Healthcare Utilization and Expenditures of the Neonatal Opioid Withdrawal Syndrome in Nevada: A Cross-sectional Analysis (2016-2018)

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Abstract

Neonatal Abstinence Syndrome (NAS), also called Neonatal Opioid Withdrawal Syndrome (NOWS), refers to a constellation of withdrawal symptoms occurring among infants born to mothers using addictive substances such as opioids during pregnancy. Nevada has consistently higher opioid prescribing rates among pregnant women compared to national estimates. While Nevada's recent incidence rates for NOWS are available, healthcare utilization and cost associated with NOWS have not been quantified. This cross-sectional study aimed to assess the healthcare resource utilization and financial burden associated with NOWS in Nevada from 2016 to 2018 among newborns diagnosed with NOWS and to draw comparisons with non-NOWS newborns. The mean hospital stay of newborns with NOWS was significantly longer than non-NOWS newborns (17 days *vs.* 2.6 days, respectively, P<0.001). Correspondingly, inflation-adjusted mean hospital charges were significantly higher for newborns with NOWS than non-NOWS newborns ($75,754, 95% CI $65,974-$85,533 *vs.* $11,673, 95% CI $11,195-$12,152, respectively, p<0.001) with over 75% ($13,074,141) of the total hospital costs to treat NOWS attributed to Medicaid. NOWS placed a significant financial strain on the healthcare system in Nevada. The findings of this study will assist in understanding the current status of statewide healthcare delivery for prioritizing the state's financial needs and challenges.

Keywords: Opioid use disorder, Healthcare, Neonatal Opioid Withdrawal Syndrome

Introduction

Neonatal Abstinence Syndrome (NAS), also called Neonatal Opioid Withdrawal Syndrome (NOWS), refers to a constellation of withdrawal symptoms occurring postnatally among infants born to mothers using addictive substances during pregnancy (Hudak & Tan, 2012; Lisonkova et al., 2019; Patrick et al., 2012). NOWS symptoms are mainly associated with the respiratory, nervous, and gastrointestinal systems, and manifest as restlessness, irritability, involuntary muscular contractions, diarrhea, poor sucking reflex, and breathing difficulties (Logan et al., 2013). Maternal substance use is a well-established risk factor for NOWS and is attributed to 75% of cases occurring among neonates (Hudak & Tan, 2012; Logan et al., 2013). Infants born to mothers with a history of substance use disorder are initially monitored with Finnegan scoring. Babies born to mothers enrolled in a controlled methadone program are assessed with the eat, sleep, and console (ESC) approach to make discharge decisions (Hudak & Tan, 2012; Lisonkova et al., 2019; Patrick et al., 2012; Logan et al., 2013). In instances where the mother experiences SUD symptoms or any social issues and babies have a Finnegan score of 8 or more × 3 or a score of 12 or more × 2 the same day, babies are transferred to the NICU (Hudak & Tan, 2012; Lisonkova et al., 2019; Patrick et al., 2012; Logan et al., 2013).

Non-pharmacological methods are used as the initial treatment. If the symptoms persist, morphine with a standardized weaning schedule is used. Sometimes methadone is used at low doses after the initial stabilization with morphine. Morphine is discontinued prior to discharge (Hudak & Tan, 2012; Lisonkova et al., 2019; Patrick et al., 2012; Logan et al., 2013). Between 2004-2014, the prevalence of opioid use disorder (OUD) per delivery hospitalizations in the United States increased five-fold from 1.4 to 6.5 (Centers for Disease Control and Prevention [CDC], 2020; Haight et al., 2018; National Institutes of Health [NIH], 2020). NOWS is a growing epidemic in the U.S., with a more than five-fold increase in incidence from 1.6 per 1,000 hospital births to 8.8 per 1,000 hospital births/year between 2000-2016 paralleling the increase in OUD among pregnant women (Ko et al., 2019; Leech, et al., 2020; Ramphul et al. 2020).

A total of 31,725 NOWS births were reported in 2016 in the U.S., which was an increase of 46% from the 21,732 NOWS births seen in 2012 (Leech et al., 2020; NIH, 2019; Ramphul et al., 2020; Agency of Healthcare Research and Quality [AHRQ], 2018). Statewide variations in the NOWS incidence were also reported, which may be attributed to several factors, including opioid prescribing practices, use of synthetic opioids, and OUD prevalence rates (Ko et al., 2016; Paulozzi et al., 2014). Statewide variations of prescribing opioid pain relievers (OPRs) and benzodiazepines were reported in 2012, with Nevada having a consistently higher OPR prescription rate than the national rate (94.1 prescriptions/100 persons in Nevada *vs.* 82.5 OPR prescriptions/100 persons, nationally) (Haight et al., 2018; Paulozzi et al., 2014). Correspondingly, the incidence of NOWS in Nevada increased from 1.1 cases per 1,000 births in 2003 to 4.8 cases per 1,000 births in 2013 (Ko et al., 2016). According to recent estimates, the incidence of NOWS in Nevada was 8.6 cases per 1,000 hospital births, comparable to both the national estimate of 8.8 cases per 1,000 hospital births in 2016 and the average rate of 9 per 1,000 hospital births across U.S. regions (Batra et al., 2020; Leech et al., 2020).

The rising incidence of NOWS has posed a significant burden on healthcare resources, including NICU utilization and associated healthcare costs (Corr & Hollenbeak, 2017; Patrick et al., 2012; Patrick et al., 2015; Strahan et al., 2019; Tolia et al., 2016). Reportedly, the average length of hospital stays (LOS) of babies with NOWS was significantly greater than hospital stays of non-NOWS infants (16 days *vs.* 2 days) in 2012 (Patrick et al., 2012). In addition, the NICU admissions rate in the U.S. quadrupled (7 to 27 per 1,000 admissions) with a significant increase in the median length of NICU stay from 13 to 19 days among newborns with NOWS between 2004-2013 (Tolia et al., 2016). NICU utilization by newborns with NOWS increased from 0.6% to 4% during the same period, which subsequently increased the healthcare burden and financial strain nationwide (Tolia et al., 2016). The average cost for treating a neonate with NOWS in the U.S. rose from $16,893 to $22,552 in 2016 compared to 2012 (Corr & Hollenbeak, 2017; Strahan et al., 2019). Additionally, newborns with NOWS have higher hospital readmission rates during their first five years of life, which also contributes to the increased healthcare cost estimates (Strahan et al., 2019; Witt et al., 2017).

Several states, including Tennessee, Ohio, Washington, West Virginia, Florida, and Wisconsin, have published reports related to NOWS healthcare expenditures; however, healthcare utilization and costs of NOWS admissions in Nevada have not been quantified (Atwell et al., 2016; Lind et al., 2015; Ohio Department of Health, 2013; Stabler et al., 2016; Wang et al., 2017; Witt et al., 2017). Given the increasing rates of opioid prescriptions, overuse of synthetic opioids, and sequelae, such as NOWS, in Nevada, it is essential to analyze the current healthcare utilization patterns and associated cost of NOWS to inform statewide prevention efforts. Therefore, the objectives of this study were to ascertain the statewide healthcare resource utilization and fiscal burden of NOWS in Nevada from 2016 to 2018 among newborns with NOWS and to draw comparisons with newborns without a NOWS diagnosis among all-payer (public, private, and self-insured) pediatric patient discharges.

Methods

Study design and setting

Using multiple cross-sectional analyses, this geographically defined, statewide, nested (within hospitals' cluster) study aimed to determine healthcare resource utilization and financial burden associated with NOWS from 2016 through 2018 in Nevada.

Data source

The study utilized a state administrative database provided by the Center for Health Information Analysis for Nevada (CHIA) (Center for Health Information Analysis, n.d.). These data were deidentified and were publicly available; therefore, this study was "excluded" (Protocol ID: 1538606) as per the University of Nevada, Las Vegas (UNLV) Institutional Review Board criteria. CHIA collects all hospital admission discharge data for all licensed hospitals in Nevada. It includes demographic information for patients, procedures (25 fields), diagnostic codes (33 fields), revenue and service codes (60 fields), length of hospital stay, discharge status, and billing information (e.g., payer and hospital charges) (CHIA, n.d.).

Sample Selection

The study population included all singleton pediatric inpatient discharge records from Nevada for the years 2016-2018 (n=796). Infants with ICD-10-CM code P961 appearing in any diagnostic field in the hospital discharge database were included in this study. Suspected cases of NOWS, without the ICD-10-CM code P961 and with codes P0414, P0417, and P041A based on the Council of State and Territorial Epidemiologists (CSTE) definition of NOWS were also included (Council of State and Territorial Epidemiologists, n.d.). Infants with drug

withdrawal following therapeutic drug exposure (ICD-CM- P962, n=23) and newborns affected by reactions and intoxications from maternal opiates and tranquilizers used during labor and delivery (P040, n=33) were excluded.

Measures and Outcomes

Newborn demographic data, including birth-assigned sex, race/ethnicity, income quartile of patient's zip code, and payer source, were included. The median household income was approximated to the patient zip code using the most recent (2019) estimates of the American Community Survey (Census Bureau, 2018). The classification criteria (according to 2019 estimates) for income quartiles (Q1-Q4) were obtained from the Health Cost and Utilization Project (HCUP) database (AHRQ, 2018; Kallen, 2004). Ten clinical characteristics (i.e., prematurity, low birth weight, transient tachypnoea, meconium aspiration syndrome, respiratory problems, respiratory distress syndrome, neonatal jaundice, feeding difficulties, seizures, and sepsis) were examined. These characteristics were a priori selected based on published literature (Lind et al., 2015; Winkelman et al., 2018). Hospital procedures to diagnose and treat respiratory, gastrointestinal, and central nervous system symptoms (commonly occurring in newborns with NOWS) were also examined for frequency across the study population. The ICD-10 medical/procedure, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes were used to define the infants' clinical conditions. The algorithm for identifying complex chronic conditions (CCC) was adapted from Feudtner et al., 2014.

For healthcare utilization and cost, the primary outcomes were mean length of hospital stay (LOS), NICU days (derived from the LOS for those admitted to the NICU), NICU admissions rate, the rate of utilization of hospital procedures, and a per-capita inflation-adjusted cost. The NICU use for each newborn was determined using the Universal Billing (UB)-92 revenue codes 174x, 173x, 172x, and 171x. The NICU category was created based on the level of service indicated by UB-92 revenue codes in a hierarchical manner, with the highest being level 4 (most acute care, 174x) and the lowest being level 1 (newborn nursery care, 171x) (Parlett et al., 2019). If a discharge record indicated that the patient had multiple revenue codes for the NICU, then the highest NICU level of service was included after excluding the lower levels. Therefore, the four mutually exclusive categories of level of NICU utilized were expressed as dummy variables, with 0 as "no admission to a particular level" and 1 as "admission to a particular level." The calculation of NICU days assumed that babies were transferred to the NICU within 24 hours of birth. For healthcare cost, total hospital charges (adjusted for inflation to 2019 U.S. dollars) were determined using the medical care component of the Consumer Price Index (Health Resources and Service Administration, 2019). Total charges reflecting the total facility fee reported for each discharge record (not including professional fees) were calculated.

Statistical Analysis

A secondary analysis of hospital administrative data was conducted. The unit of analysis was the newborn discharge/admission (inpatient) record. All statistical procedures utilized SAS software version 9.4 (SAS Institute Inc., Cary, NC). The chi-square (χ^2) test was used for comparisons of categorical variables. The follow-up contingency table analysis (post-hoc) was conducted to obtain p-values corresponding to multilevel variables. The observed p-values were Bonferroni-corrected for multiple comparisons to prevent type 1 errors. The Bonferroni-corrected p-values were obtained by multiplying the p-value resulting from the analysis by the number of tests performed. The calculated p-values were then compared to a standard alpha level (0.05) to determine statistical significance. For continuous variables, including LOS, NICU days, and total charges, the groups were compared using the independent-samples t-test. A follow-up bootstrap analysis (n = 1,000 resamples) was conducted to validate statistical significance and compare with the classical estimates obtained through chi-square tests and independent-samples t-tests. In other words, we wanted to know if the statistically significant differences across groups were due to large differences in the sample sizes or resulted from a true effect. Outcomes were reported as 95% confidence intervals. Continuous variables are presented as the mean ± standard deviation. Categorical variables were reported as percentages.

Results

Demographic and Clinical Characteristics

Among 796 newborns diagnosed with NOWS and 100,049 other hospital births, the proportion of male and female infants was comparable among newborns with NOWS and non-NOWS newborns (48.9% females *vs.* 48.6%, respectively; p=0.6; Table 1). Compared to non-NOWS newborns, babies with NOWS were significantly more likely to be white (69.1% *vs.* 45.9%; p<0.001), living in the zip codes with the lowest median income (10.5% *vs.* 6.6%; p<0.001), and Medicaid-insured (77.4% *vs.* 46.6%; p<0.001; Table 1). During the study period, health outcomes for newborns with

NOWS were significantly worse than for all other hospital births. Newborns with NOWS were more likely to have complications, including neonatal jaundice (44.8% *vs.* 14.7%; p <0.001), prematurity (24.5% *vs.* 9.1%; p <0.001), feeding difficulty (19.0% *vs.* 2.4%; p <0.001), respiratory distress syndrome (17.3% *vs.* 6.0%; p <0.001), and transient tachypnoea of newborn (26.4% *vs.* 3.2%; p <0.001; Table 1).

Healthcare Utilization Patterns

During the study period, the mean LOS for newborns diagnosed with NOWS was significantly longer compared to newborns without NOWS (17 ± 14 days *vs.* 2.6 ± 5 days, p<0.001, Table 2). In our study sample, 628 of 796 newborns with NOWS (78%) had LOS greater than 6 days. Infants with NOWS were more likely than other hospital births to utilize level 2 (13.0% *vs.* 1.2, respectively; p <0.001), level 3 (57.6% *vs.* 6.3; p <0.001), and level 4 neonatal intensive care (21.4% *vs.* 5.7; p <0.001) (Table 3). Moreover, infants with NOWS were more likely than other hospital births to undergo complicated hospital procedures, including ventilation support (13.3% *vs.* 4.0%; p <0.001), infusion of nutritional substances (11.9% *vs.* 2.5%; p <0.001), insertion of feeding device and resection of parts of the gastrointestinal tract (3.1% *vs.* 0.6%; p <0.001), and phototherapy of the skin to treat jaundice (21.7% *vs.* 7.3; p<0.001) (Table 3). The frequencies and proportions obtained from classical chi-square analysis (Tables 1 and 3) were comparable with the bootstrap estimates obtained from 1000 random samples (with replacement) drawn from the population (Appendix A).

Healthcare Cost

In the most recent study year (2018), inflation-adjusted mean hospital charges were significantly higher for each newborn diagnosed with NOWS compared to non-NOWS newborns ($75,754, 95% CI = $65,974-$85,533 *vs.* $11,673, 95% CI = $11,195-$12,152, P<0.001). The standard error and 95% confidence intervals of mean differences in the length of stays and healthcare costs were comparable which indicates that the bootstrap estimates were similar to the classical parametric estimates (Appendix B). Through all study years, most hospital charges were billed to Nevada Medicaid programs, with more than 75% of the total charges paid by state Medicaid. For NOWS births, this amounted to $11.8 million of the total healthcare cost of $14.7 million between 2016 and 2018 (Table 4).

Table 1: Demographic and clinical characteristics of newborns with NOWS vs. all non-NOWS births, 2016-2018

	Infants with NOWS **N = 796**		**All Other Hospital Births** **N = 100,049**		
	N	%	N	%	p-value[a]
Demographics					
Birth-assigned sex					
Female	387	48.9	48,933	48.6	0.9
Male	407	51.1	50,991	51.1	
Race					
White	550	69.1	45,966	45.9	<0.001
Black	84	10.6	13,425	13.4	0.02
Hispanic	70	8.8	22,491	22.5	<0.001
API[b]	18	2.3	7,021	7.0	<0.0001
Other	72	9.0	10,550	10.6	0.3
Insurance					
Private	138	17.3	45,096	45.1	<0.001
Medicaid	616	77.4	46,604	46.6	0.00004
Uninsured	42	5.3	8,349	8.3	0.001
Income quartile					
≤$47,999 (Q1)	80	10.5	6,267	6.6	<0.001
$48,000-$60,999 (Q2)	389	51.1	47,521	50.3	0.6
$61,000-$81,999 (Q3)	275	36.1	37,616	39.8	0.03
≥$82,000 (Q4)	17	2.23	3,003	3.1	0.1
Health outcomes					
Neonatal Jaundice	357	44.8	14,695	14.7	<0.001
Prematurity	195	24.5	9,114	9.1	<0.001
Feeding Difficulty	151	19.0	2,408	2.4	<0.001
RDS[c]	138	17.3	5,991	6.0	<0.001
Transient Tachypnoea	126	26.4	3,219	3.2	<0.001
Sepsis	76	9.5	2,341	2.3	<0.001
Low birth weight	73	9.2	3,199	3.2	<0.001

a. The observed p-values were Bonferroni corrected
b. Asian or Pacific Islander
c. Respiratory distress syndrome

Table 2: Health resource utilization for newborns with NOWS *vs.* Non-NOWS births, 2016-2018

Year	**2016** (Mean ± S.D.)	**2017** (Mean ± S.D.)	**2018** (Mean ± S.D.)	**2016 - 2018**
Neonatal Opioid Withdrawal Syndrome				
Number of patients	292	247	257	796
Mean Length of Stay (days)	17.2 ± 14.5	17.6 ± 13.0	16.0 ± 14.0	17.0 ± 14.0
NICU[a] days	18.5 ± 14.5	18.5 ± 12.8	17.5 ± 14.5	18.2 ± 14.0
Non-NOWS Births				
Number of subjects	33,759	33,060	33,230	100,049
Mean Length of Stay (days)	2.7 ± 5.5	2.6 ± 5.0	2.6 ± 4.8	2.6 ± 5.0
NICU days	10.8 ± 14.3	10.8 ± 13.0	10.5 ± 12.6	10.7 ± 13.4

a. Neonatal intensive care unit

Table 3: NICU use and hospital procedures (newborns with NOWS *vs.* Non-NOWS births), 2016-2018

	Infants with NOWS N = 796		**All Non-NOWS Hospital Births N = 100,049**		
	N	**%**	**N**	**%**	**p-value[a]**
NICU[b] utilization					
Level 1	63	8.0	86,825	86.7	<0.001
Level 2	104	13.0	1,166	1.2	<0.001
Level 3[c]	459	57.6	6,318	6.3	<0.001
Level 4[c]	170	21.4	5,740	5.7	<0.001
Respiratory					
Ventilation Support	106	13.3	3,922	4.0	<0.001
Endotracheal intubation repair of diaphragm, and sternum	47	6.0	1,991	2.0	<0.001
Gastrointestinal					
Insertion of feeding device, repair of esophagogastric junction	25	3.1	582	0.6	<0.001
Drainage of stomach, pleural, and peritoneal cavity with drainage device	13	1.6	237	0.2	<0.001
Infusion and Transfusion					
Infusion of nutritional substance	95	11.9	2,524	2.5	<0.001
Insertion of infusion device	38	4.8	1,646	1.6	<0.001
Other procedures					
Phototherapy of skin	173	21.7	7,345	7.3	<0.001

a. P values are Bonferroni corrected

b. Neonatal intensive care unit

c. Level 3 & 4 (for critically ill babies). Additional information can be found at https://www.marchofdimes.org/baby/levels-of-medical-care-for-your-newborn.aspx

Table 4: Aggregate hospital charges related to newborns with NOWS *vs.* non-NOWS births 2016-2018

Year	**2016**	**2017**	**2018**	
	Total Charges $ (± S.D.)			p-value
NOWS births (N=796)				
Private	**2,826,995** (60,385)	**2,312,798** (76,015)	**2,479,899** (69,129)	<0.001
Medicaid	**13,074,141** (71,931)	**11,756,758** (65,524)	**10,553,322** (67,197)	<0.001
Self-pay	**414,474** (44,857)	**221,929** (30,131)	**602,446** (41,657)	<0.001
Total	**16,315,611** (69,289)	**14,291,486** (66,985)	**13,635,668** (66,488)	-
All hospital births (N = 100,049)				
Private	**132,085,357** (45,218)	**124,757,061** (40,215)	**148,095,334** (41,712)	<0.001
Medicaid	**182,746,961** (54,408)	**179,097,978** (50,006)	**162,605,450** (42,783)	<0.001
Self-pay	**18,665,078** (37,784)	**19,564,466** (27,617)	**19,483,438** (18,865)	<0.001
Total	**333,497,396** (137,410)	**323,419,505** (117,838)	**330,184,222** (103,360)	-

Discussion

On average, the total cost of treating infants with NOWS among all payers was nearly $14,747,588 during the study period (2016-2018). The results of this study indicated that the average inpatient charge and average LOS were nearly seven times higher for newborns with NOWS compared to non-NOWS newborns in Nevada. These healthcare cost estimates do not include the costs to treat long-term complications of NOWS, such as behavioral/cognitive deficits, ear infections, lack of motor skills, and visual disturbances (Maguire et al., 2016). Infant with a history of NOWS are more likely to have educational or intellectual disabilities (with subsequent lower academic achievements) and need special education services (Fill et al., 2018; Morgan et al., 2019).

Consistent with previous reports, our results suggest that over 75% of the total hospital costs to treat NOWS was attributed to Medicaid, substantiating that NOWS placed a significant strain on the healthcare system (Corr & Hollenbeak, 2017; Patrick et al., 2015; Strahan et al., 2019). According to a recent statewide audit, the incidence of NOWS was significantly higher (13.2 cases per 1,000 hospital births, 95% CI: 11.0, 15.0) among babies born to Medicaid beneficiaries in Nevada during 2016-2018 (Batra et al., 2020). This finding was consistent with national level reports of nearly 14.4 cases per 1,000 births among Medicaid-financed births in 2014 (Winkelman et al., 2018). Infants with NOWS born to Medicaid beneficiaries were more likely to have a longer length of hospital stay than those financed by private insurance (Winkelman et al., 2018). Nationally, the aggregate hospital charges have also increased significantly from $732 Million to $1.5 Billion from 2009-2013, with over 75% of the charges attributed to Medicaid financed births (Patrick et al., 2012; Patrick et al., 2015). The higher incidence of NOWS among newborns of Medicaid beneficiaries may possibly be due to the background characteristics of the mothers belonging to lower socio-economic groups with greater medical needs (Ellwood & Kenney, 1995).

Although national cost estimates are available, to our knowledge, this is the first study to analyze the financial impact of NOWS in Nevada. Our findings of healthcare utilization and LOS are comparable to results from other states, including Tennessee, Ohio, Washington, West Virginia, Florida, and Wisconsin (Atwell et al., 2016; Lind et al., 2015; Ohio Department of Health, 2013; Stabler et al., 2016; Wang et al., 2017; Witt et al., 2017). However, direct comparisons of our findings with previous estimates should be interpreted with caution because of the transition of the ICD-9 to ICD-10 coding system in the 4th quarter of 2015. Unlike the ICD-9 code, the ICD-10 code (used in this study) allows for a clearer distinction between NOWS secondary to maternal substance use and one that follows therapeutic exposure to drugs (among critically ill infants).

A previous study suggests that an increase in NOWS incidence and concomitant hospital utilization can be attributed partially to maternal prescription opioid use (Ko et al., 2016). Between 1998 and 2011, the prevalence of maternal opioid use in the U.S. increased by 127% (0.17% in 1998 and 0.39% in 2011) (Ailes et al., 2015). Opioid-containing medications are most commonly prescribed to women of reproductive age (15-44 years), with a higher prescription rate of 1.6 prescriptions for Medicaid-enrolled women compared to 0.7 prescriptions for privately insured women in 2012 (Ailes et al., 2015; Maeda et al., 2015). The prevalence of prescription opioid use among Medicaid-enrolled women of reproductive age was higher than those privately insured (39.4% *vs.* 27.7%) (Guttmacher et al., 2019). In 2019, 6.6% of pregnant women reported prescription opioid use, of which 21.2% reported using opioids for reasons other than pain, and received the prescription from sources other than healthcare providers (Ko et al., 2016). Another contributing factor is the increased use of synthetic opioids, which can be mixed with other drugs. Synthetic opioids such as heroin and fentanyl are now the top threats in Nevada (Research Division Legislative Counsel Bureau, n.d.). In fact, a significant share of the opioid overdose deaths was attributed to the use of synthetic opioids in Nevada during 2015-2018. This points to the need for developing stringent laws and policies and refining previous laws to reduce drug trafficking in Nevada.

Between 2015 and 2019, key legislation was passed to address the opioid epidemic (Guttmacher Institute, 2019). Twenty-five states, including Nevada, require suspected prenatal drug use reporting by healthcare professionals (American Society of Addiction Medicine, n.d.). The Comprehensive Addiction and Recovery Act (CARA), which was signed into law in 2016 (American Society of Addiction Medicine, n.d.) requires the allocation of federal funds to set up substance use facilities for pregnant women and establishing state Prescription Drug Monitoring Programs (PDMPs) (Bureau of Justice, n.d.; National Alliance for Model State Drug Laws, 2018). In 2017, the Nevada legislature passed the Controlled Substance Abuse Prevention Act (AB 474), which provides training to healthcare professionals in prescribing controlled substances (Bureau of Justice, n.d.; National Alliance for Model State Drug Laws, 2018). Recently, a bill called "Prescription Drug Monitoring Act of 2019" was introduced in the U.S. Senate (Bureau of Justice, n.d.; National Alliance for Model State Drug Laws, 2018). This bill requires prescribers from each PDMP operational funded state to use PDMPs for searching a patient's drug history prior to prescribing Schedule II-IV controlled substances (Bureau of Justice, n.d.; National Alliance for Model State Drug Laws, 2018).

Another important CDC consideration was to implement mandatory clinical reporting and to set up statewide surveillance systems for NOWS (Jilani et al., 2019). Previous and current estimates for Nevada were based on hospital administrative data, which may be associated with a substantial delay in reporting needing data validation and accumulation of all usable records (Atwell et al., 2016; Patrick et al., 2012). With the existing trends of NOWS, it is critical to have cases clinically reported so that immediate preventive strategies and policies can be formulated (Jilani et al., 2019). Although NOWS was added to all states' reportable disease list in 2013, currently, only six states (Arizona, Florida, Georgia, Kentucky, Virginia, and Tennessee) have mandates for its clinical reporting (Jilani et al., 2019). CDC views the clinical reporting approach as a promising avenue to provide timely estimates for prompt preventive measures to reduce the NOWS burden across states.

To our knowledge, the current study is the first to provide recent estimates of hospital and NICU utilization of newborns with NOWS in Nevada. The findings of this study will assist in understanding the current status of statewide healthcare delivery, and this information will be vital for prioritizing the state's financial needs. This report will serve as basis for policy makers and state legislators to devise new programs/policies. Additionally, the assessment of resource utilization and associated hospital charges depending on the payment source (public/private) will be helpful to determine the burden on federally funded programs, including Medicaid. We expect that our findings will also help target prevention efforts to promote cost-effective programs, such as rooming-in (i.e., keeping babies at the mother's bedside instead of nursery), breast feeding, and Kangaroo care (i.e., holding baby on mother's chest for maximizing skin to skin contact) to curb the costs associated with NICU stay. Data related to variations in clinical practice, patient outcomes, and quality assessment of the existing cost-effective strategies will be essential to develop improved tools and resources for the evidence-based neonatology.

Limitations

The findings of this study are subject to a few limitations. First, these geographically restricted findings might not be extrapolated to other states, thus the study lacks generalizability. Second, only hospital charges (not the actual costs) were

calculated. The hospital charges indicate the amount set for hospital services before negotiating any discounts. The amount paid to the hospital is the actual cost after a negotiation between hospital and healthcare purchasers. The study database only included charges associated with hospital stay; information related to professional fees and readmission cost was not available. Moreover, the cost estimates did not include expenditures to treat long-term complications due to the inability to track patients longitudinally in the database. Costs associated with readmissions were not calculated due to the lack of a "revisit variable" in the data source, which would link multiple hospitalizations with the same record. Misclassification bias due to coding errors may have been introduced because hospital administrative data rely on billing codes for reporting conditions or diseases. Moreover, it could be subject to underreporting because administrative data typically report fewer cases than clinical reporting. Finally, our data source does not provide information related to the type of maternal exposure, which limited our ability to provide estimates following other noxious maternal exposures. Future studies can be planned utilizing sources with detailed clinical and drug consumption historical data (e.g., electronic health records).

Conclusions and implications for public health practice

NOWS poses significant health and fiscal challenges in Nevada. Findings from this study have several important implications for drug abuse treatment and prevention programs to improve the health outcomes of mother-infant dyads. A multifaceted approach, including national, state, and provider-level efforts, will be required to curb the NOWS epidemic. More importantly, Nevada's mandated clinical reporting of Neonatal Opioid Withdrawal Syndrome will be essential to provide rapid preventive efforts without the time-lag associated with reporting health insurance claim data. Clinical reporting will help document detailed maternal exposure history and the type of addictive drug used in designing targeted interventions. This study highlights the need for additional research examining the health and financial burden associated with readmission rates and long-term complications of NOWS to obtain a holistic view of the problem and establish a continuum of care. It also emphasizes implementing standardized treatment protocols to reduce the LOS and associated healthcare costs to treat NOWS.

DECLARATION

Ethical approval and consent to participate: Ethical review and approval were waived for this study due to the use of publicly available de-identified data. This study was considered as an 'excluded' study (Protocol ID: 1538606) as per the University of Nevada, Las Vegas (UNLV) Institutional Review Board criteria, according to federal regulations. Since this study involved a secondary data analysis, informed consent was not applicable. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Competing interests: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Funding: This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments
The authors wish to acknowledge Dr. Anne Weisman (Director of Wellness and Integrative Medicine, School of Medicine, University of Nevada, Las Vegas) for her valuable contribution as a member of Dr. Batra's Graduate Advisory Committee.

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Appendix A: Output of Bootstrapped Chi-square Analysis

	Newborns with NOWS (%)	All Other Hospital Births (%)	p-value
Demographics			
Birth Assigned Sex			
Female	48.90	48.60	0.6
Male	51.00	51.10	
Race			
White	69.10	45.90	<0.001
Black	10.60	13.40	
Hispanic	8.80	22.50	
API[b]	2.30	7.00	
Other	9.00	10.60	
Insurance			
Private	17.30	45.10	<0.001
Medicaid	77.40	46.60	
Uninsured	5.30	8.30	
Income quartile			
≤$47,999 (Q1)	10.50	6.63	<0.001
$48,000-$60,999 (Q2)	51.00	50.30	
$61,000-$81,999 (Q3)	36.10	39.80	
$82,000 (Q4)	2.23	3.10	
Clinical characteristics			
Prematurity	24.5	9.1	<0.001
Low birth weight	9.2	3.2	<0.001
Transient Tachypnea	26.4	3.2	<0.001
Respiratory Distress Syndrome	17.3	6.0	<0.001
Neonatal Jaundice	44.8	14.7	<0.001
Feeding Difficulty	19.0	2.4	<0.001
Sepsis	9.5	2.3	<0.001
NICU utilization			
Level 1	7.91	86.70	<0.001
Level 2	13.00	1.17	<0.001
Level 3	57.60	6.31	<0.001
Level 4	21.40	5.70	<0.001
Respiratory			
Ventilation Support	13.30	3.90	<0.001
Endotracheal intubation repair of diaphragm, and sternum	5.90	2.00	<0.001
Gastrointestinal			
Insertion of feeding device, repair of Esophagogastric junction	3.10	0.60	<0.001
Infusion			
Insertion of infusion device	4.80	1.60	<0.001
Infusion of nutritional substance	11.90	2.50	<0.001
Phototherapy of skin	21.70	7.30	<0.001

a. Bootstrap estimates were from 1000 random samples with replacement; b. Asian Pacific Islander

Appendix B: Classical and Bootstrapped t- tests results comparison

Tests	**Standard error**	**95% confidence intervals**
Classical T test		
Mean LOS	0.58 days	-15.50, -13.20
Mean healthcare cost	$2,850	-72,719, -61,523
Bootstrap estimates		
Length of stay	0.60 days	-15.60, -13.30
Mean healthcare cost	$2,937	-72,939, -61,380