in most locales can be treated without the use of pharmacologic means. We currently do not have good predictors of which infants will go on to more severe disease. For this reason, symptom scores will drive the decision for pharmacologic therapy. However, all infants, regardless of initial manifestations, should be treated with non-pharmacologic approaches. Non-pharmacologic approaches should not be considered an alternative to drug therapy, but instead the base upon which all patients are treated. Those who continue to have symptoms should have addition of pharmacologic treatment [Figure 1].

Non-pharmacological adjunct treatments

Non-pharmacological management of NAS (Box 1) is the base used for all infants with in utero opioid exposure [12, 13]. While specific interventions vary by location, ~95% of NICUs offered some aspect of non-pharmacological care [12]. Many NAS symptoms cause overstimulation in the newborn infant and non-pharmacological adjuncts utilize environmental and behavioral approaches to maximize infant comfort. Mild cases of NAS (Finnegan Score <8) are managed solely by using non-pharmacological approaches, while more severe cases require treatment with medication. Common methods of non-pharmacological care include: swaddling, positioning, quiet and dimly lit rooms, rooming-in, skin-to-skin contact, breastfeeding, and infant positioning [14].

Environmental control

Environmental control including *quiet and dimly lit rooms*, *swaddling*, *positioning*, and *bed types* are most commonly employed [14]. Adjusting environmental stimuli including *sound and lights* can ensure that hyper-aroused infants who experience withdrawal are not over stimulated.

Swaddling, a common practice which involves tightly wrapping the infant in a blanket, has been shown to decrease arousal, prolong sleep, improve neuromuscular development, decrease physiologic distress, improve motor organization, and self-regulatory ability [15]. While no study has examined swaddling in infants with NAS, it is widely accepted as a safe, effective intervention. The positive consequences of *prone position* for sleep include i) fewer awakenings and increased time in quiet sleep, more sleep with higher arousal thresholds, lower levels of activity, enhanced respiratory control, and diminished heart rate variability [16]. Maichuk *et al* randomized newborn infants with NAS to prone position (n=24) or supine position (n=24) and demonstrated that the

mean ±SD NAS was significantly higher in supine position compared prone position 7.6 ±0.7 vs 5.1 ±0.6 ($p< 0.0001$), respectively [16]. Also, supine-lying subjects had higher mean caloric intake (133±11 kcal/kg/24h) compared to than prone-lying infants (100±9 kcal/kg/24h) ($p<0.001$) [16]. Prone positioning decreases NAS symptoms potentially due to the cardiorespiratory and somatosensory effects of quieting response of prone positing [16]. Alternatively, non-oscillating waterbeds provide vestibular and tactile stimulation that is dependent on the neonate's own activities and might decrease irritability and increases periods of sleep [17]. In addition, a non-oscillating water bed (n=15) had significant lower NAS scores, earlier onset of consistent weight gain, and required up to 2mg/kg less phenobarbital compared to conventional bassinets (n=15) [17]. In contrast, D'Apolito *et al* randomized 14 infants with NAS to either a mechanical rocking bed or standard bed. Infants with the rocking bed therapy experienced a significant increase in withdrawal symptoms, poorer sleep patterns, and decreased neurobehavioral functioning on day 7 of life in infants [mean ±SD NAS score of 10±2 compared to 8±2 ($p=0.05$)] [18]. These studies suggest that *prone position* if possible combined with a *non-oscillating water bed* provides some soothing effect to newborns with NAS.

Feeding methods

Breastfeeding is one of the most commonly used non-pharmacological interventions for infants with NAS. However, there is often confusion about the safety of breastfeeding while on opioid substitution therapy [19], because previous clinical guidelines proposed potential harmful effects and from the possibility of continued concomitant illicit drug use [20]. While drugs are present in breast milk of mothers on substitution therapy, concentrations are low with low oral bioavailability, and no documented detrimental effects on infants [20]. Several studies analyzed

the breast milk of mothers on methadone for substitution therapy and reported low concentration of methadone in the breast milk not exceed 0.1mg/kg/day, amounting to only 2% of maternal dose [21]. Opioid substitution therapy is not a contraindication to breastfeeding and most mothers on substitution therapy should be encouraged to breastfeed [21, 22, 23].

Breastfeeding is consistently associated with a decrease in severity of NAS. A retrospective chart review of 190 drug-dependent mother-infant-dyads showed reduced NAS severity within the first 9 days and delayed onset, 25% reduction in need for pharmacologic treatment, and up to 20-day decrease in lengths of pharmacologic treatment, regardless of the gestation and the type of drug exposure when compared to formula fed [24]. Similarly, McQueen *et al* and Isemann *et al* also reported reduction in mean NAS scores, duration of opioid treatment, and length of hospital stay in breastfed infants [25, 26]. Welle-Strand *et al* reported a shorter mean ±SD lengths of stay of 28.6±19 in breastfed infants (n=95) vs. 46.7±26 ($p<0.05$) in formula fed infants (n=29) exposed to methadone, however no effect in infants exposed to buprenorphine was observed [27]. Despite the obvious benefits of breast milk, breastfeeding rates remain low. Wachman *et al* reported that only 24% of 276 opioid-exposed mother-infant-pairs at their baby-friendly hospital had any breast milk during their hospital stay with 60% of them discontinuing after an average of 6 days [28]. Given the documented benefit, attempts should be made to minimize potential barriers and increase breastfeeding rates in opioid-exposed infants.

Social integration

Parental presence might be beneficial due to *rooming in* or *skin-to-skin contact*, which facilitates mother and infant bonding and maternal comforting of the infant. Several studies have examined the effects of parental presences on NAS. Howard *et al* observed 86 mother-infant-dyads

and reported that maximum *parental presence* (100%) was associated with a 9 day shorter lengths of stay (r=-0.31) ($p<0.01$), an 8 day reduction of lengths of treatment (r=-0.34, $p<0.001$) and 1-point decrease in mean NAS score (r=-0.35, $p<0.01$) [29]. Similar, Abrahams *et al* and Hodgson *et al* examined the effects of *rooming-in* in infants exposed to maternal opioids in-utero [30, 31]. Infants in the rooming-in cohort had much higher breastfeeding rates (63% vs. 10% in non-rooming-in hospitals), it reduced morphine treatment (20-40% vs. 77% in non-rooming-in hospitals), length of hospital stay, and admission rates to Level II NICUs [30, 31]. The major benefit of rooming-in was the high rates of breast feeding mothers, which might have also contributed to some of the observed benefits [32].

Acupuncture

Acupuncture might possibly work by the release of endogenous opioids which in turn help restore the release of dopamine [33]. Illicit drugs can stimulate dopamine release and withdrawals are characterized by low levels of dopamine which can be restored by acupuncture [33]. Laser acupuncture is a form of non-invasive acupuncture that stimulates acupuncture points with use of a low level laser beam [33]. Raith *et al* randomized 28 preterm and term infants and reported that laser acupuncture combined with standard opioid treatment significantly decreases lengths of stay from 50 (36-66) to 35 (25-47) days in the control and acupuncture group ($p=0.19$), respectively [33]. Median (IQR) lengths of treatment was also significantly shorter with 28 (22-23) days for the acupuncture group compared to 39 (32-48) days for the control group ($p=0.48$) [33].

Most non-pharmacological treatments (exception of rocking and outpatient therapy) are safe, effective and easy to be implemented as adjuncts therapies to pharmacological treatments. While generally low risk, such interventions do require staff time and attention for implementation,

and as such a systemic evaluation of specific non-pharmacological therapies would assist clinicians in directing time and effort toward high yield intervention while decreasing effort on low yield efforts.

Pharmacological Treatments (Box 2)

The need for pharmacologic therapy is widely held to be needed for severe symptomatology. This is commonly linked to a specific threshold on a score (often an 8 on a Finnegan score) and less often explicitly linked to a goal of therapy. There is good consensus that there is a subset of infants that require pharmacologic therapy, but less so in defining the goals of care and tradeoffs associated with higher or lower threshold for treatment. Goals of pharmacologic therapy are to relieve infant discomfort, allow proper nutrition and development, and to foster parental bonding. End points in clinical trials are typically duration of therapy or length of hospitalization. These trial endpoints are not necessarily congruent with the aforementioned goals of treatment. For example, a higher threshold to start treatment and less aggressive dosing of an infant could lead to fewer days of treatment, but at the cost of a more irritable infant, poor feeding and weight gain, and parental stress. Similarly, attention is often paid to which is the best particular drug, without recognition that the drug resides within a treatment protocol with specific initial dose, up-titration schedule, maximum dose, and down titration. There have been few if any comparative studies that examine different regimens within a specific drug. As full agonists, morphine and methadone have a narrower therapeutic index than buprenorphine (partial agonist), but with inpatient monitored use, there are very few short-term safety issues with any of the commonly used opioids. With these caveats in mind, pharmacologic treatment is added when non-pharmacologic therapies adequately control NAS withdrawal symptoms. Cochrane and a variety

of narrative reviews support the use of base therapy of an opioid, with the addition of an adjunctive therapy. The opioid dose is increased until there is adequate control of symptoms, as defined using a standardized symptom instrument such as the Finnegan. After a ~48 hours of stability, the dose is slowly weaned. For those not fully controlled with an opioid alone, adjunctive drugs are added. Specific regimens and doses vary between institutions, but a representative algorithm from Royal Alexandra Hospital, Edmonton, Canada is presented in Figure 4.

Morphine

Morphine is acts as a full agonist on the μ opioid receptors and morphine solution is one of the most commonly used medications to treat NAS with ~80% of centers in the US employing it as primary agent [4, 34]. There is heterogeneity in dosing approaches, titration rates and maximal doses. The more common approach is that of weight based dosing, in which morphine is started at a dose of 0.07 mg/kg every 4 hours once a specific score trigger is crossed, for example if an infant has a Finnegan score >8 (Figure 3) [35]. An alternate approach is that the dose of morphine is not adjusted for weight, and instead the initial dose is based only on the Finnegan score. A high score, indicating severe disease, gets a high dose. The up titration is similar to the weight based approach, but the dose is not adjusted for size of the infant. These two approaches have not been directly compared to each other. Current recommendations for NAS treatment suggests oral morphine solution should be diluted to a concentration of 0.4 mg/mL [36]. In addition, many pharmacies have opted to use morphine over tincture of opium. Tincture of opium consists of opium 10mg/mL and requires a 25-fold dilution to achieve the recommended 0.4 mg/mL morphine. Care must be taken with dilution to avoid medical errors. Oral morphine is a preferred formulation. [36].

Methadone

Methadone is a long acting mu opioid agonist, currently used in 20% of US centers. It also has a NMDA antagonist effects, though how this may impact the clinical efficacy relative to morphine, is unclear. Current evidence suggests that methadone has a modest advantage over morphine based upon randomized controlled trials. (Table 1) The highest quality was that of Davis, which was a multicenter, randomized, blinded trial of 116 term infants to either methadone or morphine [39]. Compared to morphine, methadone treated infants had a significantly shorter mean length of treatment 14.7 vs 16.6 days, and length of stay and 18.9 vs. 21.1 ($p=0.02$ and $p=0.01$), respectively. A caveat to this trial was the use of a bespoke hybrid weight and symptom based dosing regimen, which is not commonly employed. In addition, the trial used an alcohol free formulation of methadone that is not commercially available. This may be difficult for some hospital pharmacies to compound, though it is not expected that alcohol containing methadone solutions should have any less efficacy than the one used in the trial. There is even greater heterogeneity in methadone regimens than in morphine, and not a generally accepted standard regimen. The development of specific regimens to date has been empiric and site specific. However, modern pharmacometric modelled dosing regimens have demonstrated improved outcomes [40]. Careful linking of pharmacokinetic data, a strict treatment protocol, and clearly defined endpoints can generate of model that can be used to simulate new treatment regimens and examine subpopulations. Refinements of these model-based approaches will likely lead to further optimization of regimens. This approach has been piloted with methadone, but model building has also been explored with morphine and buprenorphine [41,42,43].

Buprenorphine

Buprenorphine is an emerging therapy for control of acute adult opioid withdrawal symptoms and medically assisted opioid replacement therapies. It has a long half-life, which allows once a day dosing. It is a partial μ opioid agonist, which accounts for an excellent safety profile relative to the full agonist methadone. Buprenorphine has been investigated as a primary opioid for the pharmacologic treatment of NAS. Phase 1 studies investigated safety, dose finding, and initial proof of concept [44,45]. These investigations were followed by a blinded, randomized controlled trial comparing sublingual buprenorphine to oral morphine in 63 infants (the BBORN trial). Buprenorphine had a shorter median length of treatment (15 vs. 28 days) and length of stay (21 vs. 33 days) (both $p<0.0001$) [46]. Safety and need for adjunctive phenobarbital treatment was similar in both groups. This therapeutic advantage was comparable to the phase 1 program (~35% decreased length of treatment compared to morphine). In all these trials, the in utero exposure of the infants was largely methadone. External validity of these single site, prospective trials is provided by retrospective cohort data from 212 infants in the southern Ohio region. Infants treated buprenorphine demonstrated a ~30% reduction in length of treatment compared to morphine and methadone controls [47,48]. This was multicenter and infants had a more heterogeneous in utero exposure of opioids and other drugs of abuse. The Ohio cohort employed the same buprenorphine formulation, but did use a different treatment regimen (summarized in [49]).

Buprenorphine is administered sublingually in volumes of 0.5 mL or less, after which a pacifier is inserted in the mouth and absorption likely complete within 2 minutes. The current ethanol containing formulation is stable for 30 days in glass at room temperature and at least 7 days in polypropylene-dispensing syringes [50]. The ethanol provides asepsis and stability of the solution, and may promote absorption (though this has not been formally tested). Questions about the safety of the ethanol content has been raised [51]. The ethanol exposure seen in infants in the BBORN

trial were all lower than 7 mg/dL. The American Academy of Pediatrics guidance suggests a peak concentration of less than 25 mg/dL after administration of an ethanol containing medication [52]

Non-opioid Adjunct Therapy

The two agents used as adjuncts are the centrally acting alpha 2 adrenergic agonist clonidine and the GABA agonist phenobarbital. There have been a number of small studies which have compared an adjunct to an opioid. The ideal adjunct therapy or regimen has not been defined. The treatment approaches in which adjuncts are used are listed in Figure 3. In current use, adjuncts can be given only when symptoms are not controlled and weaned before cessation of the opioid. Other centers will wean the opioid first, and discontinue the adjunct later as an inpatient or outpatient. This approach is much more common for phenobarbital than clonidine. The third approach is that of parallel opioid and clonidine therapy, with a goal of reducing opioid exposure was well as length of treatment.

Clonidine

Clonidine has inhibitory effects on the release of noradrenaline which leads to a decrease in withdrawal symptoms [53]. In adults it is used for reduction of acute opioid withdrawal symptoms, but not chronic management of opioid use disorder. The highest quality evidence of efficacy in NAS is that of a randomized controlled trial of Agthe *et al* (n= 80). Clonidine added to the standard opioid treatment reduced diluted tincture of opium/kg per day compared to the placebo ($p<0.03$) and improved median length of therapy compared to placebo (11 vs 15 days, $P = 0.02$) [54]. Twelve percent of the infants in the placebo group had treatment failure while there were none in the clonidine group. A second unblinded RCT (n=68) by Surran that was stopped

early compared clonidine to phenobarbital on a base of morphine treatment. Phenobarbital had 18.2 and clonidine 13.6 days of opioid treatment (p= 0.037) [55]. Clonidine was stopped before discharge while infants were sent home on phenobarbital, often for months. The doses of both adjuncts were also high. A prospective pilot study of Bada (n= 31) compared clonidine vs. morphine as primary treatment. Clonidine has shorter median length of treatment (28 compared to 39 days). Though there were early differences in NICU Network Neurobehavioral Scale (NNNS) summary scores, at one year cognitive, motor and language scores did not differ between the groups [56] In adults, clonidine has less sedation than phenobarbital, but is subject to rebound hypertension with rapid cessation. In the inpatient setting, the side effect profile of clonidine has been reassuring.

Phenobarbital

Phenobarbital is a drug widely used for the treatment of non-opioid NAS, as well as commonly used in the NICU as an antiepileptic. Most common use is as an adjunct to an opioid. While described as and effective alternative to an opioid as base therapy, [57] the overwhelming current use is that as adjunct to an opioid when symptoms become severe. At what point phenobarbital is added is more variable between sites than that seen with clonidine. A common approach is to add when the maximal dose of the opioid is reached. Another approach is to add early, when the velocity of symptom change will suggest more severe NAS presentation [58]. In a partially randomized study of 20 infants, Coyle described decreased mean lengths of stay 79 vs 38 days when phenobarbital was added to diluted tincture of opium ($p < 0.001$) [59]. The long length of stay from this 2002 and likely different modes of non-pharmacologic treatment at the time make direct comparisons to current care less clear. However, the general vector of decreased opioid use

with addition of phenobarbital is clear. A concern limited more widespread use of phenobarbital early on is that of safety and long term neurodevelopment. The product label states use has been associated with cognitive deficits in children taking for seizures, and animal models of long term behavioral outcome are also of potential concern [60]. The issue of potential bias by indication for a seizure population makes direct comparisons to infants with NAS difficult. Long term neurodevelopmental outcome studies of infants treated for NAS are subject to occult bias due to the in utero opioid exposure, opioid used to treat NAS, and most importantly the environment the infant is raised in which make comparisons to non-phenobarbital exposed controls problematic. The widespread use of phenobarbital in the NICU, familiarity of clinicians with use, and lack of clear evidence of toxicity have led to continued use as an adjunct in NAS. Whereas clonidine has a mechanism of action more specific to opioid withdrawal, phenobarbital has a more global sedative effect which may provide added efficacy in circumstances of poly-substance exposure.

Treatment Location

Pharmacologic treatment is most commonly administered in the inpatient setting. There have been a number of sites that transition pharmacologic treatment to the outpatient setting. Opioids, particularly the long acting agent methadone, has been used in the outpatient setting. More commonly, the opioid is weaned during the inpatient stay or soon after discharge with phenobarbital being the primary pharmacologic therapy. Any attempt to transition treatment to the outpatient setting requires a robust follow up mechanism and outpatient pediatricians familiar and comfortable with managing an outpatient wean. Compared to outpatient weaning, the use of inpatient pharmacologic treatment is consistently reported as being associated with longer lengths of hospitalization, but shorter total duration of treatment [61]. The best documented experience is

a population based retrospective cohort study of 532 infants reported infants. Consistent with prior studies, the median (IQR) length of pharmacological therapy was significant shorter in inpatients compared to outpatients 19 (10-31) days vs. 60 (38-92) days; $p<0.001$) [62]. Infants treated as outpatients had have an increased number of emergency room visits within 6 months of discharge (adjusted odds ratio 1.52, 95% CI 1.06-2.17) when compared with those treated as inpatients alone [62]. While not statistically significant, the point estimate odd ratio for emergency visit at 6 weeks, or any hospitalization at 6 or 24 weeks was ~1.5 for outpatient compared to inpatient treatment. Most (82%) were treated with phenobarbital alone. These data suggest caution when considering transition to outpatient treatment, and only in circumstances where there is a comprehensive support structure to safely manage these infants.

Discussion

Non-Pharmacological treatment is the base therapy that should be administered to all infants with in utero exposure to opioids. Non-pharmacological treatments are safe, effective, and can be easy implemented. Interventions will vary by the ability of a site provide based upon physical layout, structure of maternal treatment, and staffing considerations. There has been examination of the relative merit of each specific element, but the evidence base upon which to evaluate interventions remains low. The issue is not one of safety, but instead from a menu of many non-pharmacologic interventions, infants and institutions will be best served if high impact interventions are chosen over lower. Future needs include standardized descriptions of interventions and comparative evaluation between them. Given the large matrix of possible combinations, a reasonable approach is to instead focus on comparisons of bundles with differentiation focused on high resource intensive activities. These would not necessarily need to

be randomized controlled trials but could be quality improvement initiatives or pragmatic investigations built into standard of care using electronic medical records.

Pharmacological intervention is a cornerstone in achieving growth and symptom control in severe NAS. Recent years have seen the emergence of high quality evidence to refine choices. The choice of a specific agent is important, but not the only predictor of success. The treatment regimen within which the drug resides is a key consideration. Weight vs. symptom based dosing is just one area that would benefit from investigation. Newer modeling tools such a pharmacometrics hold promise in optimizing dose selection. A pharmacokinetic/pharmacodynamic model does not guarantee to identify the ideal dose, but it is significantly more likely to do so than the old method of intuition or hunch-based empiric regimen creation. Pharmacogenetic differences and disease expression and response to treatment may be helpful eventually, but this tool for NAS remains in the discovery phase and far from providing actionable decisions. The use of an opioid as primary therapy is settled practice. What agent, doses, titration schema, as well and when to start an adjunct, which one, and how to wean all are areas under current investigation.

Practice points

- Non-pharmacological treatments are safe, effective, and can be easy implemented.
- Interventions will vary by the ability of a site provide based upon physical layout, structure of maternal treatment, and staffing considerations.
- The need for pharmacologic therapy is widely held to be needed for severe symptomatology.
- This is commonly linked to a specific threshold on a score (often an 8 on a Finnegan score) and less often explicitly linked to a goal of therapy.

- There is good consensus that there is a subset of infants that require pharmacologic therapy, but less so in defining the goals of care and tradeoffs associated with higher or lower threshold for treatment.
- Goals of pharmacologic therapy are to relieve infant discomfort, allow proper nutrition and development, and to foster parental bonding.

Research agenda

- Future studies of non-pharmacological intervention should include standardized descriptions of interventions and comparative evaluation between them. Furthermore, given the large matrix of possible combinations, a reasonable approach is to instead focus on comparisons of bundles with differentiation focused on high resource intensive activities.
- Future studies of pharmacological intervention should examine what agent, doses, titration schema, as well and when to start an adjunct, which one, and how to wean. In addition, long-term outcomes should be addressed in any future studies.

Figure 1: Representative Modified Finnegan Score (MOTHER NAS score)

Signs and Symptoms	*Severity*	*Score*
Crying	Excessive high pitched	2
	Continuous high pitched	3
Sleeps	< 1 hours after feeding	3
	< 2 hours after feeding	2
	< 3 hours after feeding	1
Moro Reflex	Hyperactive	1
	Markedly Hyperactive	2
Tremors: Disturbed	Hands or feet only, up to 3 seconds	1
	Arms or legs, over 3 seconds	2
Tremors: Undisturbed	Hands or feet only, up to 3 seconds	1
	Arms or legs, over 3 seconds	2
Increased Muscle Tone	Difficult but possible to straighten arm and head lag present	1
	Unable to straighten arm and head lag absent	2
Excoriation	Skin is red but intact or healing	1
	Skin not intact	2
Generalized Seizure		8
Fever > 37.3 C (99.2 F)		1
Frequent Yawning	>4 or more successive times	1
Sweating		1
Nasal Stuffiness		1
Sneezing (4 or more successive times)	>4 or more successive times	1
Tachypnea	Respiratory Rate >60/mm	2
Poor feeding		2
Vomiting (or regurgitation)		2
Loose Stools	Diaper is > half liquid/half solid	2
Failure to thrive	Current weight > 10% below birth weight	2
Excessive Irritability	Consoling calms infant in <5 min	1
	Consoling calms infant in 6-15 min	2
	Inconsolable	3
	Summed Score	
Recorded, unscored elements		
Convulsions Fever > 38.4 C (101.2 F) Mottling Excessive sucking Watery Stools Projectile vomiting Retractions Nasal flaring Myoclonic jerks		

Figure 2: Approach to infants with in utero opioid exposure. All infants should be provided a base of non-pharmacologic therapies. Specific measures will vary with the ability of the local site to provide. Some potential approaches are listed. Pharmacologic therapy is added only in those for whom symptoms are not controlled with non-pharmacologic means.

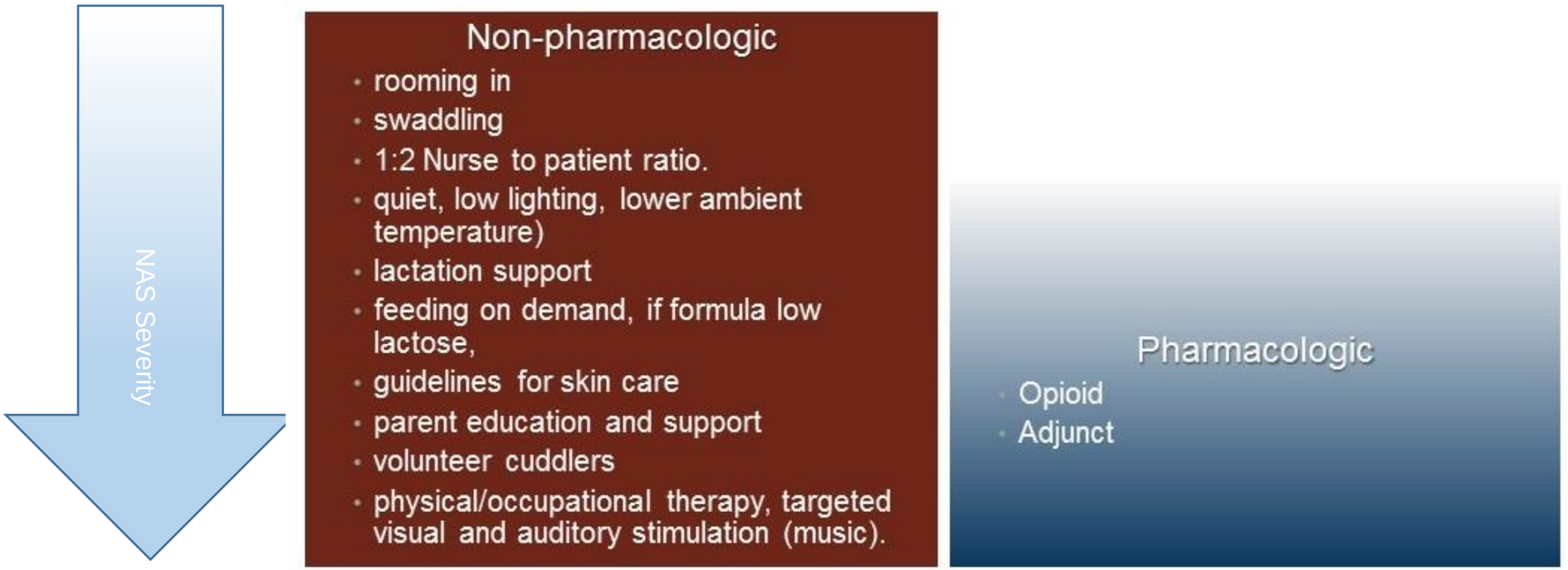

Figure 3: Role of Adjunctive Therapies. The optimal use of adjunctive therapy with an opioid has not been defined. (A) An adjunct is used only when symptoms are severe and the adjunct is weaned before the opioid. (B) The adjunct is started in those not controlled with an opioid, but the adjunct is continued after the opioid is weaned, sometimes in an outpatient setting. (C) The adjunct serves as an opioid sparing agent which is started and stopped at the same time as the opioid.

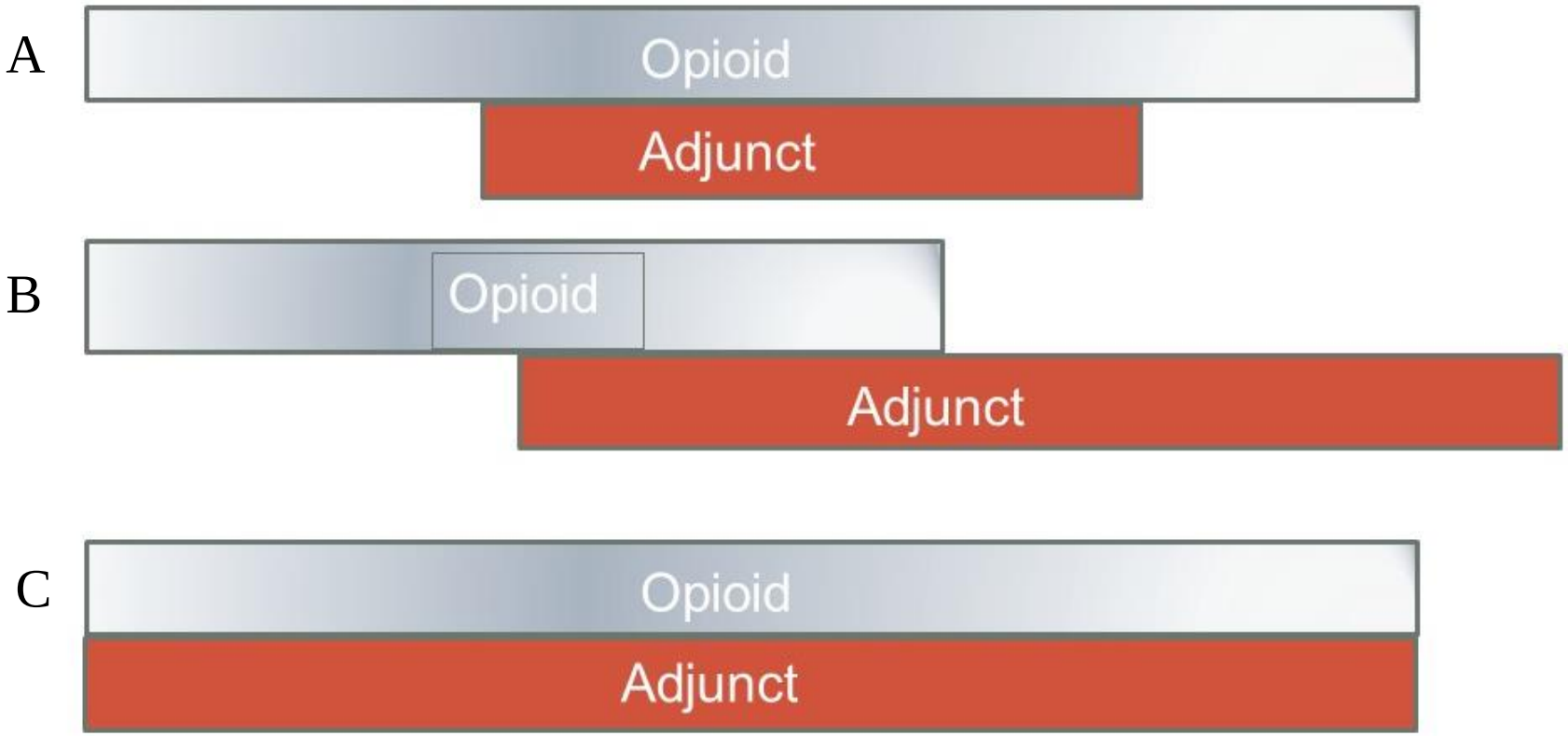

Figure 4: NAS Treatment Flowchart at the Royal Alexandra Hospital, Edmonton, Canada

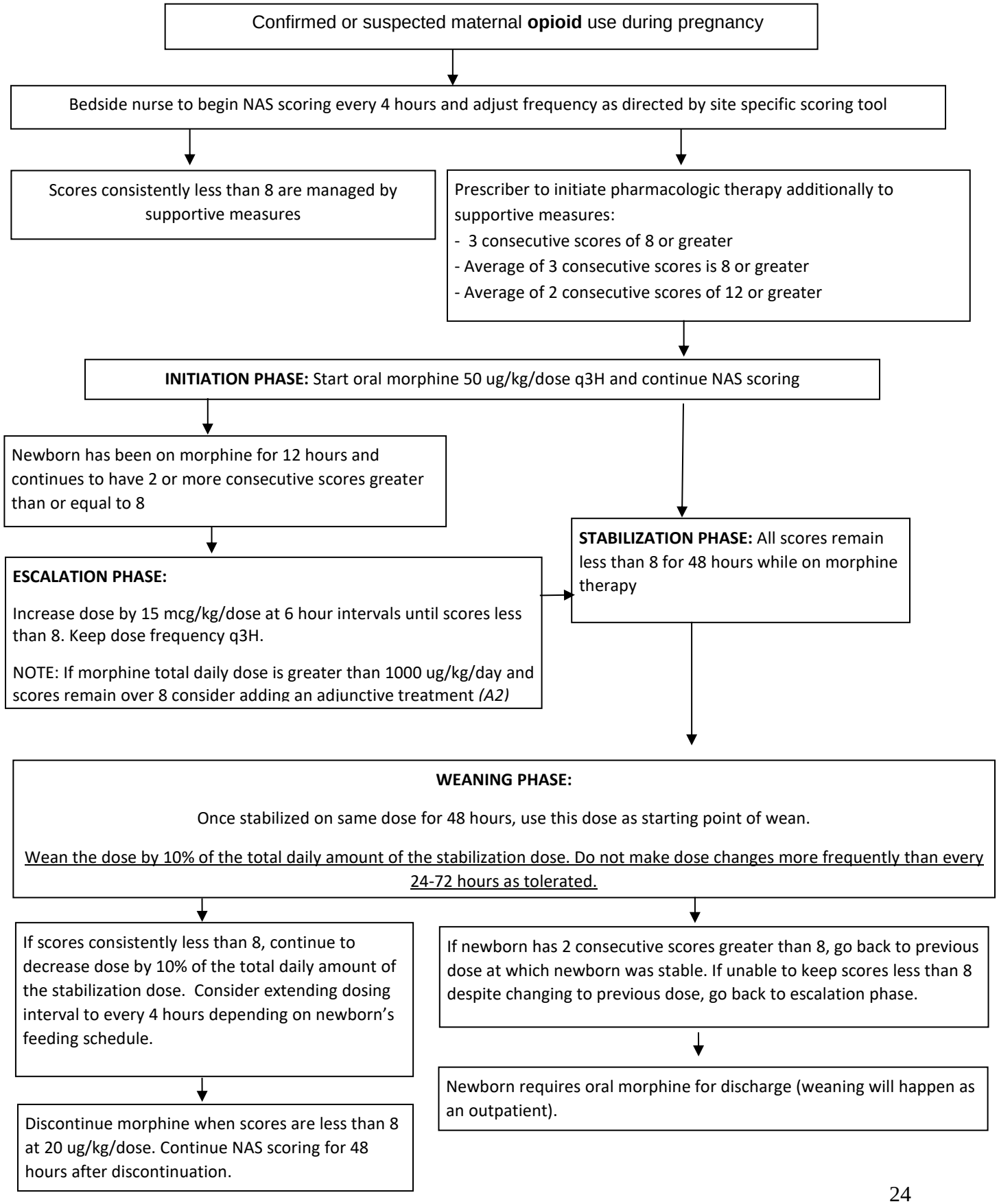

Table 1: Methadone vs. Morphine: Studies in which morphine and methadone were compared for median length of treatment**.**

Author		Design	N	Morphine	Methadone	P
Lainwala [64]	2005	Retrospective	46	36	40	>0.05
Hall [40]	2014	Retrospective	383	16*	16*	NS
Young [65]	2015	Retrospective	26	7*	38*	0.001
Brown [63]	2015	Blinded RCT	31	21	14	0.008
Davis [39]	2018	Blinded RCT	183	15	11.5	0.02

*= mean, RCT = randomized controlled trial

Box 1: Non Pharmacological Adjunct Treatments for Neonatal Abstinence Syndrome

Non Pharmacological Adjunct Treatments
Environmental control • Room lighting • Swaddling • Positioning • Bed types
Feeding methods • Breastfeeding • Formula feeding
Social Integration • Parental rooming in • Skin to Skin contact
Treatment Location • Inpatient vs Outpatient
Acupuncture

Box 2: Pharmacological Treatments for Neonatal Abstinence Syndrome

Pharmacological Treatments for NAS
Opioid • Morphine • Methadone • Buprenorphine
Non-opioid Adjunct Therapy • Clonidine • Phenobarbital

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