TESTIMONY BEFORE THE UNITED STATES HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

Hearing on H.R. 1462, The Protecting our Infants Act of 2015

Stephen W. Patrick, MD, MPH, MS
Assistant Professor of Pediatrics and Health Policy
Division of Neonatology
Vanderbilt University School of Medicine

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Summary of Testimony:

The number of infants diagnosed with neonatal abstinence syndrome, a post-natal drug withdrawal syndrome which most commonly occurs after *in utero* exposure to opioids, grew nearly 5-fold from 2000 to 2012. This increase occurred with a concurrent rise in the number of prescription opioids being used throughout the US. By 2012, one infant was born every 25 minutes having drug withdrawal, accounting for an estimated $1.5 billion in healthcare expenditures. Despite the substantial increase in the number of infants being diagnosed with neonatal abstinence syndrome, large gaps remain in our knowledge to prevent, identify and treat the syndrome. Our approach to understanding perinatal opioid use and neonatal abstinence syndrome must be grounded in a public health framework aimed at improving the health of both women and their infants. The Protecting Our Infants Act of 2015 embodies a multidisciplinary, public health approach aimed at understanding the problem and filling knowledge and service gaps.

Chairman Pits, Ranking Member Green and honorable members of the Committee, it is a privilege to speak with you today about the rising numbers of infants being diagnosed with drug withdrawal in the United States. The bill before you, HR 1462 the Protecting Our Infants Act of 2015, makes positive steps to improve the health of women and infants impacted by opioid use and misuse.

A few months ago, I was caring for a two-day-old baby in the neonatal intensive care unit (NICU) at The Monroe Carrel Jr. Vanderbilt Children's Hospital. At just 48 hours of life the infant became fussy and jittery. Over the next 24 hours, the infant continued to worsen with diarrhea, sneezing and increasing fussiness. Each of these signs are classic for drug withdrawal, however, his mother denied use of any drugs that may cause withdrawal until the baby's drug screen came back positive for prescription opioids. Once I informed the mother of the baby's drug screen, she reluctantly admitted that she had been using pain pills without a prescription. This baby remained in the hospital for over a week as we managed his symptoms.

As I reflected on this case I began to wonder, what if the infant had been discharged at the typical time of 24 hours of life only to have drug withdrawal at home? Would he have been brought back to the hospital critically ill? What systems might help his mother be more knowledgeable and forthcoming about her drug use and how could we connect her with drug treatment, particularly during her pregnancy?

This situation, unfortunately, is increasingly common.

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome is a drug withdrawal syndrome that infants exposed to opioids experience shortly after birth. Opioids pass from the mother through the placenta to the fetus. At the

time of birth, when the supply of opioids is stopped, the infant is at risk of developing drug withdrawal within the first few days of life. Infants with neonatal abstinence syndrome have difficulty feeding and are more likely to have breathing problems, tremors, increased muscle tone, fever, difficulty sleeping and inconsolability. Severe neonatal abstinence syndrome requires treatment with an opioid, like morphine or methadone, and an average hospital stay of three weeks. Watching an infant experience drug withdrawal is distressing for doctors, nurses and parents.

A Rising Diagnosis

According to the Centers for Disease Control and Prevention, the number of prescription opioids used in the United States quadrupled over the last decade. By 2012, there were 259 million prescriptions written for an opioid – more than one prescription for every American adult.[1]

The rapid increase in opioid use and misuse has impacted nearly every population in the US, including women of childbearing age[2] and pregnant women.[3] In a study our group published in May using data from the Tennessee Medicaid program, we found that of 110,000 pregnancies in a 3-year period, nearly 30 percent filled a prescription for an opioid pain reliever during their pregnancy.[3]

Throughout the country, as prescription opioid use grew, some women turned to using prescription opioids illegally or to heroin; taken together this led to an increase in the the incidence of neonatal abstinence syndrome. Using billing data from the nation's hospitals, our research team conducted a series of studies to determine national rates of neonatal abstinence syndrome. From 2000 to 2012, the number of infants diagnosed with the syndrome grew nearly 5-fold. By 2012, one infant was born every 25 minutes on average in the United States with the neonatal abstinence syndrome accounting for an estimated $1.5 billion in healthcare expenditures – 80% of which are paid for by Medicaid.[4,5] The scope of the problem is staggering in some communities. For example, some areas of my home state, Tennessee, report that 1 in 20 infants born in their community have neonatal abstinence

syndrome.[6] And in some NICUs, nearly 50% of their total annual hospital days are dedicated to treating this one condition.[7]

This rapid increase has largely caught communities and providers off guard. Today, there is no well-researched standard treatment protocol for infants with NAS and as a result, treatment and clinical outcomes vary widely throughout hospitals in the US.[8] As the Government Accountability Office (GAO) pointed out earlier this spring, there are large gaps in research and service delivery for mothers and infants impacted by opioid use and misuse.[9] These knowledge gaps are present in every facet of an affected infant's care; we have difficulty identifying infants at risk for the syndrome, we diagnose the syndrome based upon a subjective scoring system developed decades ago, and while our research suggests infants with neonatal abstinence syndrome are two and a half times as likely to be readmitted to the hospital within 30 days of discharge,[10] we have no good system to ease their transitions home. As the GAO report noted, the federal government spent only $21.6 million over a seven-year period on research related to perinatal opioid use and neonatal abstinence syndrome – quite small when you consider Medicaid alone was charged nearly $1.2 billion for neonatal abstinence syndrome hospitalizations in 2012.[5]

What We Must Do

Addressing the complexity of perinatal opioid use and neonatal abstinence syndrome requires a thoughtful public health approach targeting the pre-pregnancy, pregnancy and post-pregnancy periods for women and infants. Our goal should be to promote healthy mothers and infants by supporting prevention and recovery:

1. Primary Prevention: Enhancing public health measures to prevent opioid misuse even before pregnancy, including:
    a. Increasing education among the public

b. Bolstering prescription drug monitoring programs
c. Improving access to contraception, including long-acting reversible contraception, because research suggests that women with opioid dependency are nearly twice as likely to have an unplanned pregnancy[11]
d. Ensuring opioid prescribing is necessary and appropriate, especially among pregnant women

2. Secondary Prevention:
    a. Improving screening for drug use during pregnancy
    b. Ensuring that drug treatment is available when it is needed, and that it includes medication-assisted treatment when appropriate. Treatment should be comprehensive, gender specific and inclusive of obstetric care
3. Tertiary Prevention:
    a. Improving identification and treatment (including non-pharmacologic treatment) of infants suffering from neonatal abstinence syndrome
    b. Supporting families in the transition from the hospital to home, through care coordination and home visitation programs
    c. Providing specific pediatric care for the high-risk substance-exposed infants, including close developmental follow-up
    d. Providing acceptable contraceptive services in the postpartum period

Funding for research and care delivery for each of these domains are critically needed.

The Protecting Our Infants Act of 2015

The Protecting Our Infants Act of 2015 takes several positive steps toward a public health approach to perinatal opioid use and neonatal abstinence syndrome. The Act calls on the Department of Health and Human Services to conduct a study and develop recommendations for preventing and treating

prenatal opioid abuse and neonatal abstinence syndrome. It addresses many of the issues we have discussed this morning, including improving our understanding of:

1. Prevention, identification, treatment and long-term outcomes for infants with neonatal abstinence syndrome
2. Risk factors for opioid use among women of reproductive age
3. Barriers to identifying and treating opioid use disorders in pregnancy
4. Medically indicated uses of opioids in pregnancy
5. Improvement in treatment of opioid use disorders in pregnant and postpartum women

The GAO report released this spring also found that federal programs for pregnant women and infants impacted by opioid dependency are not well coordinated, at risk for duplication and fragmented.[9] The Act directs the Department of Health and Human Services to close gaps in research and programming for perinatal opioid use and neonatal abstinence syndrome.

Lastly, the Act directs the Centers for Disease Control and Prevention to coordinate and improve surveillance systems for NAS and to craft a public health response to the syndrome.

Summary

Mothers and infants impacted by the nation's prescription opioid abuse and heroin epidemics are in desperate need of a public health approach in addressing this problem. We cannot wait any longer to respond and the status quo is simply unacceptable. The Protecting Our Infants Act takes necessary and important steps forward to improving research and service delivery. For the patient I described in my introduction and thousands like him, we need the tools to allow us to treat him better, and perhaps even more importantly prevent him from having drug withdrawal in the first place. As a neonatologist and a researcher, I applaud the bill authors and this committee's interest in this critical public health issue that affects so many vulnerable mothers and infants in the US today.

In reference to our research findings, I would like to acknowledge our team's funders, including the Robert Wood Johnson Foundation, the National Institute on Drug Abuse at the NIH and the Tennessee Department of Health.

Mr. Chairman, thank you for the opportunity to speak today. I look forward to your questions.

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Appendix: Relevant Publications

Journal of Perinatology (2015), 1–6

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ORIGINAL ARTICLE

Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012

SW Patrick[1,2,3,4], MM Davis[5,6,7], CU Lehman[1,2,8] and WO Cooper[1,3,4]

OBJECTIVE: Neonatal abstinence syndrome (NAS), a postnatal opioid withdrawal syndrome, increased threefold from 2000 to 2009. Since 2009, opioid pain reliever prescriptions and complications increased markedly throughout the United States. Understanding recent changes in NAS and its geographic variability would inform state and local governments in targeting public health responses.

STUDY DESIGN: We utilized diagnostic and demographic data for hospital discharges from 2009 to 2012 from the Kids' Inpatient Database and the Nationwide Inpatient Sample. NAS-associated diagnoses were identified utilizing *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. All analyses were conducted with nationally weighted data. Expenditure data were adjusted to 2012 US dollars. Between-year differences were determined utilizing least squares regression.

RESULTS: From 2009 to 2012, NAS incidence increased nationally from 3.4 (95% confidence interval (CI): 3.2 to 3.6) to 5.8 (95% CI 5.5 to 6.1) per 1000 hospital births, reaching a total of 21 732 infants with the diagnosis. Aggregate hospital charges for NAS increased from $732 million to $1.5 billion ($P < 0.001$), with 81% attributed to state Medicaid programs in 2012. NAS incidence varied by geographic census division, with the highest incidence rate (per 1000 hospital births) of 16.2 (95% CI 12.4 to 18.9) in the East South Central Division (Kentucky, Tennessee, Mississippi and Alabama) and the lowest in West South Central Division Oklahoma, Texas, Arkansas and Louisiana 2.6 (95% CI 2.3 to 2.9).

CONCLUSION: NAS incidence and hospital charges grew substantially during our study period. This costly public health problem merits a public health approach to alleviate harm to women and children. States, particularly, in areas of the country most affected by the syndrome must continue to pursue primary prevention strategies to limit the effects of opioid pain reliever misuse.

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INTRODUCTION

Neonatal abstinence syndrome (NAS) is a withdrawal syndrome that occurs in opioid-exposed infants shortly after birth.[1–3] Infants with NAS have longer, more complicated postnatal hospitalizations characterized by a myriad of clinical signs ranging from feeding difficulty to seizures.[1,4,5] Recently, NAS emerged as a significant public health problem, increasing in number and healthcare expenditures.[5] By 2009, one infant was born per hour with the syndrome, accounting for an estimated $720 million in hospital charges.[5] The increase in NAS occurred temporally with an increase in opioid pain reliever (OPR) use[6] among several populations, including pregnant women.[7,8]

Data from the Centers for Disease Control and Prevention suggest that since 2009, when the most recent national estimates of NAS were reported, OPR use continued to increase. In 2012, the total number of OPR prescriptions rose to 259 million, enough for every American adult to have one bottle.[9,10] Recent data also highlight substantial variation in OPR use across different United States geographic regions.[9] To date, however, there are no national studies describing geographic variation in NAS. Understanding recent changes in NAS, including its variability in geographic regions, would inform state and local governments in targeting public health responses.

We sought to determine whether the incidence of NAS increased since 2009 in parallel with the marked increase in OPR use nationally and whether the incidence varied across the United States. Further, we aimed to determine whether healthcare utilization patterns of infants with NAS changed over time.

METHODS

Study design and setting

For this retrospective serial cross-sectional analysis, we used data from the Kids' Inpatient Database (KID) for 2009 and 2012 and from the Nationwide Inpatient Sample (NIS) for 2010 and 2011. Both data sets are compiled by the Agency for Healthcare Research and Quality as part of the Healthcare Utilization Project. The KID is the largest publicly available all-payer database for hospitalized children in the United States. The KID contains 2 to 3 million pediatric inpatient records per year from 2500 to 4100 hospitals and is created through systematic random sampling to select 10% of uncomplicated term births and 80% of other pediatric discharges. This sampling strategy gives the KID statistical power to evaluate rare conditions and provide more precise point estimates for all pediatric conditions.[11] The NIS is the largest publicly available all-payer inpatient database in the United States, containing more than 8 million hospital stays sampled from a 20% stratified sample of 1000 community hospitals.[12] Both the KID and NIS have been used broadly in national

[1]Department of Pediatrics, Vanderbilt University, Nashville, TN, USA; [2]Mildred Stahlman Division of Neonatology, Vanderbilt University, Nashville, TN, USA; [3]Vanderbilt Center for Health Services Research, Nashville, TN, USA; [4]Department of Health Policy, Vanderbilt University, Nashville, TN, USA; [5]Child Health Evaluation and Research (CHEAR) Unit, Department of Pediatrics and Communicable Diseases, University of Michigan Health System, Ann Arbor, MI, USA; [6]Gerald R. Ford School of Public Policy, University of Michigan, Ann Arbor, MI, USA; [7]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA and [8]Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA. Correspondence: Dr SW Patrick, Monroe Carell Jr Children's Hospital At Vanderbilt, Mildred Stahlman Division of Neonatology, 11111 Doctor's Office Tower, 2200 Children's Way, Nashville, TN 37232-9544, USA.
E-mail: stephen.patrick@vanderbilt.edu
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studies of pediatric[5,13,14] and adult[5,15,16] conditions. As the study used de-identified data, it was considered exempt from human subjects review by the Vanderbilt University School of Medicine.

Identification of sample

Infants with NAS were identified if the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 779.5 (drug withdrawal syndrome in a newborn) appeared in any 1 of 25 diagnostic fields.[17] Infants with presumed iatrogenic NAS from medical treatment were excluded using strategies described previously.[5] KID and NIS provide data for hospital births using *ICD-9-CM* codes (V3000 to V3901 with the last two digits of '00' or '01') if the patient is not transferred from another acute care hospital or healthcare facility. Uncomplicated births are identified using the diagnosis-related group code for 'Normal Newborn' (391, version 24).[11,12]

Descriptive variables

Infants with NAS are more likely to have neonatal respiratory complications, feeding difficulty, seizures and low birthweight.[1] Clinical characteristics of infants were obtained using the following *ICD-9-CM* codes in any one of the diagnostic fields during the birth hospitalization: transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11, 770.12), respiratory distress syndrome (769.x), other neonatal respiratory diagnoses (770.x excluding above codes and 770.7), feeding difficulty (779.3x), concern for sepsis (771.81), jaundice (774.x) and seizure (779.0, 780.3). Additional descriptive variables, including primary payer (private, Medicaid, uninsured and other) and sex were provided in the KID and NIS.

Outcome variables

National incidence rates of NAS were estimated by dividing the total number of infants with NAS by the total number of hospital births and expressed as incidence per 1000 births. Beginning in 2012, the KID and NIS samples increased, providing sufficient reliability to create estimates by the United States Census Bureau geographic division. Length of stay (LOS) data were obtained from the KID and NIS; as infants not receiving pharmacotherapy for NAS are unlikely to have LOS >6 days,[1] we evaluated LOS for all infants with NAS and then for infants with NAS who had a LOS >6 days (presumed pharmacologically treated). Throughout the article we will refer to infants presumed to be pharmacologically treated as 'pharmacologically treated'. Hospital charges were obtained from the KID and NIS and adjusted to 2012 US$.[18] Missing charges ($<3\%$) were imputed using a regression approach using the command 'impute' with diagnosis-related groups, LOS, age and NAS as predictors. Mean charges before and after imputation were compared and were not significantly different; data with imputed values are presented.

Data analysis

Statistical analyses were conducted using Stata version 13.1 (StataCorp, College Station, TX, USA). For all analyses, survey weights provided by Healthcare Utilization Project were applied to facilitate nationally representative estimates. For 2012, differences in clinical characteristics and primary payer for infants with NAS versus all other hospital births were assessed. Trends for LOS and hospital charges were evaluated using variance-weighted least squared regression.[5] NAS incidence rates were

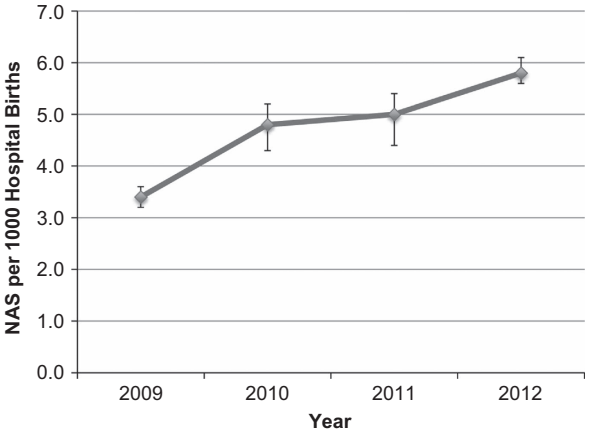
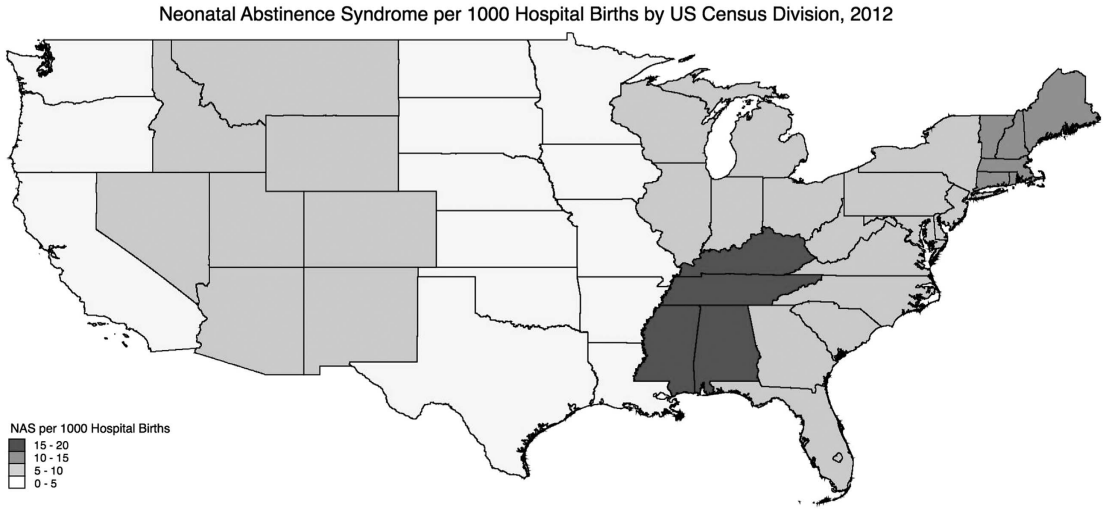


Figure 1. Incidence of neonatal abstinence syndrome per 1000 hospital births in the United States, 2009 to 2012. Data obtained from the Kids' Inpatient Database for 2009 and 2012 and from the Nationwide Inpatient Sample in 2010 and 2011. 2009: 3.4 (95% confidence interval (CI) 3.2 to 3.6); 2010: 4.8 (95% CI 4.3 to 5.2); 2011: 5.0 (95% CI 4.4 to 5.4); 2012: 5.8 (95% CI 5.5 to 6.1).

Table 1. Characteristics of infants with neonatal abstinence syndrome vs all other hospital births, 2012

	Infants with neonatal abstinence syndrome (N = *21 732*)		*All other hospital births* (N = *3 716 916*)		P-*value*
	N	%	N	%	
Female	9902	45.6	1 817 513	48.9	<0.001
Clinical characteristics					
Low birthweight	5308	24.4	267 885	7.2	<0.001
Respiratory diagnoses					
Transient tachypnea	2552	11.7	113 483	3.1	<0.001
Meconium Aspiration syndrome	613	2.8	13 235	0.4	<0.001
Respiratory distress syndrome	977	4.5	74 001	2.0	<0.001
Jaundice	7134	32.8	708 872	19.1	<0.001
Feeding difficulty	3765	17.3	111 288	3.0	<0.001
Seizures	309	1.4	4208	0.1	<0.001
Sepsis	3218	14.8	81 845	2.2	<0.001
Insurance					<0.001
Private	2688	12.4	1 717 308	46.2	
Medicaid	17 717	81.5	1 726 432	46.4	
Uninsured	853	3.9	144 137	3.9	
Other	405	1.9	118 918	3.2	

Point estimate (standard error) *N* for NAS = 21 732 (857); unweighted sample $n = 16\,254$. Point estimate (standard error) *N* for all other hospital births = 3 716 916 (55 864); unweighted sample $n = 1\,094\,748$.



US Census Division	NAS Rate per 1000 Births (95% CI)
New England	13.7 (12.5-14.5)
Middle Atlantic	6.8 (5.9-7.6)
East North Central	6.9 (6.0-7.8)
West North Central	3.4 (3.0-3.8)
South Atlantic	6.9 (6.3-7.4)
East South Central	16.2 (12.4-18.9)
West South Central	2.6 (2.3-2.9)
Mountain	5.1 (4.6-5.5)
Pacific	3.0 (2.7-3.3)

Figure 2. Incidence of neonatal abstinence syndrome per 1000 hospital births by US Census Bureau geographic division, 2012. Division 1 (New England): Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Connecticut. Division 2 (mid-Atlantic): New York, Pennsylvania and New Jersey. Division 3 (East North Central): Wisconsin, Michigan, Illinois, Indiana and Ohio. Division 4 (West North Central): Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota and Iowa. Division 5 (South Atlantic): Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia and Florida. Division 6 (East South Central): Kentucky, Tennessee, Mississippi and Alabama. Division 7 (West South Central): Oklahoma, Texas, Arkansas and Louisiana. Division 8 (Mountain): Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona and New Mexico. Division 9 (Pacific): Alaska, Washington, Oregon, California and Hawaii.

calculated by division (nine overall: New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific) for 2012. Maps were generated to evaluate geographic variation of NAS using the spmap command[19] in Stata, with map data obtained from the National Oceanic and Atmospheric Administration.[20] Throughout our analysis, all tests were two sided, with data reported with standard errors or 95% confidence intervals (CIs).

RESULTS

In 2012, there were an estimated 21 732 (95% CI: 20 052 to 23 413) infants diagnosed with NAS and 3 716 916 (95% CI: 3 607 375 to 3 826 456) other hospital births. Infants with NAS were more likely to have complications than other hospital births, including low birthweight (24.4% vs 7.2%), transient tachypnea of the newborn (11.7% vs 3.1%), meconium aspiration syndrome (2.8% vs 0.4%), respiratory distress syndrome (4.5% vs 2.0%), jaundice (32.8% vs 19.1%), feeding difficulty (17.3% vs 3.0%), seizures (1.4% vs 0.1%) and possible sepsis (14.8% vs 2.2%; $P < 0.001$). Infants with NAS were also more likely than other hospital births to be insured by Medicaid (81.5% vs 46.4%; $P < 0.001$; Table 1).

From 2009 to 2012, incidence (95% CI) of NAS increased from 3.4 (3.2 to 3.6) to 5.8 (5.5 to 6.1) per 1000 hospital births overall (Figure 1). By 2012, approximately one infant was born every 25 minutes in the United States with the syndrome. There was significant geographic variation in NAS diagnoses. In the most recent studyyear, the East South Central division (Kentucky, Tennessee, Mississippi and Alabama) had the highest incidence of NAS at 16.2 (12.4 to 18.9) per 1000 hospital births compared with the West South Central division (Oklahoma, Texas, Arkansas and Louisiana) that had the lowest national incidence rate of 2.6 (2.3 to 2.9) per 1000 hospital births (Figure 2).

From 2009 to 2012, there was no significant change in overall mean LOS for all NAS infants, pharmacologically treated NAS infants and for uncomplicated term infants with mean LOS in 2012 of 16.9 (16.0 to 17.7), 23.0 (22.2 to 23.8) and 2.1 (2.1 to 2.1) days, respectively. Inflation-adjusted mean hospital charges increased for all groups and in 2012 reached $66 700 (61 800 to

Table 2. Mean length of stay and inflation-adjusted hospital charges for all infants with neonatal abstinence syndrome, infants with neonatal abstinence syndrome with a length of hospital stay >6 days and uncomplicated term infants, 2009–2012

Year	*2009* N *(95% CI)*	*2010* N *(95% CI)*	*2011* N *(95% CI)*	*2012* N *(95% CI)*
Neonatal abstinence syndrome				
Mean length of stay (days)	16.5 (15.9–17.2)	17.2 (15.8–18.5)	16.6 (15.1–18.1)	16.9 (16.0–17.7)
Mean hospital charges (2012 US$)	53 800 (49 400–58 300)	59 000 (49 600–68 400)	62 300 (52 900–71 700)	66 700 (61 800–71 600)
Pharmacologically treated neonatal abstinence syndrome				
Mean length of stay (days)	22.7 (21.9–23.4)	22.9 (21.6–24.1)	22.8 (21.5–24.2)	23.0 (22.2–23.8)
Mean hospital charges (2012 US$)	75 700 (69 500–82 000)	80 500 (68 000–93 100)	87 700 (76 300–99 100)	93 400 (86 900–100 000)
Uncomplicated term infant				
Mean length of stay (days)	2.1 (2.1–2.1)	2.1 (2.1–2.1)	2.1 (2.1–2.1)	2.1 (2.1–2.1)
Mean hospital charges (2012 US$)	2800 (2700–2900)	3500 (3300–3800)	3700 (3400–3900)	3500 (3400–3600)

Abbreviation: CI, confidence interval. All US$ inflation adjusted to 2012 and rounded to nearest hundred.

Table 3. Aggregate hospital charges by primary payer for neonatal abstinence syndrome, 2009–2012

Year	*2009*		*2010*		*2011*		*2012*		
	Total charges ($)	*SE ($)*	*Total charges ($)*	*SE ($)*	*Total charges ($)*	*SE ($)*	*Total charges($)*	*SE ($)*	p-for-trend
Private	133 553 300	11 176 700	167 466 500	24 810 000	208 363 300	30 929 400	202 233 600	12 054 400	<0.001
Medicaid	563 809 300	33 650 300	865 649 700	79 181 000	903 654 700	94 344 100	1 170 206 600	68 789 500	<0.001
Uninsured	20 079 300	1 603 200	35 995 700	4 906 100	30 842 700	4 735 100	40 370 800	3 004 500	<0.001
Other	14 248 300	2 628 000	29 379 400	6 807 800	30 117 700	8 011 000	33 395 300	4 890 800	<0.001
Total	731 841 300	40 290 000	1 098 996 200	98 050 800	1 174 848 900	117 316 500	1 449 389 600	76 698 100	<0.001

All US$ inflation adjusted to 2012 and rounded to nearest hundred.

71 600) for infants with NAS, $93 400 (86 900 to 100 000) for pharmacologically treated NAS infants and $3500 (3400 to 3600) for uncomplicated term infants (Table 2).

During the study period, the aggregate hospital charges for NAS nearly doubled from an estimated total of $731 841 300 in 2009 to $1 449 389 600 in 2012. Through all study years the majority of hospital charges were attributed to state Medicaid programs, growing from $563 809 300 to $1 170 206 600 (Table 3, $P < 0.001$).

DISCUSSION

The incidence of NAS in the United States nearly doubled during our study period and has grown nearly fivefold since 2000.[5] NAS results in longer, more costly and complicated hospital stays compared with other hospital births. The rapid rise in NAS parallels the increase in OPR use in the United States, suggesting that preventing opioid overuse and misuse, especially before pregnancy, may prevent NAS. NAS is a rapidly increasing public health problem that merits a focused public health approach to mitigate its now far-reaching impact.

We found significant geographic variation in NAS that parallels variations in OPR prescription.[9] We found high rates of NAS in New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Connecticut; 13.7, 95% CI: 12.5 to 14.5) and the East South Central (Kentucky, Tennessee, Mississippi and Alabama; 16.2, 95% CI: 12.4 to 18.9) divisions. The New England division contains two of the top five prescribing states of long-acting OPR (Maine and New Hampshire) and the East South Central division contains three of the top five prescribing states of short-acting OPR (Alabama, Tennessee and Kentucky),[9] further supporting the association between increased OPR prescription and NAS.

As expected, we found that infants with NAS were more likely to have low birthweight, significant respiratory complications including meconium aspiration and respiratory distress syndrome, feeding difficulties, possible sepsis and seizures—all of which may have contributed to longer LOS compared with other hospital births. More difficult to measure are the associated costs to families affected by the syndrome. Hospitalization for NAS most commonly involves an admission to a neonatal intensive care unit that disrupts maternal and infant bonding. Preventing NAS will prevent the clinical complications of the syndrome and potentially improve the outcomes that are more difficult to measure, including maternal attachment.[21]

Infants with NAS had an overall mean LOS of 16 days and those requiring pharmacologic treatment had a mean LOS of 23 days. We hypothesize that overall mean LOS is positively skewed by some infants who are non-pharmacologically treated or show minimal signs of withdrawal. Interestingly, LOS did not change significantly for either group during the study period. Care for NAS is variable,[4,22] and research suggests that LOS may have decreased with protocol adherence,[23] use of clonidine as an adjunct,[24] breastfeeding when appropriate (for example, when the mother is enrolled in treatment),[25–27] rooming in[28,29] and a site of care outside of the neonatal intensive care unit environment.[30]

Notably, some cases of NAS in our cohort likely occurred in the setting of medication-assisted treatment (MAT) with methadone or buprenorphine. For pregnant women with opioid dependency, current evidence suggests that enrollment in MAT improves pregnancy outcomes including preterm birth.[31,32] However, the literature supporting MAT in pregnancy was developed in the context of heroin use; data supporting optimal management of pregnant women with OPR dependency are limited.[31] With increasing use of OPR in pregnancy,[7] there is an urgent need for research to guide appropriate management of OPR dependency in pregnancy.

Nationally, over 80% of infants with NAS are enrolled in state Medicaid programs, accounting for the majority of the estimated

$1.5 billion in total hospital charges for the syndrome. Given the length of NAS-related hospital care, some states incur substantial expenditures in their Medicaid programs for NAS. For example, the Tennessee Medicaid program estimates that infants with NAS accounted for 1.7% of live births but 13.0% of expenditures on births in 2012.[33] In addition to administering and partially funding Medicaid, states also regulate prescribers and pharmacists. Therefore, states are well positioned to employ public health interventions aimed at preventing OPR misuse. Prescription drug monitoring programs are an intervention employed in every state except Missouri.[34] Prescription drug monitoring programs vary in scope and structure and are a tool to prevent behaviors that increase risk of OPR-related complications (for example, targeting doctor shopping to mitigate risk of overdose death[35]).

Limitations

Our study contains limitations that merit discussion. First, our reliance on administrative data may lead to misclassification bias. There are few studies comparing administrative to clinical data; however, one study noted that administrative data systematically underreported actual NAS.[36] Next, it is possible that the increase in NAS we observed is secondary to observer bias, as the syndrome has received significant attention recently. However, the temporal increases in NAS we observed mirror national increases in OPR use and adverse effects (for example, overdose deaths) attributed to their use. Further, our finding of significant geographic variability in the diagnosis of NAS correlated with geographic variations in use and adverse effects in the United States.[9] In addition, it is important to note that hospital charges do not equal hospital costs and do not include professional fees. In our analysis, we assumed that infants with NAS who had a LOS < 7 days were not pharmacologically treated; however, this may not always be true.

CONCLUSION

NAS has grown nearly fivefold since 2000, accounting for an estimated $1.5 billion in annual hospital expenditures across the United States. This costly public health problem merits a public health approach to alleviate harm to women and children. Federal and state policymakers should be mindful of the impact the OPR epidemic continues to have on pregnant women and their infants, and consider these vulnerable populations in efforts aimed at primary prevention. Finally, efforts aimed at primary prevention and treatment improvements should be targeted at the most affected areas of the country.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript or the decision to submit.

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Prescription Opioid Epidemic and Infant Outcomes

Stephen W. Patrick, MD, MPH, MS[a,b,c,d], Judith Dudley, BS[d], Peter R. Martin, MD, MSc[e,f], Frank E. Harrell, PhD[g], Michael D. Warren, MD, MPH[h], Katherine E. Hartmann, MD, PhD[c,i], E. Wesley Ely, MD, MPH[c,j,k], Carlos G. Grijalva, MD, MPH[c,d,k], William O. Cooper, MD, MPH[a,c,d]

abstract

BACKGROUND AND OBJECTIVES: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is poorly described. Our objectives were to identify neonatal complications associated with antenatal opioid pain reliever exposure and to establish predictors of neonatal abstinence syndrome (NAS).

METHODS: We used prescription and administrative data linked to vital statistics for mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. A random sample of NAS cases was validated by medical record review. The association of antenatal exposures with NAS was evaluated by using multivariable logistic regression, controlling for maternal and infant characteristics.

RESULTS: Of 112 029 pregnant women, 31 354 (28%) filled ≥1 opioid prescription. Women prescribed opioid pain relievers were more likely than those not prescribed opioids ($P < .001$) to have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%) and to smoke tobacco (41.8% vs 25.8%). Infants with NAS and opioid-exposed infants were more likely than unexposed infants to be born at a low birth weight (21.2% vs 11.8% vs 9.9%; $P < .001$). In a multivariable model, higher cumulative opioid exposure for short-acting preparations ($P < .001$), opioid type ($P < .001$), number of daily cigarettes smoked ($P < .001$), and selective serotonin reuptake inhibitor use (odds ratio: 2.08 [95% confidence interval: 1.67–2.60]) were associated with greater risk of developing NAS.

CONCLUSIONS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of NAS.

WHAT'S KNOWN ON THIS SUBJECT: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is not well described. Further, factors associated with development of neonatal abstinence syndrome, a neonatal opioid withdrawal syndrome is inadequately understood.

WHAT THIS STUDY ADDS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of neonatal abstinence syndrome.

Departments of [a]Pediatrics, [d]Health Policy, [e]Psychiatry, [f]Pharmacology, [g]Biostatistics, [i]Obstetrics and Gynecology, and [j]Medicine, Vanderbilt University, Nashville, Tennessee; [b]Mildred Stahlman Division of Neonatology, Vanderbilt University, Nashville, Tennessee; [c]Vanderbilt Center for Health Services Research, Nashville, Tennessee; [h]Tennessee Department of Health, Nashville, Tennessee; and [k]Veteran's Affairs, Tennessee Valley Geriatric Research Education Clinical Center, Nashville, Tennessee

Dr Patrick conceptualized the study, conducted the analysis, and drafted the initial manuscript; Dr Cooper was involved in the analytic plan, conducted the analysis, interpreted the results, and revised the manuscript; Ms Dudley and Dr Harrell conducted the analysis, were involved in interpretation of the results, and revised the manuscript; Drs Martin, Warren, Hartmann, Ely, and Grijalva were involved in the analytic plan and interpretation of the results and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Recently, sales of opioid pain relievers (OPRs) in the United States have surged.[1] Complications of this increase have affected a wide range of the US population, including pregnant women and their infants.[2,3] Neonatal abstinence syndrome (NAS) is a postnatal withdrawal syndrome, initially described among heroin-exposed infants,[4] that presents with a wide array of clinical signs ranging from feeding difficulties to seizures.[5] From 2000 to 2009, the number of infants in the United States diagnosed with NAS grew nearly threefold, temporally associated with a fourfold increase in OPR prescriptions.[1,6] By 2009, one US infant was born per hour with NAS, accounting for $720 million in national health care expenditures.[6] Despite this temporal association, no large population-based studies have explored the association between OPR use in pregnancy and NAS.

Factors that determine which exposed infants will develop NAS are poorly understood. Rates of NAS among infants exposed to heroin or maintenance medications are reportedly as high as 80%.[5,7] For infants exposed to maintenance medications, risk of NAS seems unrelated to opioid dose[8,9]; however, the association of cumulative opioid exposure for nonmaintenance OPRs and NAS has not been studied. Some reports suggest that the use of tobacco and coprescription of selective serotonin reuptake inhibitors (SSRIs) may also increase the likelihood of developing NAS.[10–12]

Using a large retrospective cohort of pregnant women, our objectives were to identify neonatal complications associated with antenatal OPR exposures and to determine if antenatal cumulative prescription opioid exposure, opioid type, number of cigarettes smoked daily, and SSRI use were associated with a higher likelihood of developing NAS.

METHODS

Study Design and Setting

This retrospective, longitudinal cohort study was conducted by using data from TennCare, Tennessee's Medicaid program; outpatient prescription claims were linked to vital records and hospital and outpatient administrative data. These resources have been used extensively to assess the safety of medications during pregnancy.[13–16] Medicaid serves as an ideal program to study NAS because an estimated 80% of infants with NAS nationwide are enrolled in state Medicaid programs.[6]

The present 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

Maternal and infant dyads were included in the study if: (1) the mother was 15 to 44 years old at the time of delivery; (2) the mother had been enrolled in TennCare at least 30 days before delivery; and (3) the infants were enrolled in TennCare within 30 days after delivery. Last menstrual period and date of delivery were obtained from vital records.[17] Pregnancies were included if the birth occurred between January 1, 2009, and December 31, 2011. Of a total 134 450 births, 112 029 met our inclusion criteria (83.3%).

Exposures

The study's primary exposure of interest was any prescription opioid fill during pregnancy identified from TennCare pharmacy claims data. TennCare pharmacy files contain information on all outpatient prescriptions that are reimbursed by TennCare. Opioid drug types were categorized as short-acting (eg, oxycodone hydrochloride), long-acting (eg, oxymorphone hydrochloride extended release), or maintenance (eg, buprenorphine hydrochloride) medications. Opioid doses were converted to morphine milligram equivalents by using established conversion guidelines to facilitate meaningful comparisons.[18] Duration of opioid use was defined as the period between the prescription start date and the end of the days of supply (allowing up to a 5-day carryover period from previous prescriptions). SSRI prescriptions filled within 30 days before delivery were captured. Information on tobacco use during pregnancy was obtained from birth certificates and from claims by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM),[19] diagnostic codes (tobacco: 305.1, V15.82, 989.84, and 649.0x). Data regarding the number of cigarettes smoked per day were obtained from birth certificates, and medication costs were obtained from TennCare pharmacy expenditures. Antenatal exposure to benzodiazepines[20] has been associated with more severe NAS among opioid-exposed infants and was considered in our evaluation; however, the use of these drugs was rare in the study population (167 of 112 029) due to TennCare policies and was not included.

Descriptive Variables, Demographic Characteristics, and Outcomes

Maternal Characteristics

Demographic information was obtained, including maternal age, education (number of years), birth number (parity), and race from birth certificates. Given that the literature describes opioid-using populations to be at increased risk of hepatitis B,[21] hepatitis C,[21,22] HIV,[23] depression,[24–26] and anxiety,[27] data regarding these conditions were obtained from birth certificate data and from outpatient and hospital administrative records by using diagnostic codes (hepatitis B: 070.2x and 070.3x; hepatitis C: 070.41, 070.44, 070.51, 070.54, and 070.7x; HIV: 042, 079.53, and V08;

depression: 296.2x, 296.3x, and 311; and anxiety disorder: 300.x). Acute pain, chronic pain, headache or migraine, and musculoskeletal diseases were identified by using ICD-9-CM codes (acute pain: 338.1x; chronic pain: 338.2x; headache or migraine: 339.x, 346.x, and 784.0; diseases of the musculoskeletal system and connective tissue: 710.x–739.x) as potential OPR indications. Lastly, we identified women with opioid dependency (opioid-type dependence: 304.0x; combinations of opioid type drug with any other drug dependence: 304.7x).

Outcome

Infants with NAS were identified if the ICD-9-CM code 779.5 (drug withdrawal syndrome in newborn) appeared in any diagnostic field during the birth hospitalization. To establish the accuracy of administrative coding for NAS, a chart review was performed of 228 randomly selected cases and noncases. Using a standard definition of NAS as a reference, ICD-9-CM–based identification yielded an 88.1% (95% confidence interval [CI]: 83.3–91.7) sensitivity and a 97.0% (95% CI: 93.8–98.5) specificity (Supplemental Information Appendix A). Infants were further classified as having: (1) no opioid exposure; (2) opioid exposure without NAS; or (3) NAS.

Infant Characteristics

After establishing our cohort, our goal was to describe the clinical characteristics of each infant based a priori on the literature. NAS is characterized by respiratory symptoms, feeding difficulties, and seizures. Opioid-exposed infants and infants with NAS are also more likely to be born preterm or with a low birth weight.[5] Gender, gestational age, and birth weight data were obtained from birth certificates. Clinical signs of NAS, including transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11 and 770.12), respiratory distress syndrome (769.x), other neonatal respiratory diagnoses (770.x, excluding the aforementioned codes and 770.7), feeding difficulty (779.3x), and seizure (779.0 and 780.3), were obtained from hospital claims. Infants with NAS might be at greater risk for concerns of sepsis (771.81) considering their clinical presentation (eg, irritability, respiratory distress), and they may also be at an increased risk of jaundice (774.x) due to feeding difficulties. We evaluated for necrotizing enterocolitis (777.5x), given that some authors have reported an association between this condition and NAS.[28] Lastly, we examined the risk of hemolytic disease (773.x) among infants with NAS because of the possibility of previous maternal intravenous drug use.

Data Analysis

The Wilcoxon rank-sum test and χ^2 tests were used where appropriate for bivariate analyses. Candidate predictors of NAS were established a priori from the literature. The level of missing data in our predictors was evaluated; <1% of missing data was found for all variables except number of cigarettes smoked per day, which had 5.6% missing. Birth weights <400 g were deemed unreliable and considered missing. To account for missing data, we used the aregImpute function for multiple imputation by using predictive mean matching[29,30] with 5 imputations. Because of the small numbers of long-acting opioids (n = 177), this group was combined with maintenance opioids for the statistical analyses. Using our entire cohort of 112 029 pregnant women, a logistic regression model was fit with NAS as the outcome and cumulative opioid exposure, opioid type (short-acting, long-acting, or maintenance), number of cigarettes smoked per day, SSRI within 30 days of delivery, infant gender, birth weight, multiple gestations, year of birth, birth number (parity), maternal age, maternal education, and maternal race (white, African American, and other) as predictors. The nonlinear relationship of continuous variables was accounted for by using restricted cubic splines for all variables except morphine milligram equivalents, which were cube root transformed and fit by using a quadratic function to account for skewness.[29] Results for nonlinear predictors are presented graphically (with P values for tests of association) because odds ratios would compare arbitrary data points and may not fully capture their nonlinear relationship with the primary outcome (ie, NAS). Interactions were tested between opioid type × cumulative opioid exposure, number of cigarettes smoked per day × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and SSRI × cumulative opioid exposure.

Because OPR use early in pregnancy would likely not result in NAS, 2 supplemental analyses restricted to opioid prescriptions were performed that continued through the final 30 and 14 days of pregnancy to determine if restriction to these subsets changed our results. Cost estimates were created by using TennCare pharmacy expenditures and previously published estimates of NAS hospitalization charges.[6] All dollars were adjusted to 2011 US dollars by using the Consumer Price Index.[31] Statistical analyses were completed by using R version 3.1.0. (R Foundation for Statistical Computing, Vienna, Austria)[32] and Stata version 13.0 (StataCorp, College Station, TX).

RESULTS

Among the 112 029 pregnant women in our sample, 31 354 (28.0%) were prescribed at least 1 OPR during pregnancy. Compared with women with no opioid exposure, women taking OPRs were more likely ($P <$ .001) to be white (72.4% vs 65.8%); have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%),

headache or migraine (8.3% vs 2.0%), and musculoskeletal disease (23.7% vs 5.8%); use tobacco (41.8% vs 25.8%); and be prescribed an SSRI within 30 days before birth (4.3% vs 1.9%) (Table 1).

Among women prescribed opioids, the majority received short-acting medications (n = 30 192 [96.2%]); fewer received maintenance treatment of opioid use disorder (n = 853 [2.7%]) or long-acting preparations (n = 177 [0.6%]) (Supplemental Table 4). Median (interquartile range) cumulative morphine milligram equivalents were higher among those using maintenance medications (18 480 [8160–37 232]) compared with those using long-acting preparations (4029 [1508–10 800]) or short-acting preparations (150 [75–373]; $P <$ .001). Median (interquartile range) amounts paid for OPRs per individual were $1317 (586–2598) for maintenance treatment, $208 (53–756) for long-acting preparations, and $8 (5–16) for short-acting preparations. Within the last 30 days of pregnancy, 8835 women were prescribed OPRs, 93.6% of whom received a short-acting preparation (Supplemental Table 5). Lastly, 12 896 women received a >7 days' supply of opioids during pregnancy (Supplemental Table 6).

In our cohort, a total of 1086 infants were diagnosed with NAS, 701 (65%) of whom had mothers with at least 1 OPR prescription during pregnancy. Between 2009 and 2011, the quarterly rate of NAS among infants in TennCare rose from 6.0 to 10.7 per 1000 births ($P <$ .001) (Fig 1). NAS occurred more frequently among infants exposed to maintenance opioids (29.3%) and long-acting opioids (14.7%) than in those exposed to short-acting preparations (1.4%) (Supplemental Table 4). Infants with NAS were more likely than other opioid-exposed and nonopioid-exposed infants to be born with a low birth weight (21.2% vs 11.8% vs 9.9%; $P <$ .001) and preterm (16.7% vs 11.6% vs 11.0%; $P <$ .001). Consistent with the characteristics of the syndrome, when comparisons were made between nonopioid and opioid-exposed infants, those with NAS were more likely ($P <$ .001) to have respiratory diagnoses (28.7% vs 10.1% vs 8.8%), feeding difficulties (13.1% vs 2.6% vs 2.3%), and seizures (3.7% vs 0.4% vs 0.3%). Rates of necrotizing enterocolitis were similar among all groups (Table 2). Every $1 spent on short-acting and long-acting opioids (excluding maintenance) was associated with $52 and $12, respectively, in hospital charges for infants with NAS.

After adjusting for maternal age, education, race, infant gender, birth weight, multiple births, birth number (parity), year of birth, the interaction of opioid type × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and number of cigarettes smoked per day × cumulative opioid exposure, the following factors were independently associated with an increased odds of NAS: cumulative opioid exposure for short-acting OPRs ($P <$ .001), opioid type ($P <$ .001), number of cigarettes smoked per day ($P <$ .001), and SSRI use within 30 days of delivery (odds ratio: 2.08 [95% CI: 1.67–2.60]) (Fig 2). For pregnant women exposed to maintenance/long-acting opioids, the risk of NAS was consistently higher than in other exposure groups, but the risk did not vary with cumulative opioid exposure (P = .16). In supplemental analyses, restricting assessments to women who filled OPR prescriptions through 30 and 14 days before delivery, our results were similar to the findings from our primary analysis (Supplemental Tables 7 and 8, respectively).

TABLE 1 Maternal Characteristics According to Opioid Exposure in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (n = 80 675)		Any Opioid (n = 31 354)		P
	Median	IQR	Median	IQR	
Age, y	23	20–27	24	21–27	<.001
Education, y	12	12-13	12	11–13	<.001
Birth number	1	1–2	1	1–2	<.001
	N	%	*N*	%	
Race					<.001
Black	25 986	32.2	8362	26.7	
White	53 074	65.8	22 699	72.4	
Other	1298	1.6	188	0.6	
Maternal comorbidities					
Pain					
Musculoskeletal disease	4430	5.8	7439	23.7	<.001
Headache or migraine	1636	2.0	2593	8.3	<.001
Chronic pain	40	0.0	187	0.6	<.001
Acute pain	72	0.1	132	0.4	<.001
Infectious					
Hepatitis C	328	0.4	358	1.1	<.001
Hepatitis B	91	0.1	39	0.1	.61
HIV	144	0.2	43	0.1	0.13
Psychiatric					
Depression	2185	2.7	1672	5.3	<.001
Anxiety disorder	1279	1.6	1361	4.3	<.001
Opioid dependency	154	0.2	262	0.8	<.001
Additional substances used					
Tobacco	20 785	25.8	13 097	41.8	<.001
SSRI (last 30 d of pregnancy)	1529	1.9	1335	4.3	<.001

Percentages may not add to 100% because of rounding.
IQR, interquartile range.

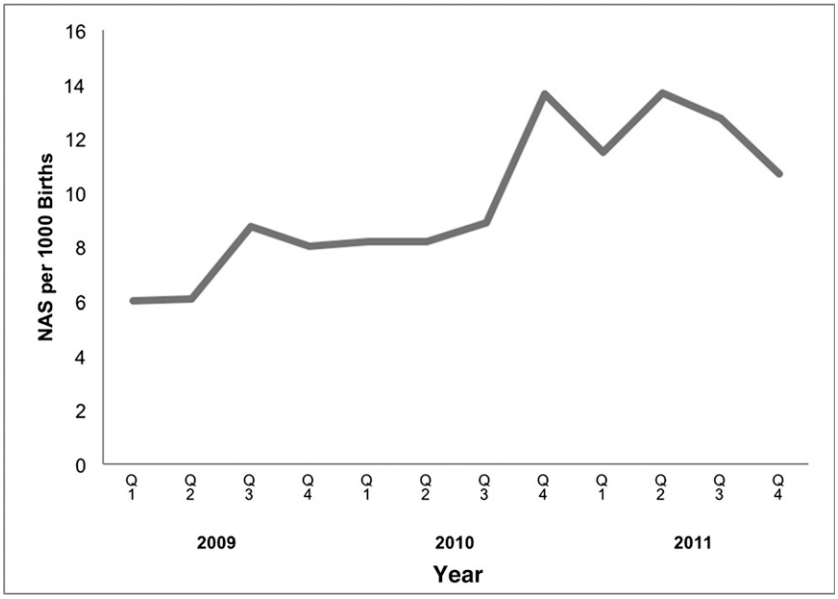

FIGURE 1
Rate of NAS in Tennessee Medicaid according to quarter, 2009 through 2011. $P < .001$.

Based on our regression model, the predicted probability of NAS among mothers who received OPRs during pregnancy varied greatly depending on drug type, cumulative opioid exposure, and number of cigarettes smoked per day. As an example, a woman who took oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks, who smoked 20 cigarettes (ie, 1 pack) per day and took an SSRI, had a 0.366 (95% CI: 0.270–0.474) probability of her infant having NAS (Table 3).

TABLE 2 Infant Characteristics for Infants With and Without NAS in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (No NAS) (n = 80 292)		Opioid (No NAS) (n = 30 651)		NAS (n = 1086)		P
	N	%	*N*	%	*N*	%	
Female	39 064	48.7	14 986	48.9	502	46.2	.2
Preterm (<37 wk)	8868	11.0	3549	11.6	181	16.7	<.001
Low birth weight (<2500 g)	7940	9.9	3615	11.8	230	21.2	<.001
Clinical conditions							
Respiratory diagnoses	7052	8.8	3083	10.1	312	28.7	<.001
Transient tachypnea of the newborn	2192	2.7	964	3.1	146	13.4	<.001
Respiratory distress syndrome	2170	2.7	1045	3.4	76	7.0	<.001
Meconium aspiration syndrome	321	0.4	106	0.3	36	3.3	<.001
Other respiratory diagnoses	4517	5.6	1965	6.4	177	16.3	<.001
Jaundice	13 963	17.4	5503	18.0	393	36.2	<.001
Feeding difficulty	1809	2.3	788	2.6	142	13.1	<.001
Sepsis	1515	1.9	692	2.3	78	7.2	<.001
Seizure	240	0.3	117	0.4	40	3.7	<.001
Hemolytic disease	1051	1.3	342	1.1	28	2.6	<.001
Necrotizing enterocolitis	136	0.2	56	0.2	**	0.1	.7

Comparisons made among mutually exclusive groups of no opioid exposure and no NAS, opioid exposure and no NAS, and NAS. Percentages may not add to 100% because of rounding.
**Value suppressed given n <10 in cell.

DISCUSSION

In this large retrospective cohort study of >100 000 pregnancies, cumulative OPR exposure for short-acting OPRs, opioid type, tobacco, and SSRI use during pregnancy was associated with an increased risk of NAS. In the study cohort, nearly 1 in 3 women used at least 1 OPR during pregnancy; 96% were nonmaintenance prescription opioids. Although NAS has previously been associated with illicit opioid use, we found that 65% of infants with NAS were exposed to legally obtained OPRs in pregnancy. These associations provide compelling evidence that OPRs and other concurrent antenatal exposures have a measurable deleterious impact on infants who are more likely than others to be born with NAS and related complications.

Maintenance medications were categorized separately, given that women using maintenance medications have different risks and different reasons for using opioids. For women with heroin dependency especially, maintenance medications have been shown to improve both maternal and neonatal outcomes, including improved fetal growth and decreased preterm birth.[33,34]

Neonatal Complications

Rates of NAS nearly doubled in TennCare during our 3-year study period, reaching 10.7 per 1000 births, exceeding previously reported rates of 3.4 per 1000 births.[6] Compared with nonopioid-exposed infants, those with NAS were more likely to have neonatal complications. Opioid-exposed infants and those with NAS were more likely than nonopioid-exposed infants to be born preterm and have low birth weight. Preterm birth imparts risk to the infant for clinical comorbidities, including respiratory distress syndrome, feeding difficulties, and jaundice (as we have shown).

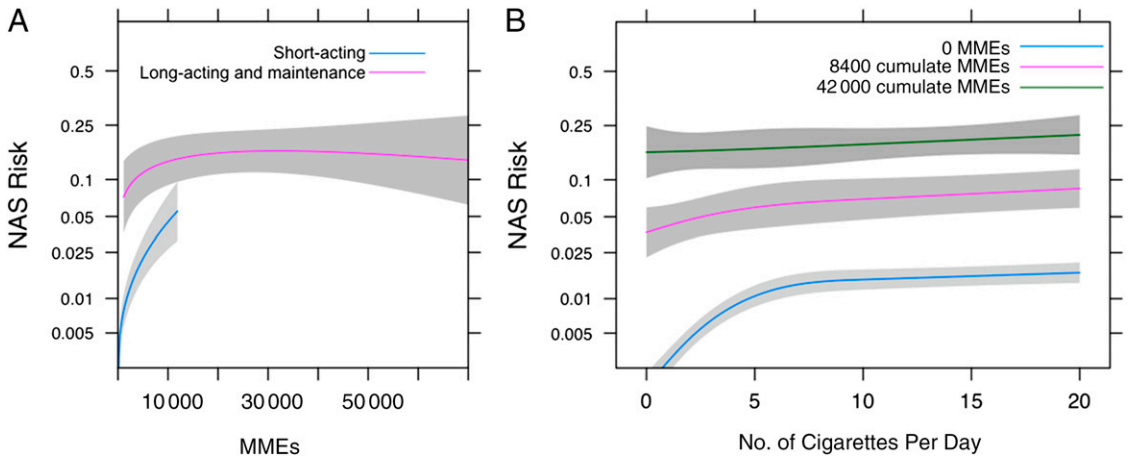

FIGURE 2

Probability of NAS. A, Opioid type and cumulative morphine milligram equivalents (MMEs). B, Number of cigarettes smoked per day and cumulative MMEs after adjusting for maternal characteristics, infant characteristics, and birth characteristics. Graph A: Cumulative MMEs and risk of NAS for short-acting opioid preparations ($P < .001$) and long-acting/maintenance opioid preparations ($P = .16$). Graph B: An increasing number of cigarettes raised the risk of NAS among women with 0 cumulative MME (ie, receiving no legal opioids; $P < .001$) receiving a cumulative total of 8400 MMEs, which equals oxycodone 10 mg q6h × 20 weeks ($P < .001$), and 42 000 MMEs, which equals buprenorphine 24 mg daily × 25 weeks ($P < .001$). The absolute risk and 95% CIs of NAS have been adjusted for cumulative opioid dose in MMEs, maternal age, maternal education, birth number, infant birth weight, year of birth, maternal race, infant gender, multiple gestations, and interaction effects of drug type × cumulative opioid dose ($P = .002$), number of cigarettes smoked per day × cumulative opioid dose ($P < .001$), and drug type × number of cigarettes smoked per day. Total sample = 112 029 mother–infant dyads, 30 651 mothers with OPR use, and 1086 infants with NAS.

In this study cohort, opioid dose for short-acting opioids, tobacco use, and SSRI use were strongly associated with NAS. Similar to previous smaller studies, we found that dose of maintenance opioids did not modify the risk of NAS.[8,9] Furthermore, our findings provide important information that builds on previous studies of OPR use in pregnancy[3,35,36] and several publications describing tobacco and SSRI use in the context of opioid maintenance.[10–12] Both tobacco and SSRIs have been described in the literature as having individual withdrawal syndromes and unique toxidromes.[5] Nevertheless, these exposures could also be associated with a constellation of other risk factors that may be difficult to measure directly (eg, substance abuse) and account for in our analyses. Polysubstance exposure is common among infants with NAS, raising the possibility that observable clinical signs (eg, hypertonia) may not be solely attributable to opioids. In many instances, clinical signs compatible with NAS may be due to multiple withdrawal syndromes and toxidromes occurring simultaneously.

State Policies

The association of increasing use of OPR, overdose deaths, and NAS garnered the attention of many state and federal policymakers.[37] States license and regulate prescribers and pharmacists, and they are financially responsible for the care received by ~80% of infants with NAS through Medicaid programs.[6,38] Nearly all states have implemented prescription drug monitoring programs[39] that aim to reduce diversion and misuse of OPR by identifying high users and high-risk behavior (eg, "doctor and pharmacy shopping"). Tennessee's program began in 2006 as an optional resource for providers and pharmacists. In 2013, the state instituted a requirement that the program must be queried before prescribing most controlled substances.[40] Our study found that ~30% of pregnant women in TennCare were prescribed at least 1 opioid before these policy changes. It will be important moving forward to evaluate the impact of new state policies on reducing opioid use in pregnancy and the incidence of NAS. Furthermore, innovative strategies to enhance prescription drug monitoring databases by including risk predictions of adverse outcomes such as NAS and overdose deaths[41] should be piloted and evaluated.

Variable Risk

The American Academy of Pediatrics recommends that all opioid-exposed infants be observed in the hospital for 4 to 7 days after birth.[5] However, our data suggest there was a wide variability in an infant's risk of drug withdrawal based on opioid type, dose, SSRI use, and number of cigarettes smoked per day by the mother (Fig 2, Table 3). Future studies should evaluate new care models for opioid-exposed infants at different risk levels of developing NAS. For instance, some low-risk infants may be safely discharged from the hospital sooner, whereas high-risk infants may require longer hospital observation.

Limitations

Our study does have several important limitations to consider, similar to other studies that rely on accurate coding of

TABLE 3 Probability of NAS According to Varying Exposures of Short-Acting Opioids and Maintenance Opioids, Tobacco, and SSRI Use

Variable	Short-Acting (eg, Oxycodone Hydrochloride) 10 mg q6h	Maintenance (eg, Buprenorphine Hydrochloride Tablet) 24 mg q24h
	Probability (95% CI)	Probability (95% CI)
5-wk duration	0.011 (0.008–0.016)	0.132 (0.085–0.199)
No cigarette use, SSRI use	0.023 (0.016–0.034)	0.241 (0.157–0.351)
5 cigarettes/d, no SSRI	0.026 (0.020–0.033)	0.165 (0.123–0.219)
5 cigarettes/d, SSRI	0.053 (0.039–0.071)	0.293 (0.217–0.383)
20 cigarettes/d, no SSRI	0.037 (0.029–0.047)	0.179 (0.137–0.231)
20 cigarettes/d and SSRI use	0.074 (0.056–0.098)	0.314 (0.239–0.399)
25-wk duration	0.048 (0.028–0.081)	0.163 (0.103–0.247)
No cigarette use, SSRI use	0.095 (0.055–0.158)	0.289 (0.188–0.416)
5 cigarettes/d, no SSRI	0.073 (0.045–0.115)	0.172 (0.123–0.236)
5 cigarettes/d, SSRI	0.141 (0.088–0.220)	0.303 (0.218–0.404)
20 cigarettes/d, no SSRI	0.104 (0.068–0.156)	0.216 (0.156–0.291)
20 cigarettes/d and SSRI use	0.196 (0.129–0.285)	0.366 (0.270–0.474)

Results shown after adjustment for maternal age, education, race, infant gender, birth weight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure ($P < .001$), and interaction of drug type and number of cigarettes smoked per day.

Probability can be interpreted as 1 = 100% certainty that an event will occur, and 0 = 0% certainty that an event will occur. As an example, a probability of an outcome equal to 0.37 can be interpreted as among a sample of 100 patients, 37 will have the predicted outcome.

As an example, a woman taking oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks smoking 20 cigarettes (ie, 1 pack) per day and taking SSRIs had a 0.366 (95% CI: 0.270–0.474) probability of delivering an infant with NAS.

hospital administrative and vital statistics data. Both errors of omission and commission are possible, leading to misclassification bias; however, our medical record review suggested that potential misclassification of outcomes was likely to be small. Next, we did not directly observe women in our cohort taking the prescribed OPR. It is possible that OPR medications were not taken as prescribed, resulting in a bias toward the null hypothesis. Next, we were unable to capture other exposures (eg, illicit drugs) that may have influenced our primary outcome (NAS). Opioids obtained by other legal sources not paid for by TennCare (ie, cash payments) were not captured in our sample, which could bias our results toward the null hypothesis. Conversion to morphine milligram equivalents, although the accepted standard, may not create perfect comparisons of various OPRs. Finally, it is possible that opioid prescribing is a surrogate for other unmeasured risk factors for NAS; residual confounding cannot be completely ruled out.

CONCLUSIONS

The use of commonly prescribed, nonmaintenance OPRs in pregnancy increased the infant's risk of developing NAS. Nearly 27% of our cohort of pregnant women was prescribed at least 1 short-acting OPR. Furthermore, NAS risk varied widely based on antenatal cumulative opioid exposure, opioid type, number of cigarettes smoked per day, and SSRI use. Public health efforts should focus on limiting inappropriate OPR and tobacco use in pregnancy. Prescribing opioids in pregnancy should be done with caution because it can lead to significant complications for the neonate.

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Address correspondence to Stephen W. Patrick, MD, MPH, MS, Monroe Carell Jr Children's Hospital at Vanderbilt, Mildred Stahlman Division of Neonatology, 11111 Doctor's Office Tower, 2200 Children's Way, Nashville, TN 37232-9544. E-mail: stephen.patrick@vanderbilt.edu

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THE HIGH COST OF WORKING: *My daughter has begun the search for a summer job or internship. Last year, she was quite fortunate as she found a paid internship in a city only 5 hours from where we live. The company, a provider of wellness packages, seemed a great fit given my daughter's interest in athletics and communication. That she was actually paid to rotate through the different departments and assist in a variety of functions made the experience all the more remarkable. One of my sons, looking for a position overseas, has not been so fortunate.*

As he has found out, and as reported in The New York Times *(Education Life: February 5, 2015), few paid overseas internships exist. Students either volunteer or pay someone else for the opportunity to do an internship. The demand for overseas positions is high. During the 2012-13 year, approximately 40,000 Americans participated in for-credit internships or interned, worked, or volunteered abroad for no credit. Given the demand for positions, companies have sprung up to arrange for internships in a wide array of industries across the globe. While the experiences can be quite gratifying and many students report that the experience helped them find a job back home in the US, the costs of obtaining the internship can be high. Students may have to pay between $8,000 and $15,000 for a six to eight week experience. The cost of the flight and food are additional. While I am supportive of overseas learning experiences, I am having a bit of trouble digesting the concept of paying so much money for the opportunity. I am hoping that my children find summer internships close to home.*

Noted by WVR, MD

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