

# Exposure to Maternal Medications: A Case of Lockjaw

*Brandi Newby and Rebecca Sherlock*

## INTRODUCTION

Many infants are exposed in utero to psychoactive medications. Despite the frequency of this occurrence, there is little information regarding outcomes for these infants. In each case, the health care team must attempt to balance maternal mental health while optimizing the safety of the developing infant. Women with mental illness that is successfully treated before pregnancy will usually continue the same treatment throughout the pregnancy, as the risks of untreated mental illness often outweigh the potential risks of the medications to the infant.<sup>1</sup> This report describes an infant who experienced lockjaw (trismus) following exposure to multiple psychoactive medications during the pregnancy.

## CASE REPORT

An infant was delivered at 35 weeks gestational age by emergent cesarean section because of preterm labour and fetal tachycardia.\* The mother had a history of heroin and cocaine use and was receiving methadone 70 mg per day. The mother was also receiving treatment for psychosis, depression, and anxiety with quetiapine 300 mg sustained release and 300 mg immediate release per day, escitalopram 20 mg per day, nortriptyline 20 mg per day, and gabapentin 1800 mg per day. For control of her “seizure”-like symptoms, she was also receiving benzotropine 1.5 mg per day. Other regular medications included zopiclone and rabeprazole. The mother was receiving her medications daily from her community pharmacy. As the pregnancy had not been detected until about 2 weeks before the delivery, the medications had not been changed for

pregnancy, and it appeared from her records that they had not been adjusted for several weeks before the delivery.

The infant had a birth weight of approximately 2.6 kg and APGAR scores of 6 and 8 at 1 and 5 min, respectively. The newborn examination revealed primitive reflexes and mildly decreased muscle tone. The infant required positive pressure ventilation for 2 min followed by continuous positive airway pressure for 2 min to manage intermittent breathing and low oxygen saturation. Transient tachypnea of the newborn was suspected, and the infant was transferred to the neonatal intensive care unit for further observation. Ampicillin and gentamicin were initiated, but were discontinued at 48 h with negative blood culture results. The results of liver function and blood chemistry tests, including blood urea nitrogen, serum creatinine, and C-reactive protein, were all unremarkable. A complete blood count revealed mild thrombocytopenia (platelet count  $122 \times 10^9/L$ ). The results of head ultrasonography on day 1 of life were normal, and the urine was negative for cocaine and heroin.

Once respiratory status had stabilized, attempts were made to bottle-feed the infant starting at about 8 h of age. At that time, clenching of the jaw was noted, and staff were unable to effectively insert a bottle; feeding by nasogastric tube was required. Because of the exposure to methadone, neonatal abstinence syndrome scoring was initiated with an adapted Finnegan scoring system.<sup>2</sup> According to this system, opioid replacement is often commenced when the infant has consecutive scores of 8 or more. This infant had a score of 10 at both 5 and 8 h of life because of symptoms of suspected withdrawal, including high-pitched cry, increased muscle tone, tremors, and sleep disturbance. These specific symptoms were most likely due to methadone withdrawal; therefore, following these consecutive elevated scores, morphine was started at about 9 h of life.

On days 2 and 3 of life, the jaw remained clenched. Expressed breast milk was given twice on day 3 only and was then withheld because of concerns about the lockjaw. The

\*Consent from the patient's mother to publish this case report was not obtained because she was not available and approval by the research and ethics board was not a standard requirement at the authors' institution at the time of the event. Certain demographic and other identifying details have been omitted to maintain privacy.

Naranjo probability scale<sup>3</sup> suggested a probable association between the extrapyramidal symptom of lockjaw, defined in this case as a clenched jaw that prevented the mouth from being opened, and in utero exposure to maternal medications. Medications used to manage extrapyramidal symptoms in adults, such as benzotropine and diphenhydramine, are contraindicated for neonates; in this case, the risks of administering either of these drugs were felt to outweigh any potential benefits and therefore no specific treatment was initiated.<sup>4</sup>

On day 4, the infant spontaneously opened the mouth and started demonstrating an ability to suck. Breast milk was not restarted because of concerns about social drug use by the mother. On day 5, the infant was able to take small amounts of formula by bottle. The neonatal abstinence syndrome score was assessed every 3 h and remained between 7 and 17 from birth through day 8. The dose of morphine was increased daily until day 8 of life, with a maximum dose of approximately 0.6 mg/kg per day. On day 7, because of continued elevation of the neonatal abstinence syndrome scores, mostly because of central nervous system disturbances, phenobarbital was added to reduce discontinuation symptoms likely resulting from the mother's multiple psychoactive medications.

On day 9 the neonatal abstinence syndrome scores were less than 10 and remained below 10 for the duration of the hospital stay. The morphine was tapered every other day starting on day 11 and was discontinued on day 45. The phenobarbital was tapered starting on day 28 and was discontinued on day 44. The infant reached full bottle feeds at about 38 weeks postmenstrual age. The infant was discharged at about 42 weeks postmenstrual age with normal results on neurologic examination. Follow-up examination by the pediatrician at about 3 months of age also showed normal neurologic status.

## DISCUSSION

Extrapyramidal symptoms can occur with many medications. Antipsychotics are known to induce extrapyramidal symptoms, with an incidence up to 90% for some typical agents.<sup>5</sup> The risk is generally less with atypical than with typical agents, and for quetiapine specifically there is an incidence of about 1% to 13%.<sup>4</sup> It is not known, however, if atypical agents pose a lower risk to infants exposed during pregnancy.<sup>6</sup> In Australia<sup>6</sup> and the United States,<sup>7</sup> a total of 88 cases of extrapyramidal or withdrawal symptoms were reported in infants following in utero exposure to antipsychotics, including atypical agents such as quetiapine. In 2011, the US Food and Drug Administration changed labelling requirements for all antipsychotics to include the risk of extrapyramidal and withdrawal symptoms in infants born to mothers who are taking antipsychotic medications during the third trimester.<sup>7</sup> In adults, selective serotonin reuptake inhibitors are also known to induce extrapyramidal symptoms, although for escitalopram the incidence is reported

to be less than 1%.<sup>4</sup> Tricyclic antidepressants, such as nortriptyline, have also been reported to cause extrapyramidal symptoms, although these are infrequent.<sup>8</sup> The other maternal medications used in this case do not usually induce extrapyramidal symptoms in adults.

In the case reported here, the infant's lockjaw was probably related to in utero exposure to maternal medications. Assuming a similar incidence for extrapyramidal symptoms in adults and infants, the medication most likely causing the lockjaw would be quetiapine. In adults, when antipsychotics are used concurrently with selective serotonin reuptake inhibitors, the risk of an adverse event is increased.<sup>8</sup> Whether the extrapyramidal symptom in the case reported here was due to a single agent or to the combination is not known. Similar to this case, most of the cases of extrapyramidal symptoms reported in neonates from Australia<sup>6</sup> and the United States<sup>7</sup> had multiple confounding factors, including concomitant medications such as antidepressants, delivery factors, and social drug use. A genetic predisposition may also have been a confounding factor in the current case,<sup>9</sup> as the mother had experienced an extrapyramidal symptom, which she described as "seizure"-like symptoms, which was treated with benzotropine for several weeks before the delivery.

It is often difficult to distinguish between extrapyramidal symptoms and symptoms associated with medication withdrawal. The symptoms commonly observed in infants experiencing withdrawal in the neonatal intensive care unit include irritability, abnormally increased or decreased muscle tone, tremor, sleep disturbances, breathing difficulties, and feeding problems. As many of the reported extrapyramidal symptoms tend to be related to abnormal tone or limb movement in neonates, these symptoms are often not explicitly defined or separated from withdrawal symptoms. However, the specific extrapyramidal symptom of lockjaw is not usually observed as a symptom of withdrawal in neonates. As far as we know, this specific symptom has not been previously reported in infants following exposure to psychoactive medications in pregnancy.

Generally, extrapyramidal or withdrawal symptoms occur soon after birth and resolve within a few days.<sup>6,7</sup> When considering the pharmacokinetic parameters of the medications in this case, it appears that the lockjaw may have been due to lingering maternal medication. In adults, quetiapine has an elimination half-life of about 6 h and its metabolite about 12 h; escitalopram and nortriptyline each have a half-life of about 30 h.<sup>4</sup> The half-life of each medication is expected to be longer in infants; therefore, resolution of the lockjaw by day 4 is consistent with anticipated medication elimination.

In this case, the infant experienced lockjaw as an adverse effect of exposure to maternal medications, most likely quetiapine or a combination of medications. Health care

professionals need to be aware that extrapyramidal symptoms can occur in neonates who have been exposed to psychoactive medications in utero and must ensure that pregnant women taking such medications are appropriately educated.

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**Brandi Newby**, BScPharm, ACPR, is a Clinical Pharmacy Specialist in the Neonatal Intensive Care Unit, Surrey Memorial Hospital, Surrey, British Columbia.

**Rebecca Sherlock**, MD, FRCPC, is a Physician in the Department of Neonatology, Surrey Memorial Hospital, Surrey, British Columbia.

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#### Address correspondence to:

Brandi Newby  
Pharmacy Department  
Surrey Memorial Hospital  
13750 96th Avenue  
Surrey BC V3V 1Z2

**e-mail:** [Brandi.newby@fraserhealth.ca](mailto:Brandi.newby@fraserhealth.ca)

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