ORIGINAL RESEARCH
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A RETROSPECTIVE STUDY OF LENGTH OF HOSPITAL STAY IN INFANTS TREATED FOR NEONATAL ABSTINENCE SYNDROME WITH METHADONE VERSUS ORAL MORPHINE PREPARATIONS

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ABSTRACT

PURPOSE: Length of hospital stay (LOS) of infants treated for neonatal abstinence syndrome (NAS) with methadone was compared to LOS of those treated with an oral morphine preparation (OMP, neonatal morphine solution, or deodorized tincture of opium).

METHODS: A retrospective review of medical records of infants treated for NAS due to in utero exposure to methadone and/or illicit drugs such as heroin or morphine was performed for birthweight, neonatal abstinence scores, infant and maternal illicit drug exposure history, maternal methadone dose (if any), and details of treatment. Length of stay was the primary outcome measure.

RESULTS: Forty-six infants met the inclusion criteria. The median LOS of infants treated with methadone versus OMP was not significant ($P > 0.05$). Prolonged LOS was associated with larger pharmacological treatment doses required to control withdrawal symptoms, larger maternal methadone dose, and increased birthweight. After adjusting for these factors, exposure to opioids in utero, maternal nicotine use, hospital of treatment, severity of withdrawal symptoms, and foster care placement were not significantly associated with LOS in univariate or multivariate analyses.

CONCLUSIONS: These results suggest that infants treated with OMP or methadone have similar LOS. Longer LOS is associated with both higher maternal methadone doses and higher opioid treatment dose requirements after birth. The potential effect of maternal methadone dose on neonatal LOS should be considered when treating expectant mothers on methadone maintenance therapy.

KEY WORDS: neonatal abstinence syndrome, length of hospital stay, neonatal morphine, methadone, deodorized tincture of opium.

The United States Department of Health and Human Services has reported that 3% of the United States population aged 12 or older has used illicit drugs.[1] The National Pregnancy and Health Survey estimated that 5.5% of all pregnant women used illicit drugs at least once during pregnancy.[2] Drugs most often abused include opiates (heroin, morphine, codeine, and oxycodone), central nervous system (CNS) stim-

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ulants (cocaine and amphetamines), and CNS depressants (marijuana and barbiturates). Newborns chronically exposed to such drugs in utero may develop physiological dependence. Neonatal abstinence syndrome (NAS) may result when in utero drug exposure is abruptly withdrawn at birth.

Review of the Literature

The clinical presentation of NAS in newborns is variable and dependent on the drug used, timing of drug use during pregnancy, and maternal and fetal metabolism and excretion. Infants with NAS present with CNS irritability (tremors, increased muscle tone, excessive crying, restlessness, seizures); gastrointestinal dysfunction (vomiting, diarrhea, poor weight gain); and autonomic instability (fever, yawning, sneezing). Fifty to 90% of infants exposed to methadone and heroin develop symptoms of withdrawal.[3] The majority require pharmacotherapy.[4]

In the last 3 decades, numerous pharmacological agents have been used to treat NAS in newborns; these include paregoric, diluted deodorized tincture of opium (DTO), morphine, methadone, phenobarbital, chlorpromazine, diazepam, and clonidine.[5-10] Few studies have adequately compared these different treatment modalities. In a prospective study of 25 infants exposed to heroin in utero, treatment with morphine alone was associated with improved control of withdrawal symptoms than treatment with a combination of phenobarbital and diazepam, or a combination of phenobarbital, diazepam, and morphine.[11]

Others have reported that infants with NAS treated with paregoric had a lower incidence of seizures than those treated with diazepam[5] or phenobarbital.[12] Seizure control was significantly better among infants with NAS treated with DTO than those treated with diazepam.[13] A comparison between phenobarbital and chlorpromazine found no significant difference in symptom control.[8]

Very few studies have compared the length of hospital stay (LOS) of infants with NAS treated with different pharmacological regimens.[3,14,15] In a prospective study of 110 infants with NAS secondary to maternal methadone and/or illicit drug use, no significant difference in LOS was noted between infants treated with methadone, phenobarbital, or diazepam.[16] However, in a prospective trial of 31 infants with NAS due to maternal methadone use, treatment with phenobarbital was associated with a significantly shorter LOS compared to treatment with paregoric (17 vs. 22 days).[17] A randomized trial of 20 infants exposed to methadone and/or heroin in utero showed that treatment with DTO and phenobarbital resulted in significantly shorter LOS (38 days) than treatment with DTO alone (79 days).[18] In contrast, a recent double-blinded randomized trial of 75 infants born to mothers with methadone and/or illicit drug use during pregnancy showed that treatment with oral morphine resulted in shorter durations of pharmacotherapy than treatment with phenobarbital alone (4 vs. 12 days).[15] A review of the literature was unable to identify studies that compared different opioid therapies such as morphine or methadone for NAS.

Although the incidence of illicit drug use during pregnancy resulting in NAS in newborns is increasing,[3] there is no consensus on the relative efficacy of different treatment modalities; such a consensus is needed. Infants with NAS may require prolonged inpatient care, with attendant medical, economic, and social consequences.[19,20] Approaches to NAS management that safely reduce LOS may help reduce such consequences.

Treatment with a pharmacological agent similar to the drug causing withdrawal may result in more effective control of NAS symptoms, reducing the necessary treatment period and shortening LOS.[3] Treatment of NAS with methadone replacement may be advantageous in methadone exposed infants. However, a review of literature identified only 1 study examining LOS in infants with NAS treated with methadone.[16]

Sidebar 1. Treatment Regimens of the 2 Groups of Infants With NAS

Methadone

- Initial loading dose 0.1 mg/kg/dose X1;
- Additional 0.025 mg/kg/dose given every 4 hr for continuing NAS scores >8 until symptoms controlled or maximum dose of 0.5 mg/kg/day reached;
- Maintenance dose determined by calculating the total methadone dose given over previous 24 hours;
- Maintenance dose administered in 2 divided doses every 12 hours.

Oral Morphine Preparations: NMS or DTO

- No loading dose;
- Maintenance dose 0.05 mg/kg/dose;
- Dose increased by 0.03 mg/kg/dose every 4 hours for serial NAS scores >8 until symptoms are controlled or maximum dose of 0.8 mg/kg/day is reached;
- Maximum maintenance dose required to control symptoms administered every 4 hours.

Abbreviations: NAS, neonatal abstinence syndrome; DTO, deodorized tincture of opium; NMS, neonatal morphine solution.

Purpose

The purpose of this study was to compare the LOS of 2 groups of infants treated for NAS with opioids. One group was treated postnatally with meth-

Table 1. Descriptive Characteristics and Comparisons Between Methadone and OMP Treatment Groups

Key Characteristics	Methadone	OMP	P Value
N = 46	17	29	
Gestational age (wks)*	39 (37 to 41)	39 (39 to 40)	1.0
Birthweight (g)*	2885 (2734 to 3295)	3010 (2731 to 3210)	0.741
Vaginal delivery	16 (94.1%)	25 (86.2%)	0.381
Race			0.396
• White	8 (47.1%)	16 (55.2%)	
• Hispanic	8 (47.1%)	13 (44.8%)	
Male	8 (47.1%)	12 (41.4%)	0.472
In utero nicotine exposure	15 (88%)	26 (89%)	0.619
In utero opiate exposure	12 (70%)	16 (55%)	0.237
Maternal polydrug use	9 (52.9%)	13 (44.8%)	0.410
Maternal methadone			
• Use	11 (65%)	25 (86%)	0.092
• Dose (mg)*	85 (72 to 85)	80 (60 to 95)	0.224
NAS score during capture period*	7 (6 to 8)	7 (6 to 8)	0.797
No. of physicians involved*	8 (7 to 10)	6 (5 to 7)	0.001
Need for foster care placement	8 (47%)	9 (31%)	0.220

NOTE. Values in parentheses represent percentages for categorical data and interquartile ranges for continuous data.
Abbreviations: OMP, oral morphine preparation; NAS, neonatal abstinence syndrome; g, grams; wks, weeks; no, number.
*Mann-Whitney *U* test was used for analyses of non-normal distributed variables.

adone, and the other with 1 of the 2 oral morphine preparations (OMP): DTO, or neonatal morphine solution (NMS). In addition, this study examined factors contributing to increased LOS in infants with NAS.

Design

Evidence about LOS in infants with NAS treated with opioids is insufficient. This study was designed as a preliminary process for future prospective studies comparing different opioid therapies for NAS. This was a retrospective cohort study performed to examine LOS and other features of the hospital course of infants with NAS at 2 Boston-area community hospitals. Between January 1997 and December 1999, both methadone and oral morphine solutions were available; they were used, at the discretion of the attending physician, to treat NAS.

Methods

A retrospective review of medical records was performed. Records of infants born between January 1997 and December 1999 at the 2 community (Level II) medical centers were identified using CPT codes for diagnosis of NAS and a thorough review of written logs. Corresponding maternal charts were also identified. Data from these charts were collected by thorough manual review by 4 reviewers.

Inclusion criteria included all infants with the following:

- Gestation age ≥36 weeks;
- Diagnosis of NAS;
- In utero exposure to methadone and/or opiates such as heroin or morphine as determined by maternal history, maternal toxicology reports during pregnancy or at the time of delivery, or infant urine toxicology reports;
- Symptoms of NAS requiring pharmacological treatment.

Exclusion criteria included infants who were:

- Transferred to another facility during treatment;
- Diagnosed with iatrogenic NAS due to postnatal exposure to opiates.

Before data collection, approval was obtained from the institutional review board (IRB) at 1 hospital, and an equivalent administrative approval was obtained from the other hospital, which did not have a formal IRB at the time of the study.

Standard treatment for NAS at both facilities was methadone or 1 of the 2 OMPs (i.e., DTO or NMS). Neonatal morphine solution is available as 0.4 mg morphine/mL oral solution and DTO as a 10 mg morphine/mL stock solution diluted to 0.4 mg/mL. Because the concentration and the dosing schedules of the active ingredient (morphine) are similar for NMS and DTO, infants treated with either of these 2 oral morphine preparations were considered in a single group for this analysis.

Infants at both hospitals were treated by the same group of physicians using common clinical guidelines and similar treatment protocols, reducing differences in care practices at the treatment sites. The total number of physicians involved in the care of each infant included in the study was recorded.

Table 2. Regression Analysis Showing Factors Associated with LOS in Infants Treated for NAS

	β Coefficient	Δ LOS, Days (95% CI)	P Value
Maximum opioid treatment dose (per 0.1 mg/kg/day)			
• Methadone	0.916	3.42 (2.53 to 4.32)	<0.001
• OMP	0.304	1.29 (0.28 to 2.31)	0.014
Maternal methadone dose (mg/day)	0.214	0.08 (0.003 to 0.2)	0.042
Birthweight (g)	0.210	0.007 (0 to 0.01)	0.038

NOTE. Factors not significantly associated with LOS: choice of treatment (methadone vs. OMP), site of treatment, gestational age, gender, in utero opiate exposure, maternal polydrug and nicotine use, NAS scores during capture period, number of physicians involved, and need for foster care placement.
Abbreviations: CI, confidence interval; Δ LOS, change in LOS; LOS, length of hospital stay; NAS, neonatal abstinence syndrome; OMP, oral morphine preparation.

Withdrawal symptoms were monitored by neonatal nursing staff who received specific education in use of the Finnegan neonatal abstinence scoring system.[21] The Finnegan scoring system is a widely used clinical tool that measures the severity of NAS withdrawal symptoms. It includes 20 signs and symptoms most often noted in infants with NAS. The severity of each symptom is ranked from 1 (mild) to 5 (severe). Individual symptom scores are added to provide a total score. For each infant, abstinence scores were recorded every 4 hours beginning shortly after birth and continuing until at least 24 hours after pharmacologic treatment was discontinued. In general, treatment was started for 3 consecutive Finnegan scores >8 or 2 consecutive scores ≥12. The dose of the treatment medication was progressively increased until abstinence scores stabilized at ≤8 as described in Sidebar 1.

Infants were maintained on this maximum dose for 48 to 72 hours or until NAS scores started to decline. The treatment dose was then weaned in decrements of 10% of maximum dose approximately every other day as tolerated. Dose adjustments were made as needed based on multidisciplinary clinical assessment and overall clinical appearance. Treatment was discontinued once the dose had been weaned to approximately 10% of the original maximum dose.

Infant records were reviewed for birth and discharge dates, gestational age, birthweight, gender, race, mode of delivery, and need for foster care placement at the time of discharge. Birth and discharge dates were used to calculate LOS. The initial, maximum, and minimum doses of treatment drug were recorded. The "capture period" was calculated as the time required to control withdrawal symptoms from initiation of pharmacological treatment to the time of the maximum treatment dose.

Toxicology screening tests (Beckman Coulter, Brea, Calif) were performed on urine of all infants born to mothers with a history of illicit drug use during pregnancy or at the time of delivery. Screens were qualitative enzyme immunoassays for determination of presence of metabolites of opiates, cocaine, barbiturates, benzodiazepines, cannabinoids, amphetamines, and phencyclidine.

Maternal records were reviewed for pertinent obstetric history, prenatal nicotine, and polydrug abuse history, and results of urine toxicology screening tests for opiates, cocaine, barbiturates, benzodiazepines, cannabinoids, amphetamines, and phencyclidine during pregnancy and at delivery. Maternal maintenance methadone dose at the time of delivery was recorded. A maternal history of opiate use during pregnancy, positive maternal urine screen for opiates during pregnancy or at delivery, or positive infant urine screen for opiates was defined as in utero opiate exposure for the infant.

Statistical Methods

Infants were divided into 2 groups based on the choice of NAS treatment, methadone or OMP. Categorical and continuous data were analyzed using the chi-square test and Mann-Whitney *U* test, respectively, due to non-normal distribution of data and the small sample size. Multivariate regression analysis was used to adjust for potential confounding factors. Data were analyzed using SPSS version 10.0 (SPSS, Chicago, Ill); $P < 0.05$ was deemed statistically significant.

Results

Fifty-three infants treated pharmacologically for NAS were identified during the study period. Three were transferred to another hospital while on treatment, 3 had NAS due to postnatal exposure to opiates, and the medical record of 1 infant was unavailable for review. Forty-six infants met inclusion criteria and were included in the analysis.

All infants in this cohort were exposed to opiates, methadone, or both in utero. Seventeen (37%) infants were treated for NAS with methadone and 29 (63%) with an OMP (DTO or NMS). There was no significant difference in gestational age, birthweight, gender, race, or need for placement into foster care

between the 2 treatment groups, as described in Table 1.

No significant difference was noted between the 2 treatment groups with regard to in utero exposure to nicotine, opiates, methadone, or maternal methadone dose. Similar numbers of infants in the 2 treatment groups were exposed to illicit drugs in utero. In the OMP treatment group, 14% of infants were exposed to benzodiazepines, 28% to cocaine, and 7% to cannabinoids. In the methadone treatment group, 12% were exposed to benzodiazepines, 41% to cocaine, and 12% to cannabinoids. Forty-one percent of infants in the OMP group and 35% of infants in the methadone group were exposed to both heroin and methadone in utero ($P = 0.5$).

There was no significant difference in the severity of withdrawal symptoms as recorded by NAS scores during the capture period in the 2 treatment groups. A significant difference in choice of treatment was found between the 2 hospitals participating in the study. Methadone was used in 65% of infants with NAS at 1 hospital and 15% at the other ($P = 0.001$). The median number of physicians involved in the care of infants in the methadone group was larger than in the OMP group.

Median LOS was 40 days (interquartile range [IQR]: 30 to 51 days) for infants treated with methadone and 36 days (IQR: 33 to 39 days) for those treated with an OMP (Fig 1). This difference was not statistically significant in univariate (Table 1) or multivariate regression (Table 2) analyses ($P > 0.05$). In multivariate regression analysis, maternal methadone dose and birthweight were significantly associated with longer LOS ($P < 0.05$). Higher maximum opioid treatment

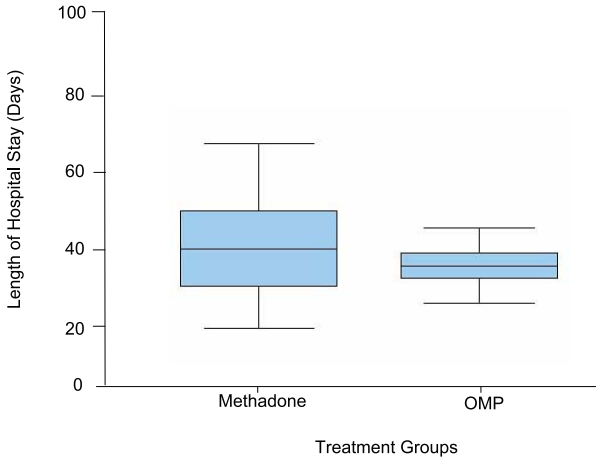

Figure 1. Length of hospital stay (LOS) of infants in methadone and OMP treatment groups. Infants treated for NAS with methadone had a median LOS of 40 days (IQR: 30 to 51 days) and those treated with OMP had a median LOS of 36 days (IQR: 33 to 39 days). These differences were not statistically significant (p = 0.142, Mann-Whitney U). Abbreviation: OMP, oral morphine preparations.

Research Tutorial #1: Limitations Related to Use of Existing Data in Retrospective Designs

Lainwala and colleagues used a retrospective design to examine whether there were differences in the length of stay (LOS) of infants treated for neonatal abstinence syndrome (NAS) with methadone compared to those treated with an oral morphine preparation (OMP). Strengths of the retrospective design include its economy and flexibility. Because retrospective designs involve the use of existing data such as medical records, the researchers do not have to expend time and resources collecting new data.

There are several design limitations that should be considered when evaluating retrospective studies. One major limitation is that the researchers have no control over the quality or the inclusiveness of the data because they rely on data that have already been collected before the beginning of the study. This limitation may have influenced the findings of the Lainwala et al study in several ways. First, the researchers noted that withdrawal symptoms were monitored by nursing staff at the 2 study hospitals by using the Finnegan neonatal abstinence scoring system.[1] There is no way to ensure that all of the nurses rated the infants consistently. Because absence of symptoms of withdrawal were a primary criterion for discharge, inconsistent application of the scoring system could have affected treatment and LOS.

A second way in which the inability to control data quality may have influenced the present study relates to the measurement of extraneous variables. For example, the researchers found that maternal methadone dose at delivery was positively associated with infants' LOS. It is not possible to evaluate the accuracy or reliability of the data about maternal methadone dose because the authors had to rely on the information charted in the maternal record. Inaccurate data represent a threat to all studies.—LLH

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dose was also significantly associated with longer LOS, regardless of choice of treatment ($P < 0.01$). For example, each increase of 0.1 mg/kg/day in maximum OMP treatment dose was associated with an increase in LOS of 1.3 days (95% confidence interval, 0.28 to 2.31; Table 2). The adjusted R^2 for this model was 0.577. After adjusting for the factors in this model, there was no significant association between LOS and choice of NAS treatment (methadone vs. OMP), gestational age, gender, maternal nicotine use, maternal polydrug use, in utero opiate exposure, severity of withdrawal symptoms, number of physicians caring for the infant, or need for foster care placement. Length of stay was not influenced by treatment site, after adjusting for the above factors.

Discussion

This study found similar LOS in infants treated for NAS with methadone versus those treated with an OMP. Regardless of choice of therapy, larger treatment doses required to control withdrawal symptoms, larger maternal methadone doses at delivery, and higher birthweights were associated with increased LOS.

Previous studies have reported a correlation between maternal methadone dose before delivery and severity of withdrawal symptoms[22-25] or duration of hospitalization.[23,25,26] A relationship between maternal methadone dose and neonatal LOS is plausible because a larger maternal dose may lead to higher neonatal plasma levels and tissue stores, resulting in more severe or prolonged withdrawal symptoms after birth.[27] However, others have not found relationships between maternal methadone dose and neonatal plasma methadone levels or severity of withdrawal.[28] The multivariate regression model in this study suggested a significant linear relationship between maternal methadone dose at the time of delivery and neonatal LOS after adjusting for other factors.

The range of LOS reported in this study (14 to 86 days) is longer than that reported in older studies[16,17,19]; however, it is similar to that reported more recently in several sources.[18,23,26,29,30] The longer hospitalizations in recent reports may in part reflect higher maternal methadone doses in contemporary cohorts compared to those in previous studies. Patients maintained on a daily methadone dose of 40 mg are at higher risk of using heroin while on methadone than those on 80 mg of methadone.[31] Similarly, better treatment compliance was noted in heroin addicts in a

Research Tutorial #2: Control Over Extraneous Variables in Retrospective Designs

A second limitation of retrospective designs is the inability to control potential confounding variables that may affect the relationships between the study variables. Extraneous variables may include characteristics of the research participants or the setting. Clinical-practice patterns are particularly vulnerable. Both of these factors may have influenced the findings in the neonatal abstinence study.

Although there were no statistically significant differences between infants in the methadone and OMP groups on potentially significant extraneous variables, the authors note that the sample size may have been too small to detect statistically significant differences that may have existed.

Data presented in Table 1 indicate that more mothers of infants in the methadone group reported polydrug use, and that the mean birthweight of infants in the methadone group was smaller than that of infants in the OMP group. Either of these factors may have contributed to LOS. Differences in physician practice has the potential to affect decisions about hospital discharge. Further, mothers could potentially select certain physicians based on their practices, creating bias in the sampling.

There were more physicians involved in the care of infants in the methadone group, suggesting less clinical continuity. These differences have the potential to influence the treatment chosen and the timing of hospital discharge.

The higher use of methadone at hospital 1 than at hospital 2 could not be controlled for without random assignment to treatment groups. Although there were no differences in LOS comparing the 2 hospitals when controlling for other potentially extraneous variables, it is still possible that there were undetected practice differences between the 2 hospitals that may have affected both NAS symptoms and LOS. Nonpharmacological measures such as swaddling and providing a quiet environment may influence withdrawal symptoms. These factors may have differed between the 2 study hospitals and among individual nursing caregivers.

Despite the limitations of retrospective designs, they are extremely useful in identifying relationships and patterns that may have clinical practice implications, thus suggesting areas for future research. In addition to the need to consider the maternal methadone dose when managing expectant mothers on methadone maintenance, the authors also recommend a prospective, blinded, randomized controlled trial to more definitively evaluate the role of methadone in the treatment of NAS. Randomized controlled trials can address many of the design limitations of retrospective studies.—LLH

methadone maintenance treatment program when methadone dose was >80 mg.[32] For these reasons, many methadone treatment programs are using higher maintenance doses than previously. A longitudinal study of multiple methadone programs showed a significant increase in the dose of methadone dispensed to patients, in patient compliance with methadone treatment, and in programs recommending longer periods on methadone treatment.[33] The median maternal methadone dose in our study was 75 mg (range, 20 to 120 mg), whereas studies from the 1970s and 1980s reported average or median maternal doses of 20 to 40 mg.[16,17,24]

We found a significant association between infant birthweight and LOS. This correlation with birthweight may be explained at least in part by tissue distribution of these drugs because opiates and methadone are highly fat soluble.[34] Infants with higher birthweights may have higher tissue-bound stores of these compounds, resulting in a longer period of withdrawal symptoms and thus a longer LOS. Also, in this cohort, 37% of infants were placed under foster care; however, there was no association between LOS and need for foster care placement, suggesting that LOS was not influenced by social factors such as delay in foster care placement after completion of medical treatment.

Limitations

This retrospective study was limited by its small sample size. Although there was no statistically significant difference in LOS of infants treated with methadone or OMP, the power of this study to detect small but potentially important differences in LOS was limited. Also, the significant difference between the 2 study sites with respect to choice of treatment raises the possibility that the study results were confounded by unidentified site-specific differences. However, after adjusting for demographic and clinical factors in regression analysis, site of treatment was not associated with LOS.

The Finnegan abstinence scoring system is a widely used clinical tool for determination of NAS severity. Infants treated for NAS using this scoring system required lower treatment doses to control withdrawal symptoms and had shorter lengths of treatment.[21] Infants monitored with Finnegan scoring had better nutritive suck compared to a group monitored with the clinical approach standard at the time of study.[21] Validity studies on this scoring system, such as interobserver reliability testing, have not been reported and deserve further study.

In our study cohort, abstinence scoring was performed by neonatal nursing staff who received standardized training as part of routine clinical caregiving. Due to the retrospective nature of this study we were unable to collect data on the number of nurses recording the abstinence scores.

This study did not exclude infants of mothers with polydrug abuse. Maternal polydrug use was not significantly different in the 2 treatment groups and was not significantly associated with LOS in multivariable regression analysis. Moreover, although this study did not examine maternal use of alcohol or serotonin reuptake inhibitor antidepressants, these drugs have not been shown to alter neonatal withdrawal symptoms in infants when used in combination with opioids during pregnancy.[35]

Nonpharmacological measures such as swaddling and providing a quiet environment have a fundamental role in control of withdrawal symptoms.[36] Although these measures are an important part of nursing care for NAS at the study sites, this retrospective study was not able to assess their effectiveness.

Clinical Implications and Future Research

There is no consensus on the choice of pharmacological treatment for NAS. Currently, use of methadone for treatment of NAS is infrequent due to its long half-life and the relative lack of reported experience compared to other alternatives. This small study suggests that methadone may be a reasonable choice of therapy for NAS because LOS of infants treated with methadone was similar to those treated with OMP. A large prospective, blinded, randomized controlled trial is warranted before the potential role of methadone in the treatment of NAS can be defined. Also, consistent with findings of others, this study found that higher maternal methadone doses were associated with longer LOS. The potential effects of maternal methadone dose on neonatal LOS should be weighed when counseling expectant mothers receiving methadone maintenance therapy.

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