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ORIGINAL RESEARCH ARTICLE

Contribution of pharmaceutical drugs of dependence to the incidence of neonatal abstinence syndrome in Western Australia between 2003 and 2018

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Abstract

Study objective: The aim of this study was to examine the incidence of neonatal abstinence syndrome (NAS) in Western Australia (WA) and estimate the contribution of pharmaceutical drugs of dependence (PDD) to NAS.

Design: A population-based birth cohort study.

Data source: Neonates were identified through the Midwives Notification Scheme. Linked medication dispensing and hospital records were used to identify exposure to PDD and NAS diagnosis.

Patients: All live born neonates born in WA between 2003 and 2018.

Measurements: The incidence of NAS and percentage of NAS diagnoses associated with exposure to PDD.

Main results: During the study period, the incidence of NAS did not significantly change (annual percentage change (APC): 0.6, 95%CI: −1.3, 2.6), with 3.8 neonates per 1,000 live births diagnosed with NAS. PDD were dispensed to 41.4% of mothers of neonates with NAS, with PDD used to treat opioid use disorders the most commonly prescribed (35.2% of neonates with NAS), while opioid PDD used in the treatment of pain contributed to 5.2% of NAS cases. Non-opioid PDD contributed to 1.7% of cases of NAS. The incidence of NAS associated with the use of opioids used to treat opioid use disorders (OUD) decreased over the study period (APC: −6.5, 95%CI: −9.5, −3.4), while NAS associated with opioids used to treat pain remained stable (APC: −2.7, 95%CI: −7.1, 1.9).

Conclusion: The incidence of neonatal abstinence syndrome in WA remained stable from 2003 to 2018. Medications used to treat opioid use disorders were a substantial driver of NAS, although NAS associated with these medications has declined over time.

KEYWORDS
medicines, neonatal opioid withdrawal syndrome, opioid use disorders, opioids, pain management, pregnancy

1 | INTRODUCTION

Neonatal abstinence syndrome (NAS) occurs following the abrupt cessation of in utero exposure to drugs taken by the mother following birth.[1] While NAS is most commonly associated with in utero exposure to opioids, NAS had been observed following exposure to other drugs including benzodiazepines,[2] selective serotonin reuptake inhibitors (SSRI),[3] and stimulants such as methylphenidate,[4] methamphetamines,[5] and cocaine.[6] NAS is characterized by range of central and autonomic nervous and gastrointestinal symptoms including hyperirritability, difficulty feeding, poor sleep, high-pitched crying, increased muscle tone, and fever.[7] While rarely fatal, NAS can be associated with significant illness in the newborn and prolonged hospitalization.[8,9]

In recent years, a number of countries have observed substantial increases in the diagnosis of NAS.[10–12] In the United States between 2010 and 2017 the rate of NAS per 1000 birth increased from 4.0 to 7.3.[12] Similarly, in Canada the rate rose from 1.8 to 5.4 per 1000 live births between 2003 and 2014.[10] Increases in the incidence of NAS is thought to be the result in increases in the prescribing of opioid drugs for pain,[13] with increases in the prescribing of opioids having also been reported.[14] However, the increases in the prescribing of many non-opioid drugs with the potential to cause NAS in pregnant and non-pregnant patients have also been observed in some countries.[15–17]

It is unclear what proportion of NAS is associated with the use prescription opioids for pain, prescription opioids for the treatment of opioid use disorders (OUD), non-opioid prescription drugs, or illicit drugs. The aim of this study was to examine the incidence of NAS is Western Australia (WA) between 2003 and 2018, and estimate the role of prescription drugs of dependence in the incidence.

2 | METHODS

2.1 | Study design and cohort

The study was a population based cohort study of all live-born neonates, born with WA between 2003 and 2018. Children were identified from the Midwives Notification Scheme, after which their linked hospital records were extracted by the WA Data Linkage Branch from the Hospital Morbidity Data Collection. Neonates diagnosed with NAS between birth and 28 days were identified from hospital records using International Statistical Classification of Diseases and Related Health Problems 10th Revision, Australian Modification (ICD-10-AM) codes assigned to each admission. Both primary and additional diagnosis codes with an ICD-10-AM code of P96.1 and P96.2 were used.

2.2 | Data sources

To examine the contribution of prescription drugs of dependence (PDD) to the development of NAS, maternal use of these drugs late in pregnancy was ascertained using linked data from the Monitoring of Drugs of Dependence System (MODDS). The MODDS contains information on the prescribing of PDD within WA. In Australia, PDD are drugs that are classified as Schedule 8 drug by the Therapeutic Goods Administration (TGA). These drugs not only have a recognized therapeutic use but also have an associated risk of misuse, abuse, and dependence. The prescribing, dispensing, and storage of these drugs are closely monitored and subject to tight control measures. Data were stored separately for medications used to treat OUD and other PDD, with some difference between the two data sets. Most notably, for medications used to treat OUD dispensing month and year was available, while for other PDD the day, month and year of dispensing was available. Neonates were classified as having been exposed to a medication used to treat OUD if their mother was dispensed a medication in the 2 months prior to birth (excluding the month of birth to avoid the capture of dispensing occurring after birth). For other PDD, neonates were classified as having been exposed if their mother was dispensed that medication in the 60 days prior to birth. The use of an approximate 2-month window for medication dispensing was done to capture medication exposure late in pregnancy, without including mothers who ceased their medication use earlier in pregnancy.

2.3 | Statistical analysis

Characteristic of neonates and mothers were summarized for by NAS diagnosis, and stratified by exposure to opioids for OUD and opioids for pain. Comparisons between NAS and non-NAS groups were made using univariable linear and logistic regression. The percentage of neonates diagnosed with NAS per year was calculated overall and by drug type (opioids for OUD, opioids for pain, and non-opioid drugs). Trends were examined using joinpoint regression, using Joinpoint Regression Program version 4.8.0.1. The percentage of neonates who were diagnosed with NAS following exposure to each drug was also calculated.

2.4 | Ethical considerations

Ethics approval for the study was provided by the WA Department of Health Human Research Ethics Committee and the University of Western Australia Human Research Ethics Committee. The study protocol was reviewed by the custodians of each data sets used in the study.

3 | RESULTS

3.1 | Incidence of NAS

Between 2003 and 2018, 401,462 live neonates were born in WA. Of these, 1528 neonates were diagnosed with NAS, equating to 3.8 per 1000 live births (Figure 1). Over the study period, the incidence

of NAS did not significantly change (Annual percentage change (APC): 0.6, 95%CI: −1.3, 2.6) (Figure S1). However, there was a significant decrease in NAS associated with opioids used for the treatment of opioid use disorders (APC: −6.5, 95%CI: −9.5, −3.4), but no significant change in NAS associated with opioids for the treatment of pain (APC: −2.7, 95%CI: −7.1, 1.9).

3.2 | Patient demographics

Neonates diagnosed with NAS and their mothers differed significantly from neonates without NAS and their mothers (Table 1). Neonates diagnosed with NAS were more likely to be male (OR: 1.18, 95%CI: 1.06, 1.30), born pre-term (OR: 2.96, 95%CI 2.61, 3.34), and born at less than 2500 g birthweight (OR: 3.69, 95%CI: 3.25, 4.18) compared with neonates without NAS. Mothers of neonates diagnosed with NAS were significantly younger (Coeff: −0.55, 95%CI: −0.83, −0.27), were more likely to have previously been pregnant (OR: 2.29, 95%CI: 1.99, 2.64), smoked during pregnancy (OR: 15.13, 95%CI: 13.59, 16.84), and lived in a low socio-economic area (OR: 2.32, 95%CI: 2.02, 2.65). In comparison, there were no significant difference between neonates with and with NAS exposed to opioids used to treat OUD. For opioids used to treat pain, neonates with NAS were more likely to be pre-term (OR: 2.38, 95%CI: 1.45, 3.93) and be born at less than 2500 g (OR: 4.53, 95%CI: 2.72, 7.54) compared with neonates without NAS. Mother of neonates with NAS were also significantly older (Coeff: 2.03, 95%CI: 0.77, 3.29) and were more likely to have smoked during pregnancy (OR: 3.99, 95%CI: 2.50, 6.35).

3.3 | Contribution of pharmaceutical drugs of dependence to NAS

Pharmaceutical drugs of dependence were likely contributors to 41.4% of NAS diagnoses, with drugs used to treat OUD the most commonly associated with NAS (Table 2). Similarly, rates of NAS were much higher for opioids used to treat OUD (62.0%) compared with opioids used to treat pain (6.8%). The incidence of NAS in non-opioid PDD was low (≤3.0%). No cases of exposure to a number of PDD, including cannabinoids, cocaine, flunitrazepam, and ketamine, in pregnancy were identified.

3.4 | Prescription drugs of dependence for the treatment of opioid use disorders

Over the study period, the number of neonates exposed to medication used to treat an OUD late in pregnancy declined, from a high of 75 in 2004 to a low of 21 in 2018. Over the study period, the percentage of neonates exposed to an OUD who were diagnosed with NAS did not change overall (OR: 1.00, 95%CI: 0.97, 1.03), or for neonates exposed to methadone (OR: 1.01, 95%CI: 0.97, 1.06) or buprenorphine (OR: 1.01, 95%CI: 0.95, 1.07).

PDD used to treat OUD were significantly more likely to be associated with NAS compared with opioids used to treat pain (OR: 22.27, 95%CI: 17.09, 29.02) and compared with non-opioid PDD (OR: 56.00 (37.13, 84.43).

4 | DISCUSSION

The incidence of NAS in WA was comparable to other countries including the United Kingdom and Canada,[18] but was substantially lower than recent reports from the United States.[19,20] Unlike countries such as the United States and Canada, increases in NAS were not observed.[10–12] The incidence of NAS was higher than measured in a previous WA study (2.7 per 1000 births),[18] but were similar to rates in New South Wales (Australia) between 2006 and 2011 (3.4 per 1000 births).[21] Interestingly, while the incidence of NAS was stable in WA, the incidence of NAS associated with the treatment of OUD was decreasing and the incidence of NAS associated with the treatment of pain was stable.

While the use of PDD likely contributed to NAS in 41.4% of cases, it is unclear what drugs contributed to the remaining cases.

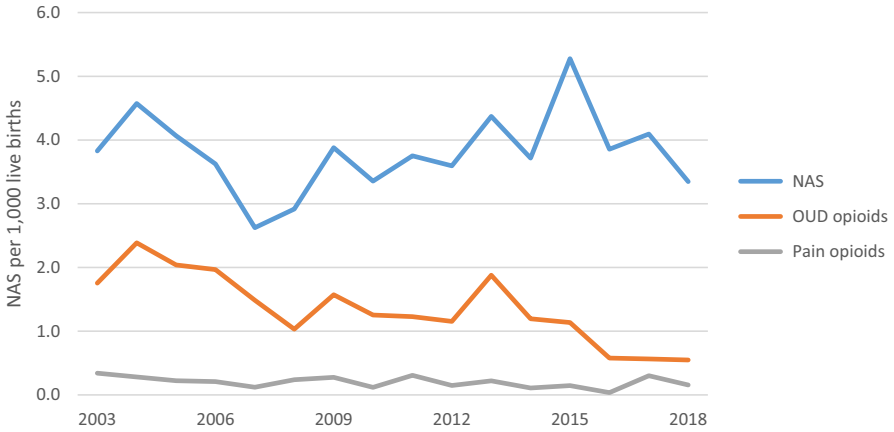

FIGURE 1 Number of neonates born in Western Australia diagnosed with neonatal abstinence syndrome (NAS) per 1000 live births, overall and associated with opioids for opioid use disorders (OUD) and pain

TABLE 1 Characteristics of neonates and their mothers by neonatal abstinence syndrome (NAS) diagnosis, and stratified by exposure to opioids used to treat opioid use disorders (OUD) and pain

	Whole population		Opioids for OUD		Opioids for pain	
	NAS −	NAS +	NAS −	NAS +	NAS −	NAS +
Number	399,934	1528	330	538	1093	80
Neonate						
Baby sex (male), *n* (%)	205,242 (51.3%)	846 (55.4%)*	165 (50.0%)	279 (51.9%)	554 (50.7%)	43 (53.8%)
Pre-term (<37 weeks), *n* (%)	33,371 (8.3%)	324 (21.2%)**	57 (17.3%)	98 (18.2%)	175 (16.0%)	25 (31.3%)*
Low birth weight (<2500 g), *n* (%)	25,146 (6.3%)	303 (19.8%)**	65 (19.7%)	93 (17.3%)	105 (9.6%)	26 (32.5%)**
Mother						
Maternal age (years), mean ± SD	30.4 ± 5.6	29.9 ± 5.8**	30.2 ± 5.1	30.2 ± 5.1	31.3 ± 5.6	33.3 ± 5.3*
Previously pregnant, *n* (%)	286,908 (71.7%)	1304 (85.3%)**	301 (91.2%)	490 (91.1%)	884 (80.9%)	69 (86.3%)
Smoked during pregnancy, *n* (%)	47,593 (11.9%)	1026 (67.2%)**	242 (73.3%)	423 (78.6%)	194 (17.8%)	37 (46.3%)**
Low socio-economic area,[a] *n* (%)	31,965 (8.0%)	256 (16.8%)**	47 (14.2%)	89 (16.5%)	111 (10.2%)	8 (10.0%)
Metropolitan residence,[b] *n* (%)	263,803 (66.0%)	1044 (68.6%)	217 (65.8%)	366 (68.0%)	741 (68.0%)	50 (62.5%)

*$p < 0.01$, **$p < 0.001$.

[a]Residing in an area within the lowest 20% score for the Index of Relative Socio-Economic Advantage and Disadvantage at the time of birth.

[b]Residing within a major city (Perth) based on the Accessibility and Remoteness Index of Australia at the time of birth.

Other possible contributors to NAS are illicit opioids (e.g., heroin), prescription opioids that are not classified as PDD such as low does codeine preparations and tramadol, and other non-opioid medications that are not classified as PDD (e.g., SSRI). Heroin use in Australia is relatively uncommon, with less than 0.1% of Australians reporting heroin use in the past 12 months in 2019, down from 0.2% in 2001.[22] However, in neonates exposed to heroin in utero, around half will require treatment for NAS.[23,24] The decline in the prescribing of medications to treat OUD in pregnancy may also reflect a decline in the use of heroin in pregnancy.

PDD for the treatment of opioid use disorders made up 35.2% of NAS, with high rates of NAS following in utero exposure to methadone, buprenorphine, and buprenorphine-naloxone (≥40%). The percentage of neonates exposed to methadone or buprenorphine diagnosed with NAS was consistent with the current literature.[25–27] While the use of illicit opioids such as heroin may have also contributed to the occurrence of NAS in some neonates, the use of methadone and buprenorphine has been associated with a significant reduction in illicit opioid use in non-pregnant patients.[28] The decline in NAS associated with PDD used to treat OUD was not associated with a change in the proportion of exposed neonates developing NAS, which may have occurred as a result of improved maternal and neonatal care or an increase in the portion of neonates exposed to buprenorphine over methadone (typically associated with a lower risk of NAS). It is likely that this decrease reflected a decreased demand for methadone and buprenorphine and a decrease in illicit opioid use.

The risk of NAS can be a reason for avoiding the use of opioids for the treatment of pain in pregnant women. A reluctance to use opioids during pregnancy can results in inadequate pain relief and maternal suffering. With limited information about the risk of NAS following exposure to opioids for the treatment of pain, the reliance has been observations made in neonates exposed to opioids used to treat OUD. However, the risk of NAS associated with opioids for the treatment of OUD appears to be substantially greater than for opioids used to treat pain. While their other considerations associated with the use of opioids for the treatment of pain in pregnancy, it is hoped that these results will mitigate some of the concerns surrounding the use of opioids for the treatment of pain in pregnancy.

Interestingly, 1.7% of NAS cases occurred in neonates exposed to non-opioid PDD and less than 3.0% of neonates exposed to either alprazolam, dexamphetamine or methylphenidate diagnosed with NAS. While NAS has been observed in neonates exposed to benzodiazepines and stimulants in utero, it is uncommon for these drugs alone to result of NAS..[2,5,6] These cases may reflect the use of these drugs in addition to other drugs including opioids.

Compared with neonates without NAS, neonates diagnosed with NAS were more likely to be born pre-term and be classified as low birth weight. This may reflect the effects of exposure to opioids and other drugs, as well as other risk factors such as the high percentage mothers smoking during pregnancy and being from low socio-economic areas. Maternal characteristics differed between women who used opioids for OUD and opioids for pain, particularly in terms of smoking during pregnancy. This highlights important of examining maternal and neonatal outcomes associated with opioids for OUD and pain separately.

4.1 | Limitations

Unfortunately, it was not possible to distinguish the contribution of illicit and non-schedule 8 medications to NAS. Additionally, there

TABLE 2 Percentage of neonates with and without neonatal abstinence syndrome (NAS) exposed to pharmaceutical drugs of dependence (PDD) late in pregnancy

	Any exposure			Single medication exposure		
Exposure	NAS +	NAS −	Exposed neonates with NAS (%)	NAS +	NAS −	Exposed neonates with NAS (%)
All neonates	1528	399,934	0.4	–	–	–
Any PDD	632 (41.4%)	2299 (0.6%)	21.6	–	–	–
Opioids for OUD						
Any opioid for OUD	538 (35.2%)	330 (0.1%)	62.0	528	321	62.2
Methadone	384 (25.1%)	194 (0.1%)	66.4	376	190	66.4
Buprenorphine alone	149 (9.8%)	126 (0.0%)	54.2	143	119	54.6
Buprenorphine + naloxone[a]	8 (0.5%)	12 (0.0%)	40.0	7	10	41.2
Opioids for pain						
Any opioid for pain	80 (5.2%)	1098 (0.3%)	6.8	73	1074	6.4
Codeine[b]	8 (0.5%)	394 (0.1%)	2.0	6	381	1.6
Buprenorphine	6 (0.4%)	37 (0.0%)	14.0	<5	–	12.9
Fentanyl	6 (0.4%)	12 (0.0%)	33.3	<5	–	27.3
Hydrocodone	<5 (<0.3%)	–	22.2	<5	–	16.7
Methadone	5 (0.3%)	14 (0.0%)	26.3	<5	–	23.1
Morphine	16 (1.1%)	46 (0.0%)	25.8	13	39	25.0
Oxycodone	45 (3.0%)	596 (0.2%)	7.0	34	560	5.7
Pethidine	<5 (0.3%)	–	5.6	0	–	0.0
Tapentadol	<5 (0.3%)	–	16.7	0	–	0.0
Non-opioids	26 (1.7%)	893 (0.2%)	2.8	20	877	2.2
Benzodiazepines						
Alprazolam[c]	<5 (0.3%)	–	2.9	0	–	0.0
Stimulants						
Dexamphetamine	25 (1.6%)	810 (0.2%)	3.0	19	796	2.3
Methylphenidate	<5 (0.3%)	–	1.9	0	–	0.0

Abbreviations: NAS, neonatal abstinence syndrome; OUD, opioid use disorders; PDD, pharmaceutical drugs of dependence.

[a]Buprenorphine + naloxone first became readily available in 2006.

[b]Schedule 8 codeine preparations only.

[c]Changed from a schedule 4 medication to a schedule 8 medication dated February, 01 2014.

was no available information on NAS including the severity, requirement for treatment, or the method of diagnosis (e.g., modified Finnegan scale or Rivers score). Additionally, the data provided did not include indications for use, and we are unable to determine if the medication was taken following dispensing. During the study period, there were some changes to the classification of schedule 8 medications, for example, alprazolam was changed from a schedule 4 to a schedule 8 medication in 2014.

5 | CONCLUSION

The incidence of NAS in WA between 2003 and 2018 was stable at 0.38 per 1000 live births. While methadone and buprenorphine were substantial contributors to NAS, the portion of neonates with NAS associated with these medications decreased over the study period.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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