JPPT | Single Center Retrospective Study

A Preliminary Assessment of the Effects of Pharmacist-Driven Methadone Stewardship for the Treatment of Neonatal Abstinence Syndrome at a Tertiary Children's Hospital

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OBJECTIVE Lack of a standardized opioid wean guideline for the treatment of neonatal abstinence syndrome (NAS) has the potential to increase the length of the wean and subsequently the length of stay for neonates in the neonatal intensive care unit (NICU). The purpose of this study was to assess the effect of a pharmacist-driven methadone stewardship program for NAS treatment.

METHODS The NAS stewardship program consisted of provider, pharmacist, and nursing education, a pharmacy surveillance system rule, and an updated clinical practice guideline. The pre- and post-intervention period were defined as patients admitted to the NICU from July 2019–October 2019 and August 2020–November 2020, respectively. The primary objective was to assess the effect of the stewardship program on the duration of opioid treatment in days. Secondary outcomes included number of dose titrations and length of hospital stay.

RESULTS A total of 21 patients were included in this study. Neonates treated following the adoption of the stewardship program (n = 8) experienced a 34% decreased median duration of treatment (29 days vs 19 days; p = 0.84). Secondary endpoints of median number of titrations and length of stay were decreased by 15% (1.5 titrations; p = 0.52) and 24% (8 days; p = 0.85), respectively, leading to an average cost savings of $60,020 per patient.

CONCLUSIONS Implementation of a standardized stewardship guideline for treatment of NAS resulted in a favorable decrease in all considered endpoints. Implications of the study further support the need for more evidence-based standardized guidelines for optimal treatment of patients with NAS.

ABBREVIATIONS NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit

KEYWORDS methadone; neonatal abstinence syndrome; neonatal intensive care unit; neonatal opioid withdrawal syndrome; pharmacologic treatment; weaning

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Introduction

Neonatal abstinence syndrome (NAS) continues to be a prevalent disease state in the neonatal population with incidence rates continuing to increase from 2.8 per 1000 births in 2004 to 14.4 per 1000 births in 2014 as reported by the Centers for Medicaid Services.[1] Consequently, treating it has been a challenge, as the percentage of neonatal intensive care unit (NICU) days attributed to NAS increased from 0.6% in 2004 to 4% in 2013.[2] In 2009, a National Survey on Drug Use and Health documented that 4.5% of pregnant women reported recent use of illicit drugs, such as cocaine, hallucinogens, heroin, methamphetamines, and non-medical use of prescription medications.[3] Some of these substances can produce similar signs and symptoms of withdrawal in the neonate. To illustrate these similarities, Supplemental Table S1 lists some common drug-specific signs of withdrawal and Supplemental Table S2 lists common clinical features of NAS. Maternal use of multiple substances also can potentially affect the infant in regard to severity of withdrawal symptoms and duration of withdrawal treatment, which can make pharmacologic treatment more challenging to manage. Currently the mainstay treatment of the condition is doing a slow wean of either morphine or methadone. However, there is no standardized method on how to approach this opioid wean in neonates, resulting in a wide variability among hospitals in treatment outcomes such as duration of therapy or length of stay.

Part of the decision process to pharmacologically treat NAS babies comes from several scoring systems (e.g., Lipsitz tool, Finnegan Neonatal Abstinence Severity Score and modified versions, and the Neonatal With-

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Figure 1. Implemented guideline developed for Studer Family Children's Hospital.

Methadone Wean Guideline	
Dosing weight <3 kg	**Dosing weight ≥3 kg**
Step 1: 0.25 mg PO q6h × 4 doses	Step 1: 0.35 mg PO q6h × 4 doses
Step 2: 0.25 mg PO q12h	Step 2: 0.35 mg PO q12h
Step 3: 0.18 mg PO q12h	Step 3: 0.25 mg PO q12h
Step 4: 0.13 mg PO q12h	Step 4: 0.18 mg PO q12h
Step 5: 0.1 mg PO q12h	Step 5: 0.14 mg PO q12h
Step 6: 0.08 mg PO q12h	Step 6: 0.11 mg PO q12h
Step 7: 0.05 mg PO q12h	Step 7: 0.07 mg PO q12h
Step 8: 0.05 mg PO q24h	Step 8: 0.07 mg PO q24h
Step 9: Discontinue methadone	Step 9: Discontinue methadone

If 3 consecutive modified Finnegan neonatal abstinence syndrome (NAS) scores are ≥8 or 2 consecutive scores are ≥12, begin methadone at step 1. After 24 hours of methadone treatment at step 1, average the NAS scores and proceed as follows:

- If the average modified Finnegan NAS score is <8 for the past 24 hours, then wean to the next step.
- If the average modified Finnegan NAS score is 8 to 12 for the past 24 hours, do not wean and continue the current dose.
- If the average modified Finnegan NAS score is >12 for the past 24 hours, then consider an extra dose at the current step or return to the previous step.

After each progression to the subsequent step, evaluate the average modified Finnegan NAS scores for the following 24 hours and proceed as appropriate on the basis of scores.

Patients should be scored 30 to 60 minutes after feeds, which corresponds to about every 3 hours. Average daily scores can be calculated by taking the sum of all scores in the past 24 hours and dividing by the number ofscores obtained in the past 24 hours.

Persistent Modified Finnegan NAS Scores >12	**Persistent Modified Finnegan NAS Scores >12 + Polydrug Exposure**
Clonidine: 0.5–1 mcg/kg/dose PO q4–6h	Phenobarbital: 16 mg/kg PO once, then 1–4 mg/kg/dose PO q12h
Consider consulting pharmacy when adding adjunctive medications to therapy	

Once off methadone, the infant should be monitored for 3 to 7 days, based on post-discontinuation scores prior to discharge. If scores are increasing after 3 days off methadone, continue to monitor and treat if scores dictate therapy. The patient's scores should be <8 for at least 3 days prior to discharging the infant to home.

drawal Inventory) that use most of the clinical features listed in Supplemental Table S2 and are allotted a score on the basis of severity of that symptom. Current practice at our facility is the use of the Modified Finnegan Neonatal Abstinence Severity Score[4] as shown in Supplemental Table S3. The modified scoring system was created to limit the number of symptoms assessed in order to expedite the scoring process. If the infant is at known risk for NAS, scoring usually begins at 2 hours of life, using one of these site-specific scoring systems. Typically, once therapy is initiated, the neonate will follow a weaning protocol associated with the drug of choice for that site. Current methadone weaning practices at our institution, however, are provider specific with opportunities to standardize care and optimize treatment outcomes. The purpose of this study was to assess the effect of a pharmacist-driven methadone stewardship program on the length of opioid wean in days for NAS treatment.

Methods

Study Design. This retrospective study evaluated the length of methadone weans used for NAS treatment in the NICU at a tertiary care pediatric hospital. The NAS stewardship program consisted of provider, pharmacist, and nursing education; a pharmacy surveillance tool; and a clinical practice guideline. The pharmacy surveillance tool used was Sentri7 (Wolters Kluwer, Waltham, MA), a web-based platform integrated within the electronic health record that identified NAS patients and helped monitor treatment progress. The clinical practice guideline consisted of a methadone dosing protocol as shown in Figure 1.

Withdrawal symptoms for neonates at risk were monitored and scored with the modified Finnegan scoring tool found in Supplemental Table S3. Patients were scored 30 to 60 minutes after feeds, which corresponds to about every 3 hours. Treatment began when a neonate scored >8 for 3 consecutive evaluations or scored >12 on 2 consecutive evaluations.

Methadone was used at our institution owing to its longer half-life, resulting in a much lower incidence of withdrawal symptoms. From pre-interventional data, we divided the methadone wean into 2 separate weight-based groups with a specific dose for each step as the wean progresses. Both groups have a loading dose of 0.1 mg/kg by mouth every 6 hours for 4 doses followed by several subsequent dose reductions until a final step where methadone is dosed once daily. Progression down this dosing guideline is based on an average modified Finnegan score for the past 24 hours (i.e., total sum of the scores for the past 24 hours divided by number of scores obtained in the past 24 hours). A standardized flat-dose weaning schedule was used in this study to reduce the need for dosing calculations and reduce potential medication dosing errors. In addition to methadone therapy, the protocol included guidance on when to add adjunctive medications to aid in weaning patients consistently scoring greater than 12 on this scale (see Figure 1).

Once therapy had been discontinued, the infants

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were monitored for 3 to 7 days, based on post-discontinuation scores prior to discharge and treated if scores dictated therapy.

Inclusion criteria included patients admitted to the NICU, patients receiving methadone for treatment of NAS, and patients born at ≥34 weeks' gestational age. Exclusion criteria included patients receiving intravenous continuous sedation prior to the initiation of methadone, patients being treated for iatrogenic opioid withdrawal, patients who required surgical intervention or mechanical ventilation, and patients with incomplete medical documentation.

The pre-intervention period was defined as patients admitted to the NICU between July 2019 and October 2019. A trial program was implemented in May 2020. The post-intervention period was defined as patients admitted to the NICU from August 2020 to November 2020.

Objectives and Data Collection. The primary objective was to assess the effect of pharmacist-driven methadone stewardship on the duration of opioid treatment in days. Secondary outcomes included (1) number of dose titrations and (2) identifying the length of hospital stay.

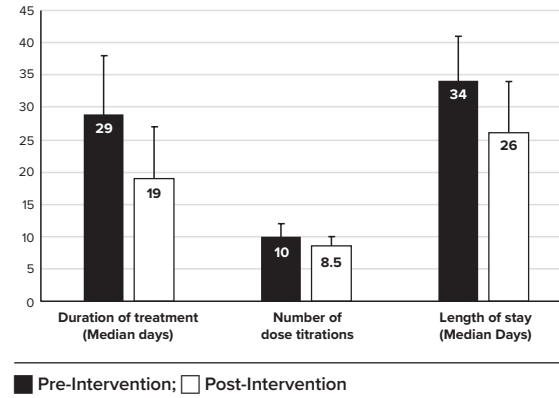
Demographic data collected included age, weight, sex, and highest level of care. Maternal characteristics were also recorded including age and exposure to legal and/or illicit drugs. Daily methadone regimens and length of stay in days were recorded by using the patient's medication administration record. To analyze the appropriateness of the methadone regimen, average daily modified Finnegan scores were collected and compared with the changes made to the patient's methadone regimen. Any adjunctive agents used for the indication of NAS as well as the type of diet (formula or breast milk) were noted.

Statistical Analysis. Demographic and clinical characteristics were analyzed and reported with descriptive statistics. Frequencies (%) were used to report categorical data. Medians were used to express primary and secondary endpoints to accommodate for outliers. Differences in infant and maternal characteristics before and after implementation of the stewardship program were tested with chi-square test for categorical data and *t*-tests for continuous data.

Results

We identified 21 total patients diagnosed with NAS during our study periods. Pre-implementation of the new NAS stewardship program, involving a weaning protocol (n = 13), provider education, and pharmacy surveillance, spanned the months of July through October 2019. Between these months the median duration of treatment was 29 days, median number of titrations was 10, and median length of stay was 34 days (Figure 2). After implementation of the NAS stewardship program (n = 8), duration of treatment decreased by 34% (10 days; p = 0.84); number of titrations decreased by 15% (1.5 titrations; p = 0.52); and length of stay, by 24% (8 days; p = 0.85) (Figure 2). Baseline characteristics were well balanced across both study groups (Table). Only 1 patient in this study required adjunctive clonidine for consistently high modified Finnegan scores.

Figure 2. Pre- and post-interventional endpoints.Error bars in graph denote median absolute deviation. Number of titrations was defined as any adjustment in medication dose or frequency. Length of stay refers to length of total hospital admission.



Discussion

To streamline therapy for this population, standardization of care has been a focus for NICU providers for a few years now. In 2012, the American Academy of Pediatrics released a policy statement calling for the standardization of care delivered to infants with NAS,[5] where subsequently, several facilities participated in a study assessing the use of NAS-focused guidelines and the effect of those guidelines on patient outcomes. The results from the study showed a correlation between the increased use of NAS-focused guidelines and decreases in median length of pharmacologic treatment and infant length of stay.[6] Another multisite study in Ohio showed benefit in implementing NAS guidelines, specifically in relation to pharmacologic weaning. By using a stringent pharmacologic weaning protocol, this study produced evidence of shorter duration of treatment and length of stay and a lower rate of adjunctive drug therapy,[7] further supporting the use of a standardized practice guideline to provide better patient outcomes. By creating a standardized dosing guideline, we reduced the length of stay and duration of treatment to a value comparable to the national average of 15 to 16 days and 19 to 21 days, respectively. Whether or not our guideline had a direct effect on modified Finnegan scores itself was not recorded in this study. However, with the reduction in all endpoints we could safely deduce that modified Finnegan scores were most likely reduced as well. Although length of stay was found to be decreased in this study, its true effect is difficult to quantify because

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Table. Baseline Demographics

Total Patients (N = 21)	Pre-Intervention (n = 13)	Post-Intervention (n = 8)	p value
Male, %	53.8	50	0.44
Gestational age, average (range), wk+days	39+1 (35+2 to 40+6)	37+4 (36+0 to 39+1)	0.96
Birth weight, average (range), kg	3.107 (2.135–3.915)	2.856 (2.375–3.48)	0.84
Maternal age, average (range), yr	30 (23–36)	31 (23–38)	0.65
Maternal drug exposure, %			
Methadone	61.5	37.5	
Tobacco	61.5	37.5	
THC	23.1	0	
Subutex	23.1	12.5	
Adderall	7.7	37.5	
Cocaine	7.7	12.5	
Heroin	7.7	25	
Kratom	7.7	0	
Methamphetamines	7.7	12.5	
Opiates	7.7	25	

THC, tetrahydrocannabinol

length of stay is highly influenced by factors other than the specific care procedures outlined in the NAS guideline. Occasionally, infants developed late medical complications that were unrelated to NAS management. Interrater variability of modified Finnegan scores is also something to be considered, because minute inaccuracies could be the difference between continuing the wean schedule, halting the wean, or moving back a step on the weaning schedule.

Institutions nationwide have begun to discharge patients on methadone to decrease length of stay for NAS patients. While this has not yet begun at our institution, the results of our study provide high clinical value to explore outpatient treatment of NAS. The reduced number of dose titrations seen with our new guideline decreases day-to-day dose variability and may increase caregiver accessibility and convenience in the outpatient setting.

In addition to the positive clinical implications of our standardized guideline, there are also positive financial implications. Patrick et al[8] reported that the mean hospital charge for NAS in 2012 was $66,700 and that the estimated nationwide aggregate hospital charges for NAS in 2012 were $1.5 billion. It is hypothesized that the lack of a standardized guideline at this site has led to an excessive amount of methadone waste and therefore an increase in costs associated with the treatment of each NAS patient. With an average cost of $7,502 per day for a NICU admission at our institution, potential cost savings could translate to up to $60,000 per patient given our decreased length of stay with this disease state.

This study was not without multiple limitations. There was inability to control for concomitant maternal drug use as seen in the variability to drug exposure in the Table. Although clinically important, owing to the relatively small sample size, statistical significance was not achieved in this study. In addition, because this study was conducted at a single site, generalizability to other institutions is difficult. Lastly, it is uncertain what non-pharmacologic interventions each patient received during treatment owing to the lack of charting.

We believe that with larger multicentered studies, in conjunction with the success and shortcomings of this study, we could solidify a consensus guideline that institutions can adopt for treatment of NAS.

Conclusion

In this retrospective study, implementation of a standardized stewardship guideline for treatment of NAS resulted in a favorable decrease in all considered endpoints. Our findings are consistent with previous studies, demonstrating improved NAS outcomes following adoption of a multidisciplinary weaning guideline. Results of this study offer promise for additional improvement in NAS outcomes through widespread adoption of evidence-based, protocol-driven weaning. Additional research efforts should focus on the refinement of weaning protocols such as in this study.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution.

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