Outpatient Pharmacotherapy for Neonatal Abstinence Syndrome

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Objective To determine differences in lengths of stay, length of therapy, emergency department (ED) utilization, and hospital readmissions between infants with neonatal abstinence syndrome (NAS) treated exclusively with inpatient pharmacotherapy compared with those discharged on outpatient pharmacotherapy.

Study design This retrospective cohort study of infants enrolled in the Tennessee Medicaid program used administrative and vital records data from 2009 to 2011. Medical record review was used to confirm cases of NAS and classify treatment type. Negative binomial regression was used to compare length of therapy and ordinal regression was used to determine frequency of ED visits and hospital readmissions.

Results Among a cohort of 736 patients with confirmed NAS, 72.3% were treated with pharmacotherapy of which approximately one-half (45.5%) were discharged home on outpatient medications. For infants discharged on outpatient pharmacotherapy, initial hospital length of stay was shorter (11 vs 23 days; $P < .001$) and length of therapy was longer (60 vs 19 days; adjusted incidence rate ratio [aIRR] 2.84, 95%CI 2.31-3.52). After adjusting for potential confounders, infants discharged on outpatient pharmacotherapy had a greater number of ED visits within 6 months of discharge (adjusted odds ratio [aOR] 1.52, 95% CI 1.06-2.17) compared with those treated as inpatients alone.

Conclusions Outpatient pharmacotherapy for NAS was associated with higher length of therapy and higher rates of ED utilization when compared with infants treated exclusively as inpatients. Future research should focus on improving the efficiency of NAS management while minimizing postdischarge complications. *(J Pediatr 2018;■■:■■-■■).*

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome that most commonly occurs after in utero opioid exposure. Signs of NAS include irritability, tremors, hyperactive reflexes, feeding problems, and in rare cases, seizures.[1] As opioid use became increasingly common in the US,[2] the nationwide incidence of NAS increased by nearly 5-fold over the last 15 years.[3,4] Infants with NAS have prolonged hospitalizations, with average length of stay of 19 days, and comprise a significant portion of neonatal intensive care unit (NICU) days.[5] These hospitalizations also tend to be costly, with mean hospital charges of $93 400 per patient.[3]

Treatment of NAS can require prolonged courses of pharmacotherapy, which traditionally occurs exclusively in the inpatient setting. However, some centers combine inpatient and outpatient treatment, discharging patients home on medications.[6] Although this practice is not well-studied, it is estimated that about one-third of NICUs in the US discharge patients with NAS home on medication.[6] In a few small studies, a combination of inpatient and outpatient treatment has been shown to decrease length of hospital stay,[7-10] but data assessing whether this practice has unintended consequences are sparse. Further, outpatient pharmacotherapy is commonly done with phenobarbital, of particular concern, because phenobarbital has been shown to have deleterious effects on brain development and cognitive outcomes in animal[11,12] and human studies.[13]

We aimed to compare the lengths of stay and therapy between patients treated as inpatient only and those discharged on a regimen that included outpatient pharmacotherapy in a large state-based population. In addition, we sought to determine if outpatient pharmacotherapy for NAS was associated with postdischarge adverse events, including hospital readmissions and emergency department (ED) visits.

Methods

This was a retrospective cohort study of 112 029 infants born to women enrolled in TennCare, Tennessee's Medicaid program, from 2009 to 2011. Medicaid serves as an ideal study population for infants with NAS because the program is financially responsible for 80% of infants diagnosed with the syndrome.[4] Hospital and

ED	Emergency department
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
NAS	Neonatal abstinence syndrome
NICU	Neonatal intensive care unit

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Supported by the National Institute on Drug Abuse of the National Institutes of Health (K23DA038720 [to S.P.]). The content is solely the responsibility of the authors and does not necessarily represent the official views of any funding organizations. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.03.048

outpatient administrative data were linked to birth certificates and outpatient prescription claims.[14] Administrative data were used to identify cases of NAS based on the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 779.5 (drug withdrawal syndrome in newborn) in any diagnostic field.[2-4] As an analysis of deidentified data, this study was approved with a waiver of informed consent by the Vanderbilt University institutional review board, the State of Tennessee Department of Health, and the Bureau of TennCare.

Cohort Assembly

Patients were included if the mothers were between 15 and 44 years old at the time of delivery, the infants were enrolled in TennCare within 30 days after birth, and the infants were born between January 1, 2009 and December 31, 2011. Medical records for the identified cases were requested from the infant's birth hospital. Each medical record was reviewed by 2 investigators to independently confirm the diagnosis of NAS and obtain infant treatment data. Patients were included if they had NAS and gestational age >35 weeks at birth (**Figure 1**). To reduce the risk of misclassification given that *ICD-9-CM* code 779.5 entails all cases of NAS and to reduce overestimating duration of therapy because phenobarbital is also a treatment for seizures, patients were excluded if they had iatrogenic (ie, drug withdrawal from postnatal medications) NAS (n = 9), a diagnosis of seizures at any time during the study period by the presence of *ICD-9-CM* code 779.0, 780.3, 780.39 in the inpatient and outpatient claims data (n = 53), missing demographic information (gestational age) (n = 4), or if there was insufficient documentation to adjudicate whether they were discharged home on medication (n = 7). We also grouped the medical centers where patients were treated into the 3 geographically defined regions of the state: East, Middle, and West (http://sos.tn.gov/sites/default/files/Pg.%20639%20Three%20Grand%20Divisions.pdf).

Covariates

Demographic information was obtained for mothers and infants in our cohort using birth records. Maternal data included age, education, and race. Infant data included gestational age, birth weight, and sex. Data for antenatal exposures were obtained from prescription claims (immediate release/sustained release/maintenance opioids, selective serotonin

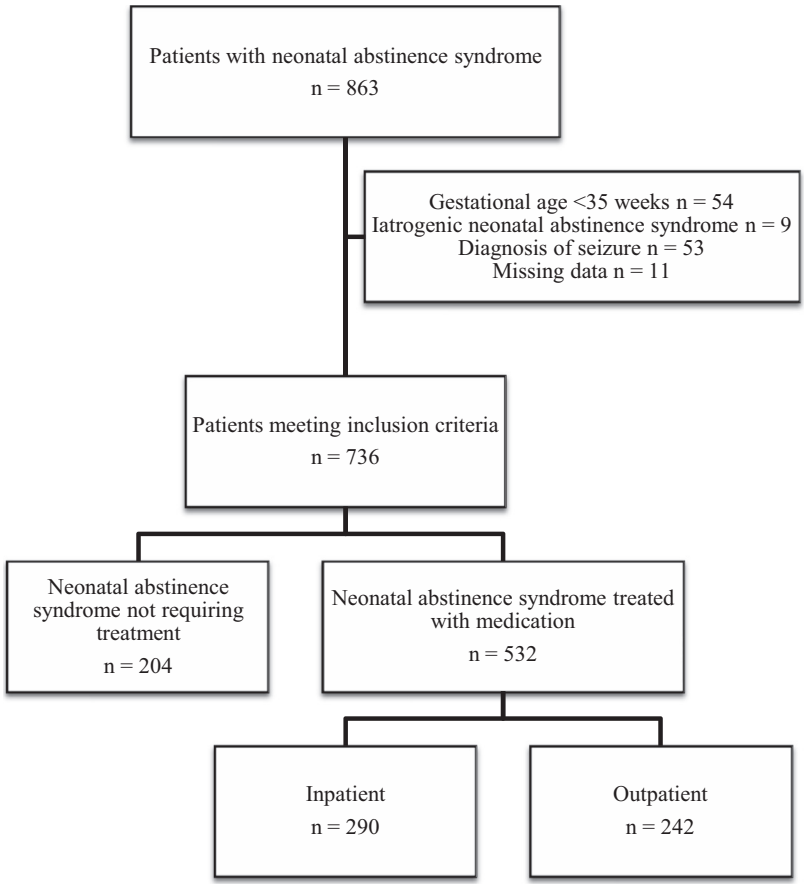

Figure 1. Study population.

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reuptake inhibitors, and benzodiazepines), birth certificates (number of cigarettes smoked), and medical record review that included toxicology screens (benzodiazepines).

Outpatient Treatment

We categorized patients as receiving outpatient pharmacotherapy ("outpatient") if they were discharged home on a medication. We categorized patients as not receiving outpatient pharmacotherapy if they were treated for NAS with pharmacotherapy, but were not discharged on a medication ("inpatient"). We identified the infants discharged on medications based on physician documentation, either in progress notes or discharge summaries. Medicaid prescription data were used to identify the cases in which a prescription for phenobarbital and/or methadone was filled for outpatient treatment. Prescriptions were excluded if they represented denied or unapproved claims, had prescription filling gaps of more than 30 days, or were for a tablet form indicating that these prescriptions were not intended for the infant.

Primary Outcome: Length of Therapy

The length of stay was calculated using the admission and discharge dates obtained from the administrative data (**Figure 2**; available at www.jpeds.com). To accurately estimate the length of therapy, a chart review of 100 patients was performed to identify the number of days of observation prior to initiating medication and after discontinuing therapy. In the inpatient group, the mean duration of observation off of therapy was 2 days pretreatment and 2 days post-treatment. Thus for neonates treated as inpatient only, the length of therapy was calculated by subtracting 4 days from the length of stay. In the outpatient group, the chart review revealed a mean pretreatment observation period of 3 days. Length of treatment for the outpatient group was calculated by subtracting 3 days from the length of stay and adding to the duration of total filled prescriptions for each case. In the event where a patient was discharged home on 2 medications, the prescription for the longer duration was used. Only prescription claims for phenobarbital and methadone were captured, as they were the vast majority of medications used as an outpatient.

Secondary Outcome: Readmissions and ED Visits

TennCare claims data were used to identify the number of hospitalizations and ED visits within 30 days and 6 months of discharge from the hospital.

Statistical Analyses

The Wilcoxon test and Pearson test were used for bivariate analyses. To account for the potential confounding effect of maternal and infant characteristics as well as antenatal exposures on our primary outcome (length of treatment), negative binomial models were fit accounting for infant sex, birth weight, opioid type used, selective serotonin reuptake inhibitor use, benzodiazepines use, and number of cigarettes smoked. Infants treated as an outpatient without complete data for prescription claims were excluded in multivariable analyses of length of treatment. To study the relation between outpatient treatment and number of hospital readmissions and ED visits, an ordinal regression model was fit with occurrences of ED visits or hospitalizations as the outcome and whether they had an outpatient pharmacotherapy as the predictor. This model was adjusted for region of treatment and birth weight. All analyses were conducted using R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria) and STATA v 14.2 (StataCorp, College Station, Texas).

Results

The cohort included 1086 infants identified using the presence of *ICD-9-CM* code 779.5, among whom 863 were confirmed to have NAS. One hundred twenty-seven were excluded because of gestational age <35 weeks (54), iatrogenic NAS (9), diagnosis of seizure (53), or missing data (11). The final cohort included 736 infants. Of the confirmed cases of NAS, 532 (72.3%) were treated with medication. Among those treated with medications, 290 (54.5%) patients were treated as inpatients and 242 (45.5%) as outpatients (**Figure 1**).

The maternal and infant characteristics of both groups are shown in **Table I**. Infants treated as inpatient vs outpatients were similar in terms of maternal age, education, gestational age, and sex; however, outpatients had higher birth weights (3002 vs 2902 g; $P = .04$) and were more likely to be treated in a hospital in the eastern region of Tennessee (90% vs 68%, $P < .001$).

We found substantial variation in medications used to treat infants with NAS between both treatment groups (percentages may exceed 100% because of multiple medications used in treatment). For inpatients, the majority were treated with morphine (63%), followed by methadone (28%) and phenobarbital (26%). In comparison, among outpatients, inpatient treatment was more commonly with phenobarbital (89%), followed by dilute tincture of opium (40%), methadone (19%), and morphine (7%).

Table II lists the medications used for outpatient treatment of NAS in our cohort. Among outpatients, 81% were discharged home on phenobarbital alone, 9.1% were discharged home on methadone alone, 7.4% were discharged home on both of those medications, and the remaining 2.5% were discharged home on other medications including clonidine and dilute tincture of opium.

The median hospital length of stay for outpatients was 11 days (IQR 7-18) compared with 23 days (IQR 14-35) for inpatients ($P < .001$). Prescribing data were complete for 79 (33%) of infants treated as an outpatient. The median length of treatment for outpatients was 60 days (IQR 38-92) compared with 19 days (IQR 10-31) for inpatients ($P < .001$; **Figure 3**). After accounting for differences in infant characteristics and maternal exposures, infants treated as outpatients had length of therapy that was nearly three times greater than those treated as inpatients (adjusted incidence rate ratio [aIRR] 2.84, 95% CI 2.31-3.52).

In unadjusted analyses of health care utilization patterns after discharge, ED utilization was common among both groups, with at least 1 ED visit within 6 months in 99 (35%) and 96

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Table I. Maternal and infant characteristics for infants treated for neonatal abstinence syndrome inpatient only compared with those discharged on outpatient weans

	Inpatient n = 290	Outpatient n = 242	*P* value*
Maternal characteristics			
Maternal age (y)	26	26	.41
Maternal race, n (%)			.72
White	283 (97.5)	234 (96.7)	
Other	†	†	
Maternal ethnicity, n (%)			.071
Hispanic	†	†	
Non-Hispanic	281 (96.9)	231 (95.5)	
Maternal education, n (%)			.44
Less than high school	90 (31.0)	67 (27.7)	
High School	117 (40.3)	111 (45.9)	
More than high school	80 (27.6)	61 (25.2)	
Infant characteristics			
Gestational age (wk)	39	39	.22
Birth weight (g)	2902	3002	.037*
Female sex	133 (45.8)	107 (44.2)	.70
Region of Tennessee			<.001*
East	196 (67.6)	217 (89.7)	
Middle	69 (23.8)	16 (6.6)	
West	24 (8.3)	9 (3.7)	

Data may not round to 100% because of missing data.
**P* value from Wilcoxon test and Pearson test.
†Values with less than 10 observations suppressed.

Table II. Medications used for outpatient treatment of neonatal abstinence syndrome

Medication	n	%
Phenobarbital	198	82
Methadone	21	9
Phenobarbital + Methadone	17	7
Other*	6	2

*Includes clonidine, morphine, and dilute tincture of opium

(42%) in the inpatient and outpatient groups, respectively ($P = .075$). Hospital readmissions within 6 months occurred in 21 (7%) and 22 (10%) in the inpatient and outpatient group, respectively ($P = .13$).

In adjusted analyses accounting for birth weight and region of treatment, the outpatient group was more likely to have a greater number of ED visits within 6 months after discharge than the inpatient group (aOR 1.52, 95% CI 1.06-2.17, Figure 4). However, there was not a significant difference in hospital readmissions between the outpatient and inpatient groups (aOR 1.49, 95% CI 0.78-2.85). The primary diagnosis for ED visits between groups was similar. The most common diagnoses were infectious (eg, upper respiratory infections; 80% outpatient vs 71% inpatient) followed by signs of drug withdrawal (10% outpatient vs 11% inpatient).

Discussion

In this large retrospective cohort study, we found that outpatient pharmacotherapy was common among infants with NAS, resulted in substantially longer lengths of medication therapy, and was associated with higher rates of ED utilization

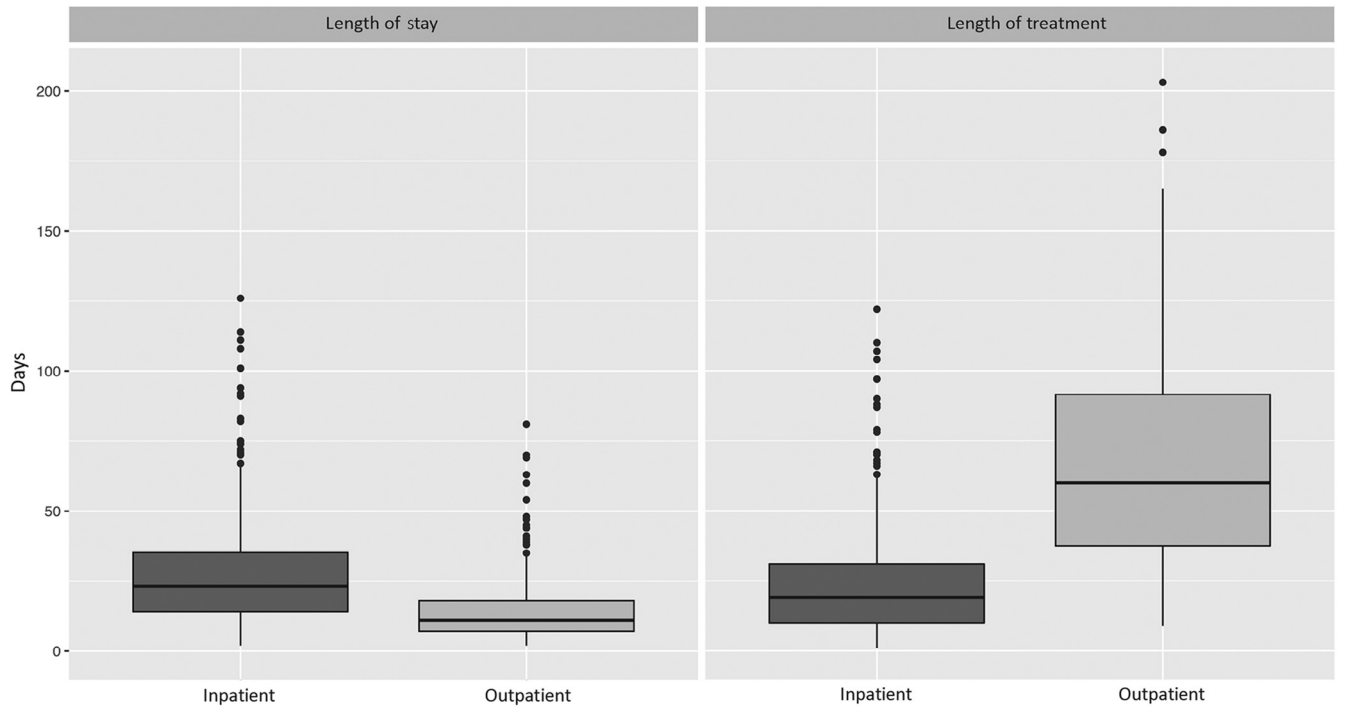

Figure 3. Difference in length of stay and length of treatment between infants treated as inpatient and outpatients.

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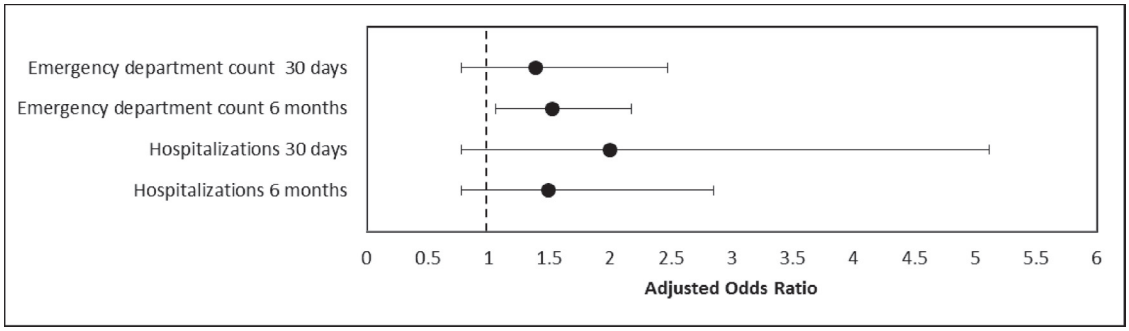

*Ordinal logistic regression accounting for birth weight and geographic location of treating hospital.

** Results can be interpreted as, for example, the patients treated with a combination of inpatient and outpatient pharmacotherapy were 1.52 (95% CI 1.06 – 2.17) more likely to have a greater number of ED visits within 6 months after discharge than those completing pharmacotherapy exclusively as an inpatient.

Figure 4. Adjusted odds of emergency department and hospital utilization after discharge among infants treated as inpatient compared to outpatients.

compared with inpatient treatment alone. Among infants treated as an outpatient, median length of therapy was 3 times that of infants treated solely as inpatients, with some infants receiving treatment for more than 200 days.

In the US, medical treatment of NAS traditionally occurs in the inpatient setting and aims for a controlled opioid replacement weaned over a period of time. Because weaning medications may take several days to weeks, patients with NAS have prolonged hospitalizations and, therefore, increased healthcare costs.[4] Several centers advocate a combination of inpatient and outpatient pharmacotherapy. In a multicenter audit in Australia, Abdel-Latif et al followed 202 patients treated for NAS and noted that 71% of those infants were discharged home on medication.[15] In a survey of 179 NICUs in the US, 34% of them offered home treatment programs.[6] Another report from the United Kingdom noted that 29% of 235 NICUs surveyed allowed patients to be discharged on medications.[16] Oei et al showed in a retrospective study of 51 infants with NAS that establishing a coordinated follow-up clinic increased the rate of outpatient therapy from 30% to 90%.[7] Our study of 532 infants treated with pharmacotherapy for NAS found that 45% of infants receiving pharmacotherapy were discharged home to continue treatment. As incidence of NAS increases, there is an urgent need to understand the potential consequences of outpatient management of the syndrome.

Although the practice of outpatient management of NAS is common, only a few studies have assessed the impact of this practice on length of hospitalization. These retrospective studies had relatively small sample sizes (51-139 infants) in the US, United Kingdom, and Australia and found that this strategy significantly decreased the length of stay by 10-21 days.[7-10] We found that the patients treated as outpatients had shorter hospitalizations (median difference of 12 days compared with inpatients); however, this practice was associated with substantially longer length of therapy (median of 60 days, maximum of 203 days). We also found that in patients discharged home on medications as indicated on their hospital discharge summary, many did not fill a postdischarge prescription. This could be because medications were given from the hospital to wean at home (ie, no outpatient pharmacy claims) or could represent an abrupt cessation of medications.

The vast majority (89%) of infants with NAS treated as outpatients in our study were given phenobarbital, a known sedative that has been associated with poor neurologic outcomes in animals and humans.[12,13] Bittigau et al showed that rat pups exposed to phenobarbital had apoptotic neurodegeneration in their brains.[12] In a randomized controlled trial of infants with febrile seizures treated with phenobarbital compared with placebo, the group treated with phenobarbital had worse cognitive scores at 2 years of age.[13] Prolonged weans with phenobarbital may, therefore, place the developing brain at additional risk of developmental delays.

We found substantial geographic differences, but little patient-level variation, among infants treated for NAS as inpatients and outpatients, suggesting that the reason for discharge home may be due to hospital (eg, capacity) or physician factors (eg, preference) rather than patient characteristics. In our study, 53% of patients treated for NAS were discharged on outpatient weans in eastern Tennessee, compared with only 27% and 19% in the western and middle regions of the state, respectively. Criteria for discharging patients on pharmacotherapy are not well established. Patients discharged home on medications need to have constant follow-up for dose management and weaning[7] to reduce risk of this practice including overuse, inability to fill prescriptions, and nonadherence to therapy. However, in many communities resources

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required for medical management and close monitoring might not always be readily available. The extended length of therapy coupled with higher rates of ED visits among infants treated as an outpatient raises the concern that infants treated in the outpatient setting may have suboptimal follow-up.

Patients with NAS have increased hospital readmission rates in childhood,[17,18] which creates an additional emotional and financial strain on families and the healthcare system. However, the hospital readmission and ED visit rates are not well defined for the subgroup of patients with NAS treated and discharged as outpatients. In our study, we noted that patients discharged on outpatient pharmacotherapy were likely to have more ED visits within 6 months of discharge than those treated as inpatients. Patients had on average 1-2 ED visits within 6 months of discharge, and some were seen up to 4 times. The association of outpatient pharmacotherapy with increased ED utilization merits further investigation. Possible reasons for this association could be ongoing clinical signs of NAS, complications of the medication weans, or unmeasured differences in patient populations such as social factors.

The rapid rise of NAS throughout the US has placed stresses on many parts of the healthcare system. Over the last several years, hospitals have engaged in quality improvement efforts to improve hospital outcomes for patients with NAS. Many of these efforts, however, have exclusively focused on reducing length of stay without a focus on postdischarge outcomes. Dickes et al studied the effect of initiating high-risk patients on treatment early on overall hospital charges.[19] Other studies have focused on other ways of shortening length of hospitalization as well as length of therapy. This could be achieved by implementing standardized approaches to therapy, which has been shown to reduce length of stay, in addition to decreasing the proportion of patients discharged home on medication.[20,21] Other efforts have focused on decreasing the need for pharmacologic therapy with interventions such as infant-centered scoring, rooming-in, and treatment of NAS on the pediatric ward rather than the NICU.[22] Exclusive focus on inpatient length of stay may fail to consider long-term postdischarge outcomes, with subsequent prolonged and potentially unstandardized outpatient weans. Additional research is needed to better understand how different NAS pharmacotherapies and treatment strategies after birth may influence developmental outcomes.

Our study has potential limitations. The use of administrative data to identify NAS treatment patterns could lead to misclassification; however, this was mitigated by an adjudication process by 2 physicians to confirm treatment status at the time of discharge. We did not directly observe the patients taking the medications. As a result, the use of prescription data to infer length of outpatient therapy could lead to inaccurate estimations of treatment duration. To minimize this, we excluded any interruptions in outpatient prescriptions. In support of our method, studies have demonstrated that filled prescriptions are reasonable proxies of medication use.[23] Lastly, our study only involved infants in the Tennessee Medicaid program, which may limit its generalizability to other settings.

We found that infants treated for NAS as outpatients have substantially longer durations of therapy than infants treated as inpatients, and also have higher rates of postdischarge ED utilization. Clinicians should consider that outpatient pharmacotherapy may put infants at risk for prolonged exposure to potentially harmful medications. Future research should focus on improving the efficiency of NAS management while balancing the risk of postdischarge complications. ■

Acknowledgments available at www.jpeds.com.

Submitted for publication Dec 18, 2017; last revision received Feb 14, 2018; accepted Mar 19, 2018

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Acknowledgments

We thank Ann Stark for her guidance and input on the manuscript and William Walsh for his guidance throughout the process of developing this work. We acknowledge the Vanderbilt University Dance Marathon Fund for partially supporting this work. We are indebted to the Tennessee Bureau of TennCare of the Department of Finance and Administration that provided the data and the Tennessee Department of Health, Office of Health Statistics for providing vital records data.

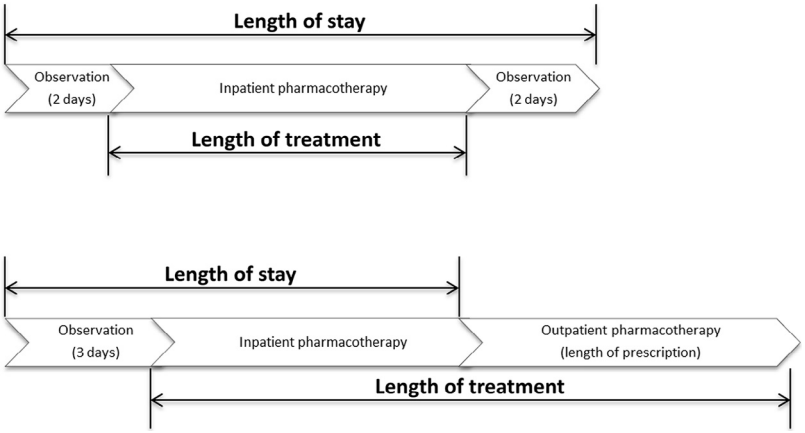

Figure 2. Calculation of length of stay and length of therapy.

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