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Neonatal Abstinence Syndrome and Associated Health Care Expenditures

United States, 2000-2009 FREE

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ABSTRACT

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Context Neonatal abstinence syndrome (NAS) is a postnatal drug withdrawal syndrome primarily caused by maternal opiate use. No national estimates are available for the incidence of maternal opiate use at the time of delivery or NAS.

Objectives To determine the national incidence of NAS and antepartum maternal opiate use and to characterize trends in national health care expenditures associated with NAS between 2000 and 2009.

Design, Setting, and Patients A retrospective, serial, cross-sectional analysis of a nationally representative sample of newborns with NAS. The Kids' Inpatient Database (KID) was used to identify newborns with NAS by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code. The Nationwide Inpatient Sample (NIS) was used to identify mothers using diagnosis related groups for vaginal and cesarean deliveries. Clinical conditions were identified using *ICD-9-CM* diagnosis codes. NAS and maternal opiate use were described as an annual frequency per 1000 hospital births. Missing hospital charges (<5% of cases) were estimated using multiple imputation. Trends in health care utilization outcomes over time were evaluated using variance-weighted regression. All hospital charges were adjusted for inflation to 2009 US dollars.

Main Outcome Measures Incidence of NAS and maternal opiate use, and related hospital charges.

Results The separate years (2000, 2003, 2006, and 2009) of national discharge data included 2920 to 9674 unweighted discharges with NAS and 987 to 4563 unweighted discharges for mothers diagnosed with antepartum opiate use, within data sets including 784 191 to 1.1 million discharges for children (KID) and 816 554 to 879 910 discharges for all ages of delivering mothers (NIS). Between 2000 and 2009, the incidence of NAS among newborns increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001). Antepartum maternal opiate use also increased from 1.19 (95% CI, 1.01-1.35) to 5.63 (95% CI, 4.40-6.71) per 1000 hospital births per year (P for trend < .001). In 2009, newborns with NAS were more likely than all other hospital births to have low birthweight (19.1%; SE, 0.5%; vs 7.0%; SE, 0.2%), have respiratory complications (30.9%; SE, 0.7%; vs 8.9%; SE, 0.1%), and be covered by Medicaid (78.1%; SE, 0.8%; vs 45.5%; SE, 0.7%; all P < .001). Mean hospital charges for discharges with NAS increased from \$39 400 (95% CI, \$33 400-\$45 400) in 2000 to \$53 400 (95% CI, \$49 000-\$57 700) in 2009 (P for trend < .001). By 2009, 77.6% of charges for NAS were attributed to state Medicaid programs.

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Conclusion Between 2000 and 2009, a substantial increase in the incidence of NAS and maternal opiate use in the United States was observed, as well as hospital charges related to NAS.

A recent national study indicated that illicit drug use is 16.2% among pregnant teens and 7.4% among pregnant women aged 18 to 25 years.¹ Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome in newborns following birth. The syndrome most commonly occurs in the context of antepartum opiate use, although other drugs have also been implicated.²⁻⁵ In addition to NAS, illicit drug use (specifically opioid dependence) during pregnancy is associated with a significantly increased risk of adverse neonatal outcomes such as low birthweight (<2500 g) and mortality.⁶⁻⁹ Neonatal abstinence syndrome is characterized by a wide array of signs and symptoms including increased irritability, hypertonia, tremors, feeding intolerance, emesis, watery stools, seizures, and respiratory distress.¹⁰ Symptoms of withdrawal associated with NAS have been described in 60% to 80% of newborns exposed to heroin or methadone in utero.¹¹

Recently, analyses from Australia¹² and the Florida Medicaid program (D. Aronberg, JD, written communication, November 30, 2011) found that the incidence of NAS has been increasing. To date, there are no national estimates of the incidence of NAS over time in the context of incidence of maternal opiate use at the time of delivery. Our primary objectives were to examine patterns in the national incidence of NAS and maternal opiate use at the time of delivery using the most recent national data. In addition, we sought to describe clinical comorbidities and health utilization patterns for NAS in a nationally representative sample.

METHODS

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Study Design and Setting

Infants with NAS were identified from a serial cross-sectional analysis of pediatric discharges in 2000, 2003, 2006, and 2009, using the Healthcare Cost and Utilization Project's (HCUP) Kids' Inpatient Database (KID), compiled by the Agency for Healthcare Research and Quality.¹³ The KID is a nationally representative database that samples 80% of pediatric discharges and 10% of uncomplicated births to increase the statistical power to detect and evaluate rare conditions among hospitalized children; the data set has been used widely for national analyses of children's hospitalization patterns.¹⁴⁻¹⁸ Discharges are weighted based on the sampling scheme to permit inferences for a nationally representative population. In 2009, the most recent year for which the KID is available, the KID contained deidentified information for 7.4 million weighted discharges from 4121 hospitals in 44 states. The HCUP provides additional details to facilitate statistical analyses that permit national inferences.¹⁹ Because the analysis was of deidentified national data, our study was considered exempt from institutional review board approval by the University of Michigan Medical School.

The characteristics of maternal deliveries associated with substance abuse were identified in the Nationwide Inpatient Sample (NIS), which was developed by the Agency for Healthcare Research and Quality's HCUP in 2000, 2003, 2006, and 2009.²⁰ The NIS is a nationally representative database that samples 20% of discharges from US community hospitals (including public hospitals and academic medical centers). Discharges are weighted based on the sampling scheme to permit inferences for a nationally representative population. The NIS contained deidentified information for 7.8 million weighted discharges from 1100 hospitals and 44 states in 2009 (representing 96% of the US population). The HCUP provides additional details to facilitate statistical analyses in the NIS that permit national inferences.²¹

Identification of Sample

Using the KID, hospitalizations for patients with NAS were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code of 779.5 (drug withdrawal syndrome in a newborn) in any 1 of 15 discharge diagnosis fields. Using the NIS, delivering mothers were identified by common delivery diagnosis related groups (version 24, groups 370-375). Mothers dependent on opiates (304.0x, 304.7x), using opiates (305.5x), and taking long-term methadone or other opiate analgesics (V58.69) were also identified for the analysis.

Descriptive Variables

Patients with NAS are known to have an increased incidence of seizures, respiratory symptoms, feeding difficulties, and low birthweight; these diagnoses were included to describe the NAS population.^{12,22} After identifying our cohort of newborns with NAS, these signs of withdrawal were identified using *ICD-9-CM* diagnosis codes for seizure (779.0, 780.3), respiratory symptoms (769.x, 770.x), and feeding difficulties (779.3).

Birthweight was defined using a multistep process. First, birthweight was classified into 3 categories (very low birthweight as <1500 g; low birthweight as 1500-2499 g; and normal birthweight as ≥2500 g) using the birthweight variable included in the KID database and reported by some states. Second, *ICD-9-CM* diagnosis codes that indicate birthweights were included (764.0x, 764.1x, 764.2x, 764.9x, 765.0x, and 765.1x). Third, diagnosis related group codes 391 (normal newborn) and 389 (>37 weeks' gestation and ≥2500 g term neonate with problems) were assumed to reflect newborns with birthweights of 2500 g or more. This process reduced the number of missing values to less than 3% of all hospital births in all study years. This level of missing data was thought to be sufficient for analysis and did not prompt imputation.

Iatrogenic NAS

Prolonged neonatal intensive care unit care may result in complications and require extended use of opiate medications, resulting in withdrawal symptoms in newborns not exposed to opiates in the antenatal period. These newborns were identified if they were very low

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birthweight, had intraventricular hemorrhage (code 772.1x), periventricular leukomalacia (code 779.7), necrotizing enterocolitis (code 777.5x), spontaneous intestinal perforation (code 777.6), or bronchopulmonary dysplasia (code 770.7). We classified these discharges (≥ 1 of the above) as possible cases of iatrogenic NAS. In total, these newborns included fewer than 5% of all NAS births in all study years. Given that the etiology of withdrawal among iatrogenic NAS is inherently different than those newborns with antenatal exposure to opiates, newborns with iatrogenic NAS were excluded from our analysis.

Demographics

To describe the socioeconomic status and burden of health care utilization in both infants and mothers, primary insurance type (payer) and average income quartile for the zip code of the patient's residence were included. Primary payers were grouped into public sources (Medicaid and Medicare), private sources, self-pay, and other types (including no charge and other sources). Given that less than 0.2% of hospital births and NAS were attributed to Medicare, public sources are referred to as Medicaid throughout the study. Additional demographic information (eg, age in days, race/ethnicity, secondary payers) were also available in the KID but were missing for more than 20% of cases or were otherwise inconsistent across data years and therefore were not used.

The KID contains hospital characteristics, including urban vs rural hospital and teaching status. The National Association of Children's Hospitals and Related Institutions classifies hospitals as (1) not a children's hospital, (2) children's general hospital, (3) children's specialty hospital, and (4) children's unit in a general hospital. For our analysis, we defined children's hospital as the National Association of Children's Hospitals and Related Institutions classifications 2, 3, and 4.

Health Care Utilization and Outcome Variables

Discharge-level information such as length of stay (LOS) and total hospital charges were evaluated. Total charges reflected the total facility fees reported for each discharge record (not including professional fees). Total charges were missing in less than 5% of discharges. To estimate aggregate charges for various groups, missing total charge values were treated as missing at random and estimated using multiple imputation (based on a regression model that estimates the missing value using known variables). Age, LOS, and diagnosis related group were included as covariates in the imputation analysis consistent with prior studies.¹⁴ Multiple imputation of total charges was performed with STATA version 11.1 (STATA Corp) by using imputation by chained equations.²³ All charges were converted to 2009 US dollars using the medical consumer price index.²⁴

Data Analysis

Statistical comparisons were performed using STATA version 11.1. When nationally representative estimates were desired, analyses were weighted by Agency for Healthcare Research and Quality–specified discharge values. For 2009 discharges, differences in patient characteristics for NAS discharges vs discharges for all other hospital births, and for discharge for delivering mothers with opiate use vs all other delivering mothers, were assessed using survey weighting and reported with 95% confidence intervals.

Changes in the number of discharges and health care utilization over time were described in 2000, 2003, 2006, and 2009 using national estimates. The number of discharges for NAS in each year was described as the rate of discharge per 1000 hospital births per year, as were the number of maternal discharges complicated by opiate use. Trends in mean LOS, as well as mean hospital charges for all NAS discharges, were described. The trends in mean LOS and mean hospital charges for all hospital births are presented for comparison. The statistical significance of all time trends was analyzed by assessing *P* for trend across the 4 study years by using variance-weighted regression for categorical and continuous variables.^{14,25} Throughout our analysis, all testing was 2-sided, with data reported with SEs or 95% confidence intervals.

RESULTS

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Discharges for NAS vs All Other Hospital Births in 2009

In 2009, NAS was diagnosed in newborns at a rate of 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year. Compared with all other hospital births, newborns with NAS were significantly more likely to have respiratory diagnoses (30.9%; SE, 0.7%), to have low birthweight (19.1%; SE, 0.5%), have feeding difficulties (18.1%; SE, 0.7%), and have seizures (2.3%; SE, 0.2%). Newborns with NAS were also more likely to be covered by Medicaid (78.1%; SE, 0.8%) and reside in zip codes within the lowest income quartile (36.3%; SE, 1.3%) (Table 1).

Table 1. Characteristics of Newborns Diagnosed With Neonatal Abstinence Syndrome vs All Other US Hospital Births in 2009^a

Characteristics	Neonatal Abstinence Syndrome Discharges (n = 164) (%) (n = 164/4)	All Other US Hospital Births (n = 1413) (%) (n = 1413/10)	P Value
Sex			
Male	82 (50.0)	706 (50.0)	.95
Female	82 (50.0)	707 (50.0)	
Clinical conditions			
Respiratory distress	50 (30.5)	395 (28.0)	.001
Low birthweight (< 3500 g)	31 (19.0)	134 (9.5)	<.001
Feeding difficulty	29 (17.7)	87 (6.2)	<.001
Seizure	4 (2.4)	33 (2.3)	.001
Insurance			
Medicaid	128 (78.1)	500 (35.4)	<.001
Private payers	36 (21.9)	513 (36.4)	
Other	0 (0.0)	40 (2.8)	
Zip code income quartile			
I (lowest)	61 (36.6)	268 (19.0)	<.001
II	20 (12.1)	174 (12.3)	
III	23 (14.0)	200 (14.2)	
IV (highest)	18 (10.9)	141 (10.0)	
Hospital characteristics			
Urban	107 (65.2)	953 (67.5)	.87
Teaching	100 (61.0)	710 (50.3)	.001
Children's	130 (79.3)	140 (10.0)	<.001

^a Data were obtained from the Wide Hospital Database. Subcategories of the pregnancy history may not sum to total number of hospital stays.

Discharges for Delivering Mothers Using Opiates vs All Other Births in 2009

In 2009, delivering mothers were diagnosed as dependent on or using opiates at the time of delivery at a rate of 5.63 (95% CI, 4.40-6.71) per 1000 hospital births per year. Similar to newborns diagnosed with NAS, mothers using opiates were more likely than mothers not using opiates to be covered by Medicaid (60.0%; SE, 6.3%) (Table 2).

Table 2. Characteristics of Mothers With a Diagnosis of Antepartum Opiate Use vs All Other Mothers With Hospital Deliveries in 2009^a

Characteristics	Mothers Diagnosed With Antepartum Opiate Use		All Other Mothers With Hospital Deliveries	
	Unweighted No. (n = 4563)	Weighted % (95% CI)	Unweighted No. (n = 816,034)	Weighted % (95% CI)
Race/ethnicity				
White	2142	45.2 (41.3)	365,235	44.7 (41.3)
Hispanic/Latino	1566	33.7 (30.8)	266,549	32.7 (30.8)
Black	144	3.1 (2.5)	20,052	2.4 (2.0)
Other	708	15.2 (13.6)	124,200	15.2 (13.6)
25 th percentile income quartile				
1 (lowest)	1272	27.3 (24.6)	209,116	25.7 (24.6)
2	1222	27.2 (24.5)	208,386	26.2 (24.5)
3	1426	30.7 (27.8)	244,430	29.4 (27.8)
4 (highest)	643	13.8 (12.3)	108,000	13.3 (12.3)

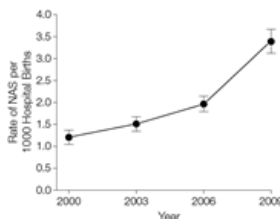
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Change in Incidence of NAS, 2000-2009

Between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (*P* for trend < .001) (Figure 1). Between 2000 and 2009, the number of mothers using or dependent on opiates increased from 1.19 (95% CI, 1.01-1.35) to 5.63 (95% CI, 4.40-6.71) per 1000 hospital births per year (*P* for trend < .001) (Figure 2).

Figure 1. Weighted National Estimates of the Rates of NAS per 1000 Hospital Births per Year

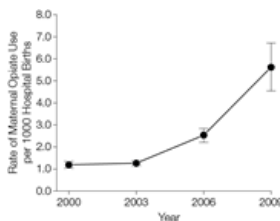
NAS indicates neonatal abstinence syndrome. Error bars indicate 95% CI. *P* for trend < .001 over the study period. The unweighted sample sizes for rates of NAS and for all other US hospital births are 2920 and 784 191 in 2000; 3761 and 890 582 in 2003; 5200 and 1 000 203 in 2006; and 9674 and 1 113 123 in 2009; respectively.



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Figure 2. Weighted National Estimates of the Rates of Maternal Opiate Use per 1000 Hospital Births per Year

Error bars indicate 95% CI. *P* for trend < .001 over the study period. The unweighted sample sizes for mothers diagnosed with and without antepartum opiate use are 987 and 833 494 in 2000; 1058 and 849 133 in 2003; 2160 and 879 910 in 2006; and 4563 and 816 554 in 2009; respectively.



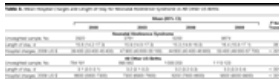
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Trends in Health Care Utilization and Expenditures for NAS, 2000-2009

Between 2000 and 2009, mean hospital charges for newborns diagnosed with NAS increased from \$39 400 (95% CI, \$33 400-\$45 400) to \$53 400 (95% CI, \$49 000-\$57 700); 35% increase; *P* for trend < .001, and charges for all other hospital births increased from \$6600 (95% CI, \$5800-\$7300) to \$9500 (95% CI, \$9000-\$9900); 30% increase; *P* for trend < .001. The LOS remained relatively unchanged for NAS during the study period (approximately 16 days; *P* for trend = .06) compared with a slightly increasing LOS for all other hospital births of approximately 3 days during the study period (*P* for trend < .001) (Table 3). Medicaid was the primary payer for the majority of hospital

charges for NAS in infants, increasing from 68.7% of aggregate charges in 2000 to 77.6% of aggregate charges in 2009 (Table 4).

Table 3. Mean Hospital Charges and Length of Stay for Neonatal Abstinence Syndrome vs All Other US Births



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Table 4. Proportions of US Hospital Charges for Neonatal Abstinence Syndrome by Payer^a



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Change in National Estimates

Between 2000 and 2009, total hospital charges for NAS are estimated to have increased from \$190 million (95% CI, \$160-\$230 million) to \$720 million (95% CI, \$640-\$800 million), adjusted for inflation (P for trend < .001). In 2009, the estimated number of newborns with NAS was 13 539 (95% CI, 12 441-14 635), or approximately 1 infant born per hour in the United States with signs of drug withdrawal.

COMMENT

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Increasing Incidence and Expenditures

To our knowledge, this is the first study to assess US trends in NAS and maternal opioid use using nationally representative data. Between 2000 and 2009, the annual rate of NAS diagnosis among newborns in the United States increased almost 3-fold. These findings are consistent with other studies that found similar increases in smaller geographic areas.¹² Our study also finds that the rate of maternal opiate use increased nearly 5-fold, similar to a single-center study by Kellogg et al.²⁶ This observation is consistent with the trend of increasing opiate use across the United States, which is not limited to illicit drugs. The Centers for Disease Control and Prevention found that sales and deaths related to opiate pain relievers quadrupled between 1999 and 2008 in the United States.²⁷ The growth of maternal opiate use outpaces the incidence of NAS, likely reflecting that not all opiate-exposed newborns exhibit signs of withdrawal.¹¹

In our study, state Medicaid programs were the predominant payer for mothers using opiates (60.0%) and newborns with NAS (78.1%). As a consequence, our data have specific relevance to state Medicaid budgets. In the state of Florida, where opiate pain reliever-related deaths now account for 4 times the number of deaths as all illicit drugs²⁸ and the number of newborns diagnosed with NAS has increased 5-fold in the last 6 years (D. Aronberg, JD, written communication, November 30, 2011), the situation has garnered special attention. Recently, both the Florida House of Representatives and Senate passed legislation that will form a task force to evaluate the relationship between maternal opiate pain reliever use and NAS in the state and propose strategies for NAS treatment and prevention.²⁹ At the time of this writing, the measure awaits the governor to sign it into law.

Despite this recent attention, literature regarding health care utilization of newborns with NAS is limited. A report by the US General Accounting Office, now 2 decades old, estimated median hospital charges of drug-addicted newborns at \$5500.³⁰ A study by Backes et al³¹ describes mean cost for newborns with NAS traditionally treated at a single institution to be \$27 000. When adjusted for inflation, both estimates are less than our estimates of mean hospital charges, which exceeded \$53 000 in 2009. Throughout all study years, hospital charges for NAS and other hospital charges increased by similar rates; however, mean hospital charges for NAS exceed those of other hospital charges by at least 5-fold in each year. Our analysis has advantages when compared with previous analyses given that our sample is (1) nationally representative, and (2) derived from the most recent decade of data.

Improving Efficiency and Outcomes in NAS Care

Our study finds that LOS for newborns diagnosed with NAS has not declined during the last decade. The mean LOS for NAS was 16 days, identical to reports by Burns and Mattick³² (16 days) and Agthe et al³³ (15-17 days). This finding raises the possibility that care for expectant mothers using opiates and their newborns might be able to be delivered in a more efficient and effective manner, which could shorten LOS and reduce expenditures.

The standard treatment for opioid-dependence during pregnancy is providing methadone maintenance therapy.³⁴ Methadone is intended to prevent withdrawal and reduce the risk of accidental overdose by providing a stable dosing regimen supervised by health care professionals.³⁵ By enrolling in methadone programs, pregnant women are given the added benefit of improved access to the health care system, including drug treatment, obstetric, and medical care. **Despite acceptance into the health care system, women enrolled in methadone treatment programs continue to have higher rates of adverse maternal and neonatal outcomes than the general population, likely related to their underlying medical and social circumstances than treatment programs alone.**³⁶⁻³⁸ Treatment with methadone requires intensive

antepartum management, consisting of obstetric management, substance abuse counseling, as well as the evaluation and treatment of medical comorbidities such as psychiatric disorders, hepatitis C, human immunodeficiency virus/AIDS, and psychosocial risk factors (alcohol and tobacco use). Relapse and continued illicit drug use is common and many coexisting psychosocial risk factors fail to be addressed.³⁹

During the last several years, buprenorphine has emerged as an alternative to methadone for narcotic replacement therapy. A recent randomized, double-blind trial found that newborns whose mothers were treated with buprenorphine required 89% less morphine and spent 43% less time in the hospital.³⁸ Possible advantages to buprenorphine include patient-administered dosing, which relieves patients from daily visits to outpatient methadone distribution clinics and has the potential to decrease health care utilization and costs.

Although there is consensus that opiates (oral morphine, methadone) should be first-line treatment for newborns with NAS,^{10,40} there remains considerable variation in treatment in the United States.⁴¹ Some studies have suggested that combinations of an opiate plus phenobarbital⁴² or clonidine³³ might decrease symptom duration and decrease LOS. In addition, studies suggest that breastfeeding of newborns with NAS might be beneficial,⁴³ but described breastfeeding rates for newborns with NAS are quite low.⁴⁴

An additional consideration is that newborns with NAS are frequently cared for in neonatal intensive care units, which are more costly than care in a general pediatric ward. Studies suggest that care for NAS delivered in hospital settings outside of the neonatal intensive care unit⁴⁵ and outpatient management reduces LOS and cost.³¹

Study Limitations

Our study has several limitations, common to studies using nationally representative discharge data obtained from hospital discharge abstracts. These data rely on accurate coding and errors of omission and commission may occur. One study³² suggests that hospital billing data underreport the clinical diagnosis of NAS. Therefore, we may underestimate both national incidence and aggregate hospital-related expenditures attributed to NAS. In addition, unlike NAS, maternal opiate use might occur without any symptoms. Unless a mother reports opiate use and it is documented in the medical record, it would not be coded in the discharge abstract; therefore, we likely underestimated maternal opiate use at the time of delivery.

It is also possible that the increased incidence of NAS during the study period, as well as complications attributable to NAS, is attributable to heightened clinician awareness of the syndrome and its complications. However, the associated increase of maternal opiate use described in our study, and the general population trend described by the Centers for Disease Control and Prevention,²⁷ makes this phenomenon less likely. Because part of our exclusion criteria included birthweight of less than 1500 g, we possibly underreported low birthweight associated with NAS. Our study used data on hospital charges, which may not accurately reflect actual hospital costs. In addition, hospital billing practices might change over time accounting for the reported increase hospitals charge for NAS.

CONCLUSION

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In conclusion, newborns with NAS experience longer, often medically complex and costly initial hospitalizations. The increasing incidence of NAS and its related health care expenditures call for increased public health measures to reduce antenatal exposure to opiates across the United States. In addition, further innovation and standardization of treatment of NAS may mitigate NAS symptoms and reduce hospital LOS. States are poised to seek innovative solutions to decreasing the burden of NAS, because the majority of hospital expenditures for this condition are shouldered by state Medicaid programs.

ARTICLE INFORMATION

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Author Contributions: Dr Patrick had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Patrick, Schumacher, Davis.

Acquisition of data: Patrick, Benneyworth, McAllister.

Analysis and interpretation of data: Patrick, Schumacher, Benneyworth, Krans, Davis.

Drafting of the manuscript: Patrick, Schumacher, Benneyworth.

Critical revision of the manuscript for important intellectual content: Patrick, Schumacher, Benneyworth, Krans, McAllister, Davis.

Statistical analysis: Patrick, Benneyworth.

Obtained funding: Patrick.

Administrative, technical, or material support: Davis.

Study supervision: Schumacher, Krans, Davis.

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