Neonatal opioid withdrawal and antenatal opioid prescribing

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ABSTRACT

Importance: The incidence of neonatal opioid withdrawal is increasing in both the United States and Canada. However, the degree to which the treatment of pain with opioids, rather than the misuse of prescription opioids or heroin, contributes to the prevalence of neonatal opioid withdrawal remains unknown.

Objective: To determine what proportion of women who deliver an infant with neonatal abstinence syndrome were prescribed an opioid before and during pregnancy, and to determine the incidence of neonatal abstinence syndrome in Ontario between 1992 and 2011.

Design, Setting and Patients: A retrospective, serial, population-based, cross-sectional study between 1992 and 2011 in Ontario, Canada.

Exposures: Antenatal opioid prescribing during 3 time periods: the 100 days before delivery, between one year and 101 days before delivery, and between 1 and 2 years before delivery.

Main Outcomes and Measures: Incidence of neonatal abstinence syndrome according to hospital discharge records.

Results: The incidence of neonatal abstinence syndrome in Ontario increased 15-fold over the study period, from 0.28 per 1000 live births in 1992 to 4.29 per 1000 live births in 2011. During the final 5 years of the study period, we identified 927 deliveries of infants with neonatal abstinence syndrome in Ontario to mothers who were public drug plan beneficiaries. In this subset, 67% of women received an opioid prescription in the 100 days preceding delivery, including 53% who received methadone, an increase from 29% in the interval spanning 1 to 2 years before delivery ($p < 0.001$). Prescription for non-methadone opioids decreased from 38% to 17% ($p < 0.001$) over the same time periods.

Conclusions and Relevance: Most women in Ontario who deliver an infant diagnosed with neonatal abstinence syndrome have been prescribed an opioid before and during pregnancy. More careful prescribing of opioids to women of childbearing age may reduce the incidence of neonatal opioid withdrawal.

INTRODUCTION

Newborn infants exposed to opioids *in utero* frequently experience opioid withdrawal shortly after birth.[1;2] The associated clinical findings primarily relate to the effects of opioid withdrawal on the central nervous system (e.g., tremors, irritability, increased crying, myoclonus, and seizures), gastrointestinal tract (e.g., poor feeding, vomiting, diarrhea, and consequent intravascular volume depletion) and the autonomic nervous system (e.g., diaphoresis, temperature dysregulation and tachypnea). Collectively, these clinical findings are often referred to as the neonatal abstinence syndrome, although that term also applies to signs of withdrawal from other drugs such as antidepressants, benzodiazepines and alcohol.[1] Infants born to mothers who misuse opioids are also more likely to be premature, have low birth weight and have higher mortality rates.[3;4] Neonatal opioid withdrawal often necessitates care in a neonatal intensive care unit, and the resulting mother-infant separation may have a negative impact on the attachment between mother and child.[5] Primarily for these reasons, as well as the economic implications of increased health services utilization,[6] the prevention of neonatal opioid withdrawal has emerged as an important public health priority.[7-9]

Historically, the opioids most commonly responsible for neonatal opioid withdrawal have been heroin and methadone.[10;11] Over the last 20 years, coincident with the increased prescribing of opioids for chronic non-cancer pain,[12]

several studies have documented an increased incidence of neonatal abstinence syndrome.[6;8;13;14] However, no large studies have examined antenatal opioid prescribing records, and the degree to which the treatment of pain with prescription opioids contributes to the present-day incidence of neonatal abstinence syndrome is unknown. Due to concern that the rising incidence of neonatal abstinence syndrome reflects increased prescribing of opioids for pain, the National Association of Attorneys General recently asked the Food and Drug Administration to consider placing a related "black box warning" on opioids.[7]

We conducted a study with several objectives. First, we sought to determine trends in the annual incidence of neonatal abstinence syndrome in a large population over a 20 year period. Second, in a contemporary population of infants diagnosed with neonatal abstinence syndrome whose mothers were eligible for publicly funded prescription drugs at the time of delivery, we sought to determine the proportion of mothers who were treated with prescription opioids. Third, among these mothers, we compared demographic and health care utilization characteristics of those prescribed opioids with those who were not. We also compared the health care utilization and health outcomes of the corresponding infants.

METHODS

Setting

We conducted a retrospective, population-based study of births between January 1, 1992 and December 31, 2011 in Ontario, Canada. Ontario is an ethnically diverse province with a population of more than 13 million people, all of whom have public coverage for physician and hospital services. Prescription data are available for individuals aged 65 years and older as well as younger people who receive publicly-funded prescription drug coverage, who are primarily of lower socioeconomic status.

Data sources

The following databases were used to complete this study: the Canadian Institute for Health Information Discharge Abstract Database (data from all hospital admissions), the Ontario Drug Benefit database (records of prescription medications dispensed to public drug plan beneficiaries), the Registered Persons Database (demographic information including date of death for all Ontario residents), the National Ambulatory Care Reporting System (data from all emergency department visits), and the Ontario Health Insurance Plan database (data from all inpatient and outpatient physician services). These databases were anonymously linked using encrypted identifiers and have been shown to be complete and of high-quality and are routinely used to study the safety and effectiveness of prescription medications.[15-18]

Cohort identification

We identified all infants with a diagnosis of neonatal abstinence syndrome on their hospital discharge record over the study period (ICD-9 code of 779.5 from January 1, 1992 to March 31, 2002; ICD-10 code of P961 from April 1, 2002 to December 31, 2011). From April 1, 2002 onward, we matched infants to mothers using a unique maternal-newborn matching number. Prior to this date, the records of mothers and infants were linked by matching the hospitals they were admitted to and their admission and discharge dates. This algorithm, when applied to births after 2002, has a sensitivity of 96% and a specificity of 99%,and has been used previously for research purposes.[19;20]

We determined whether mothers were public drug plan beneficiaries at the time of delivery by examining antenatal prescription records. Because many women avoid prescription drugs during pregnancy, we used the period between 101 and 365 days prior to delivery to determine whether a woman had received publicly funded prescription drugs. We used this period to ensure that each mother had continuous eligibility for publicly funded prescription drugs during the 100 days prior to delivery, and in so doing minimized the risk of overestimating the rate of opioid prescribing in the period immediately before birth.

Opioid prescribing before delivery

We examined prescriptions dispensed to women who were eligible for publicly

funded prescription drugs at the time of delivery and who delivered an infant diagnosed with neonatal abstinence syndrome during the last 5 years of the study period. We focused on this period to better understand contemporary opioid prescribing patterns in mothers of infants diagnosed with neonatal abstinence syndrome. For each mother, we examined antenatal prescribing during 3 time periods: 100 days prior to delivery, 101 to 365 days prior to delivery and one to two years prior to delivery. We included both methadone and non-methadone opioids, but considered methadone separately because it is almost exclusively used for opioid dependence rather than the treatment of chronic non-cancer pain in Canada. In the 100 days preceding delivery, we also examined prescriptions for other psychotropic drugs, including sedative-hypnotics, barbiturates, anti-convulsants, cyclic antidepressants, non-cyclic antidepressants, antipsychotics, psychostimulants and lithium.

Demographic characteristics, health care utilization and outcomes

Among mothers of infants diagnosed with neonatal abstinence syndrome between 2007 and 2010 (to allow one year of follow up) who were eligible for publicly funded prescription drugs at the time of delivery, we compared demographic characteristics and of those who were prescribed opioids during the 100 days prior to delivery with those not prescribed opioids during this period. We also compared the health care utilization and outcomes of the corresponding infants. Specifically, we examined the infant's gestational age at birth, birth weight and sex, as well as the mother's age and neighborhood income quintile.

We also determined whether the mother had undergone a Cesarean section. For the infant, we examined various health care utilization variables and important health outcomes such as length of stay, physician visits and mortality.

Data analysis

We calculated the incidence of neonatal abstinence syndrome for each year of the study period, and used McNemar's test to compare opioid prescribing in public drug plan beneficiaries between the different antenatal time periods. We compared demographic characteristics, health care utilization and outcomes using chi-squared tests for categorical variables and the Kruskal-Wallis test for continuous variables. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

Ethical approval

This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre.

RESULTS

Incidence of neonatal abstinence syndrome

We identified 1901 infants diagnosed with neonatal abstinence syndrome during the study period. The incidence increased from 0.28 per 1000 live births in 1992 to 4.29 per 1000 live births in 2011, representing a 15-fold increase in incidence in two decades. Most of this increase occurred during the last 5 years of the study (Figure 1).

Antenatal opioid prescribing

During the last 5 years of the study period, 930 (49%) of the 1901 infants diagnosed with neonatal abstinence syndrome were born to 884 women who were eligible for publicly funded prescription drugs at the time of delivery. There were 3 pairs of twins among the 930 infants, resulting in 927 separate deliveries. In each of the 3 antenatal time periods studied, most women received one or more prescriptions for an opioid (Figure 2).

We observed a shift from other opioids to methadone as delivery approached. The proportion of women prescribed methadone increased from 29% at 1 to 2 years preceding delivery to 53% in the 100 days prior to delivery ($p < 0.001$). Conversely, the proportion of women prescribed a non-methadone opioid decreased from 38% at 1 to 2 years preceding delivery to 17% in the 100 days prior to delivery ($p < 0.001$).

Details regarding publicly funded opioids and other psychotropic medications prescribed during the 3 time periods we examined are provided in Table 1.

Health service utilization and health outcomes

Infant and maternal characteristics for neonatal abstinence syndrome cases between 2007 and 2010 are shown below in Table 2. Infants born to mothers prescribed opioids in the 100 days preceding delivery had a longer length of stay during the hospitalization where neonatal abstinence syndrome was diagnosed index hospitalization (median of 19 vs. 10 days, $p < 0.001$) and more outpatient physician encounters during the year after birth (median of 25 vs. 17 visits, $p < 0.001$) as compared to infants born to women with no opioid prescriptions. We found no difference in birth weight, gestational age at the time of delivery, or gender of the infant, and very few infants in this sample died during the year after birth. Women prescribed opioids during the 100 days prior to delivery were more likely to undergo a Cesarean section (30% vs. 22%, $p = 0.03$).

DISCUSSION

In this population-based study spanning 20 years, we observed a 15-fold increase in the incidence of neonatal abstinence syndrome in Ontario, most of it during the last 5 years. Approximately half of the mothers of these newborns were eligible for publicly funded prescription drugs, and the majority of these women were prescribed opioids before and during pregnancy. As women approached delivery, the proportion of women receiving prescriptions for methadone increased, while prescription of other opioids decreased.

The availability of prescription drug records in Ontario, and our ability to link these records with hospital discharge data, allowed us to definitively establish that the majority of neonatal abstinence syndrome cases occurred in infants born to mothers prescribed opioids during pregnancy. Furthermore, we found that almost two-fifths of public drug plan beneficiaries were receiving non-methadone opioids prior to conception. A substantial proportion of women received methadone, particularly in late pregnancy, which in Canada is prescribed almost exclusively for opioid addiction rather than for pain. In recent years in Ontario, addiction to prescription opioids has supplanted heroin addiction as the most common reason to initiate treatment with methadone.[21] Collectively, these observations suggest that most pregnant women treated with methadone in our study were previously dependent on opioids prescribed for pain. Our study provides the strongest evidence yet that more liberal prescribing of opioids for

chronic non-cancer pain is a major reason why the number of infants born with neonatal opioid withdrawal has increased.

Two previous studies documenting a similar increase in the incidence of neonatal abstinence syndrome in the United States did not have access to antenatal prescribing records.[6;13] Based on an analysis of hospital discharge data, Creanga et al found that 41.7% of infants diagnosed with neonatal abstinence syndrome in Washington State in 2008 were exposed to opioids. They also found that the type of drugs neonates were exposed to was unknown in approximately half the infants diagnosed with neonatal abstinence syndrome. In contrast, we found that 70% of infants diagnosed with neonatal abstinence syndrome in Ontario were born to mothers who were prescribed opioids in the 100 days prior to delivery. The proportion of infants exposed to opioids in our study would almost certainly be greater than 70%, because exposure to heroin and opioids can obviously occur without a prescription. In addition to demonstrating that the incidence of neonatal abstinence syndrome in the United States increased from 1.20 per 1000 births in 2000 to 3.39 per 1000 births in 2009, Patrick et al also observed that newborns with neonatal abstinence syndrome were more likely to have low birth weight and suffer respiratory complications. Patrick et al also observed that mean hospital charges for infants discharged with neonatal abstinence syndrome were $53 400 in 2009.

Our finding that the length of stay for infants born to mothers who were not prescribed opioids was much shorter than for infants born to mothers who were prescribed opioids has several possible explanations. First, methadone use is likely to be much more common in the second group, and is associated with a longer length of stay for infants with neonatal abstinence syndrome than exposure to opioids with a shorter duration of action. It is also possible that infants born to mothers who were not prescribed opioids were diagnosed with neonatal abstinence syndrome on the basis of maternal exposure to a different class of drugs, and consequently had a less severe illness than neonates exposed to opioids.

The results of our study suggest opportunities for prevention. Prescribers should consider the risks of addiction and subsequent neonatal opioid withdrawal before initiating opioid therapy for chronic non-cancer pain in women of childbearing age. To support this practice, the Food and Drug Administration should consider the request made by the National Association of Attorneys General for a “black box warning” indicating that opioid dependence in pregnancy is likely to result in neonatal opioid withdrawal.[7] Women of childbearing age who use opioids should be provided with counseling, particularly because unplanned pregnancies are very common amongst opioid-dependent women.[22] Such counseling might include a discussion about whether opioids can be tapered or discontinued, the need for contraception if pregnancy is not desired, and the risks and consequences of neonatal opioid withdrawal as well as opioid agonist therapy.[8;23]

Women dependent on opioids can be safely treated with methadone or buprenorphine,[8;24] although only methadone was readily available to our study population. Our observation that methadone use increases near the time of delivery indicates that many women are being identified as opioid-dependent during pregnancy. Despite this increase, our finding that approximately 40% of women who delivered a baby with neonatal abstinence syndrome did not receive methadone prior to delivery suggests that many women with opioid dependence are either not being identified during pregnancy or are declining treatment with methadone.

Several limitations of our work merit emphasis. First, we relied on administrative data to determine whether an infant experienced symptoms of neonatal opioid withdrawal. More physicians are aware of the diagnosis of neonatal abstinence syndrome than they were 20 years ago, and the increased incidence that we observed may be partly an artifact of greater awareness. Conversely, however, neonatal opioid withdrawal may still be under-recognized, particularly when symptoms are mild.[25] Second, although the diagnosis of neonatal abstinence syndrome is most commonly used when an infant experiences opioid withdrawal, some cases in our study may have represented withdrawal from other psychotropic medications. Our reliance on antenatal prescribing records also meant that we were unable to determine with certainty which opioids women were actually using. In particular, we have no information about heroin use or drug diversion. It is worth noting, however, that complications of heroin use in

Ontario were much less common than complications of prescription opioid use during the study period.[21;26] We also did not have information regarding buprenorphine use, because the formulation of buprenorphine that is used in pregnancy is only available through a special federal program in Canada.[8] However, for this same reason, it is likely that only a very small number of women in our study would have been prescribed buprenorphine.

In conclusion, we observed a large increase in the number of infants born with neonatal abstinence syndrome over a 20 year period in Ontario, especially during the last 5 years. We found that a substantial proportion of women who deliver babies with neonatal opioid withdrawal are prescribed opioids indicated for the treatment of chronic pain before and during pregnancy. Our findings support the need for strategies to reduce the incidence of neonatal opioid withdrawal.

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CONFLICTS OF INTEREST

Dr. Mamdani has served on Advisory Boards for Hoffman La Roche, Glaxo Smith Kline, Eli Lilly and Company, Bristol-Myers Squibb, Novartis, Novo Nordisk,

AstraZeneca and Pfizer. The rest of the authors have no potential conflicts of interest to disclose.

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Figure 1. Annual incidence of neonatal abstinence syndrome in Ontario, 1992 to 2011.

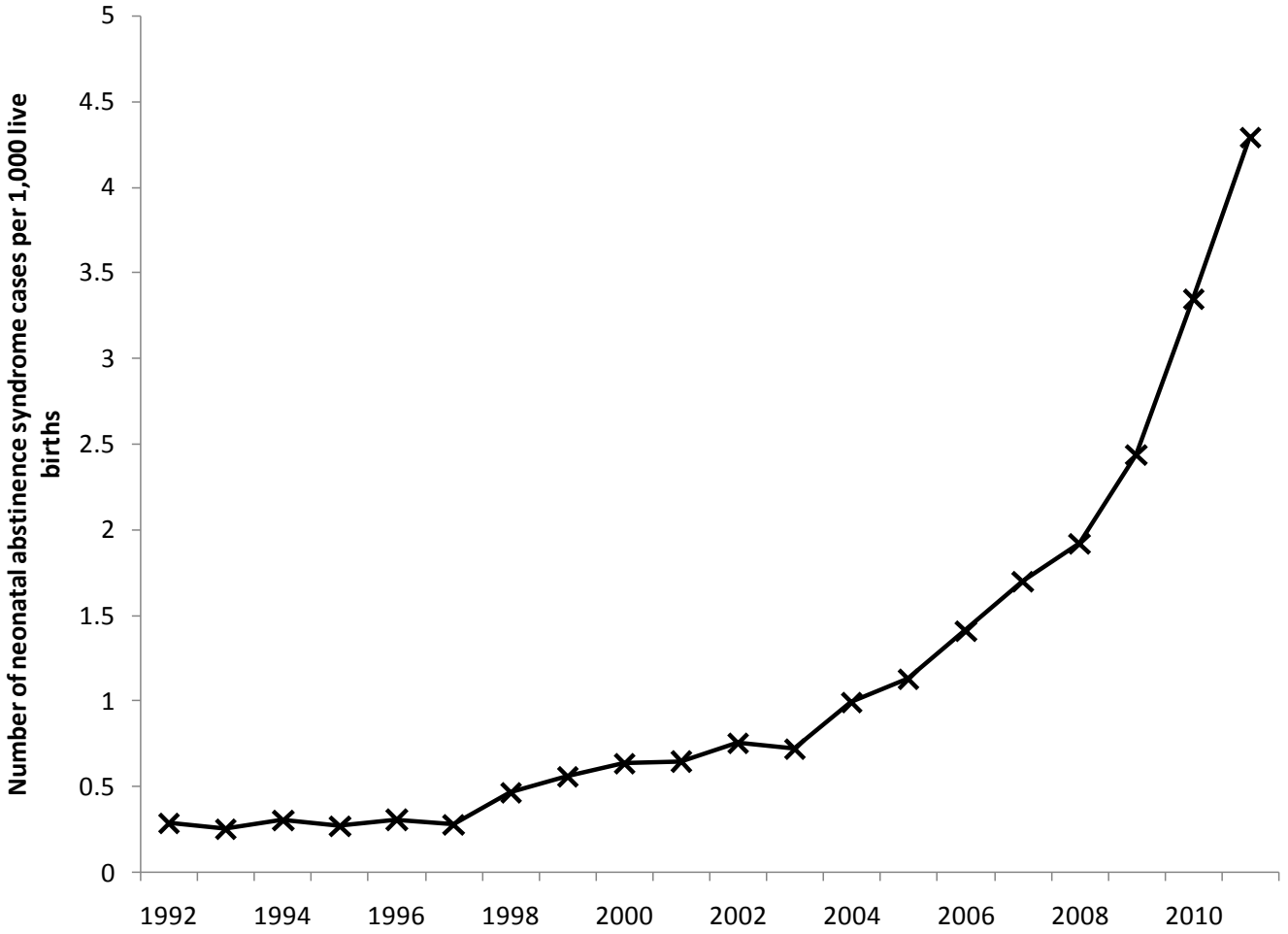

Figure 2. Opioid prescribing before 927 deliveries of infants diagnosed with neonatal abstinence syndrome between 2007 and 2011, during 3 time periods before delivery.

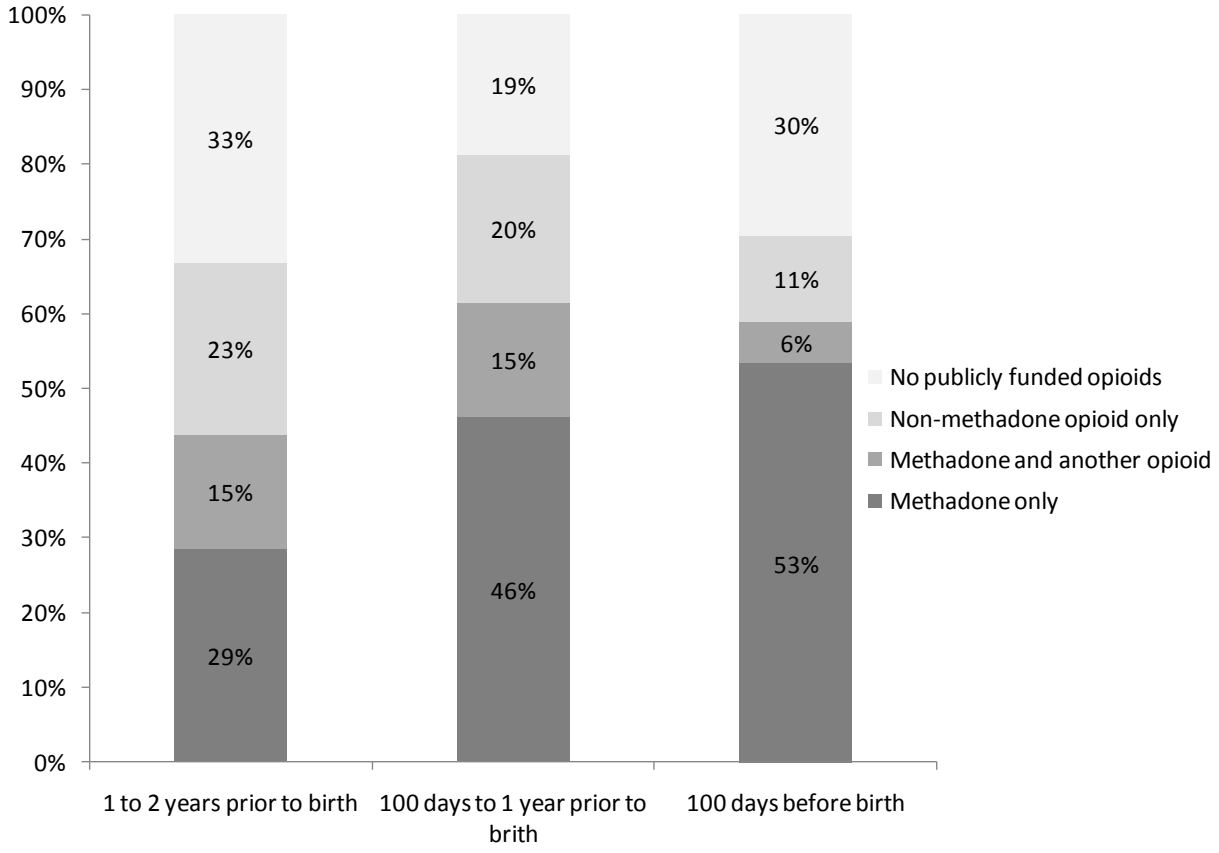

Table 1. Publicly funded psychotropic prescriptions before 927 deliveries of infants diagnosed with neonatal abstinence syndrome.

	1 to 2 years prior to birth	101 days to 1 year prior to birth	100 days before birth
Any opioid prescription – no. (%)	619 (67)	753 (81)	653 (71)
Opioid prescribed for addiction – no. (%)	406 (44)	570 (61)	547 (59)
Methadone only – no. (%)	265 (29)	428 (46)	494 (53)
Methadone and another opioid – no. (%)	141 (15)	142 (15)	53 (6)
Non-methadone opioids – no. (%)	354 (38)	325 (35)	159 (17)
Oxycodone – no. (%)	220 (24)	185 (20)	85 (9)
Hydromorphone – no. (%)	33 (4)	29 (3)	17 (2)
Morphine – no. (%)	35 (4)	37 (4)	30 (3)
Fentanyl – no. (%)	16 (2)	13 (1)	10 (1)
Codeine – no. (%)	196 (21)	161 (17)	51 (6)
Other – no. (%)	11 (1)	≤ 5*	≤ 5*
Other psychotropic medications – no. (%)	495 (53)	511 (55)	283 (31)
Sedative/hypnotics – no. (%)	247 (27)	232 (25)	123 (13)
Barbiturates – no. (%)	0 (0)	0 (0)	0 (0)
Anticonvulsants – no. (%)	16 (2)	14 (2)	≤ 5*
Cyclic antidepressants – no. (%)	178 (19)	157 (17)	38 (4)
Non-cyclic antidepressants – no. (%)	324 (35)	312 (34)	155 (17)
Antipsychotics – no. (%)	164 (18)	165 (18)	85 (9)
Stimulants – no. (%)	34 (4)	31 (3)	16 (2)
Lithium – no. (%)	16 (2)	17 (2)	≤ 5*

*In accordance with institutional policy, the exact number is suppressed when the cell size is ≤5.

Table 2.Neonatal and maternal characteristics of neonatal abstinence syndrome cases born to public drug plan beneficiaries.

	Opioids prescribed in the 100 days prior to birth (N = 421)	Opioids not prescribed in the 100 days prior to birth (N = 197)	P value
Infant characteristics			
Gestational age in weeks (median, IQR)	39 (37-40)	38 (37-40)	0.15
Birth weight in grams (median, IQR)	2,990 (2,685-3,391)	2,947 (2,615-3,370)	0.28
Male sex (n, %)	202 (48)	97 (49)	0.77
Maternal characteristics			
Age (median, IQR)	27.5 (24.5-31.8)	27.8 (24.7-32.3)	0.46
Cesarean section (n, %)	127 (30)	43 (22)	0.03
Neighborhood income quintile (N, %)			
Lowest	210 (50)	83 (42)	0.07
Second lowest	83 (20)	50 (25)	0.11
Middle	58 (14)	31 (16)	0.52
Second highest	38 (9)	19 (10)	0.80
Highest	31 (7)	12 (6)	0.56
First NAS			

hospitalization (index)			
First NAS diagnosis during the birth hospitalization (n, %)	396 (94)	175 (89)	0.02
Neonatal intensive care unit admission for infant (n, %)	339 (81)	155 (79)	0.59
Hospital length of stay in days (median, IQR)	19 (9-31)	10 (5-20)	<.0001
Year following birth (for baby)			
Mortality (%)	≤5*	0 (0)	N/A
Outpatient physician encounters (median, IQR)	25 (16-38)	17 (12-27)	<0.001
Number of hospitalizations (median, IQR)	1 (1-1)	1 (1-1)	0.834
Number of emergency department visits (median, IQR)	1 (0-2)	0 (0-2)	0.004

*In accordance with institutional policy, the exact number is suppressed when the cell size is ≤5.