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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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

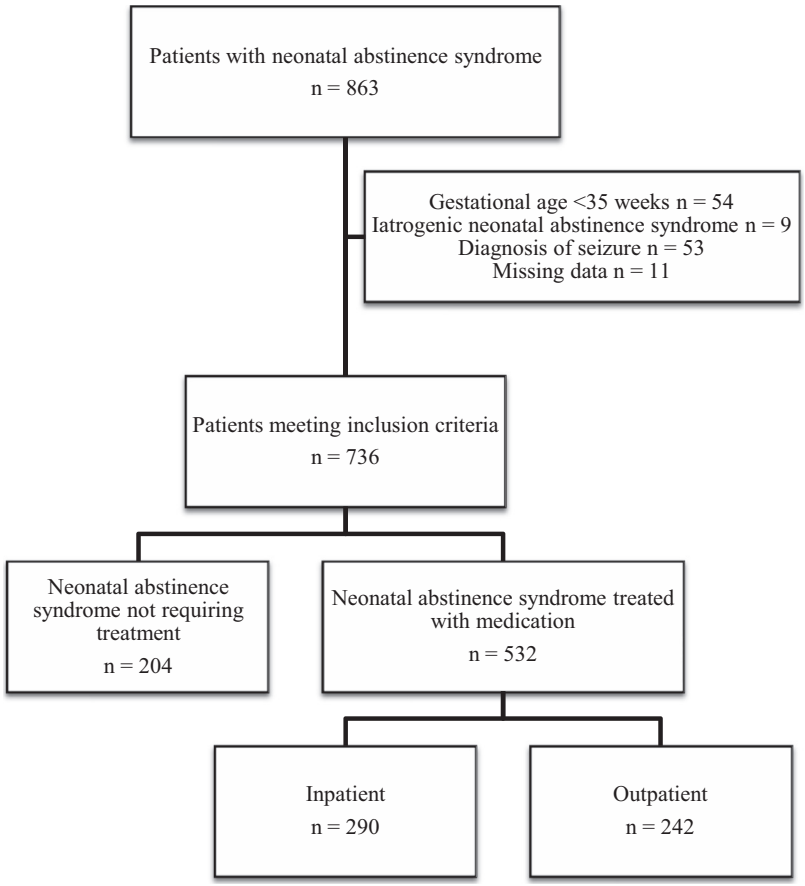

Figure 1. Study population.

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