JPPT | Case Series

Gabapentin as Adjunctive Therapy in Neonatal Opioid Withdrawal Syndrome: A Case Series

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OBJECTIVE We describe a single center experience with gabapentin as adjunctive therapy in infants with neonatal opioid withdrawal syndrome (NOWS).

METHODS We performed a retrospective chart review of infants receiving gabapentin for NOWS. Data points collected included patient's sex, gestational age, maternal opioid exposure, NOWS medication dosing and length of therapy, number of failed wean attempts, time to successful morphine wean and duration of morphine wean, length of stay in the neonatal intensive care unit (NICU), and NOWS medications at discharge.

RESULTS Six infants received gabapentin as adjunctive treatment for NOWS. All infants failed 2–4 morphine weans before initiation of gabapentin despite the addition of clonidine. All infants that received gabapentin were successfully weaned off morphine. The time to wean off morphine after gabapentin initiation varied from 4–35 days. Maximum gabapentin doses ranged from 15 – 42.7 mg/kg/day. Five infants were discharged from the NICU on gabapentin.

CONCLUSIONS Gabapentin appeared to facilitate successful morphine weans in six patients with NOWS who were previously unable to wean despite the initiation of clonidine.

ABBREVIATIONS OUD, opioid use disorder; NOWS, neonatal opioid withdrawal syndrome; AAP, American Academy of Pediatrics; NICU, Neonatal Intensive Care Unit; THC, tetrahydrocannabinol.

KEYWORDS case series; clonidine; gabapentin; morphine; neonatal opioid withdrawal syndrome; neonatal abstinence syndrome

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Introduction

Opioid use disorder (OUD) is a well-known problem in the United States affecting pregnant women with increasing frequency.[1] Maternal OUD rates at delivery have more than doubled from 3.5 cases per 1 000 deliveries in 2010 to 8.2 per 1 000 deliveries in 2017.[2] This increase in opioid use while pregnant directly corresponds to an increase in the incidence of neonatal opioid withdrawal syndrome (NOWS) at birth, a constellation of physiologic effects from cessation of chronic *in utero* opioid exposure. According to data from the Healthcare Cost and Utilization Project, 7.3 newborns were diagnosed with NOWS for every 1 000 hospital births nationwide in 2017.[3] This increase has implications both for the affected infant, as well as the healthcare system. Infants with NOWS are at risk for adverse health outcomes including seizures and have longer and more expensive hospital stays than other infants.[4]

In a recent policy statement, the American Academy of Pediatrics (AAP) recommends non-pharmacologic therapy as the preferred first-line treatment for infants with NOWS.[5] For infants who continue to exhibit signs of withdrawal despite non-pharmacologic treatment strategies, either morphine or methadone is recommended as a first-line pharmacologic agent. However, some infants fail to respond to opioid monotherapy or are unable to wean and require additional agents for treatment of symptomatic withdrawal. In fact, approximately twenty-five percent of infants require the use of two or more pharmacologic agents to control their withdrawal symptoms.[4] Clonidine and phenobarbital have been used in this role; however, phenobarbital use is discouraged in AAP guidance due to well-documented adverse neurodevelopmental outcomes leaving clonidine as the principal second-line agent.[5,11] Despite the addition of clonidine, there remains a subset of infants who are unable to wean opioid therapy, warranting consideration of a third-line agent.

Gabapentin has the potential for use in the treatment of NOWS due to a unique mechanism of action, binding voltage-gated calcium channels containing the alpha-2-delta-1 subunit in the locus coeruleus.[6] After binding,

gabapentin prevents the influx of calcium into neurons and blocks the release of an excess of norepinephrine which contributes to the symptoms of NOWS. In adults experiencing opioid withdrawal, gabapentin has been shown to reduce withdrawal symptoms as well as overall opioid exposure.[7] In neonates, there is little information available describing the use of gabapentin for any indication. Limited series describe gabapentin efficacy for neuropathic pain, and even less published evidence characterizes utilization for NOWS.[8,9] A single case report describes the use of gabapentin as a third-line agent for an infant with NOWS who failed several methadone weans despite the addition of clonidine.[10] After the addition of gabapentin, the infant was able to successfully wean off methadone. Over several years, a multi-disciplinary group of pharmacists, neonatologists, and neonatal neurologists at our center collaboratively used gabapentin for NOWS in patients unable to wean morphine despite the addition of clonidine. In this study, we describe our institutional experience with the patient population that received gabapentin for NOWS and their response to the medication.

Methods

Cohort Selection. We retrospectively identified all infants with a diagnosis of NOWS admitted to the Neonatal Intensive Care Unit (NICU) at St. Louis Children's Hospital who received gabapentin between June 1st, 2018 and August 14th, 2020. Patients were included if they were exposed to an opioid prenatally based on maternal drug testing or self-report and received gabapentin as therapy in addition to morphine and clonidine for treatment of NOWS.

Standard Clinical Practice. To assess the severity of withdrawal symptoms, all patients at risk for NOWS at our institution are evaluated using the modified Finnegan score every three hours.[11] Infants with three consecutive scores ≥8 or two consecutive scores ≥12 were started on oral morphine 0.4 mg/mL after optimization of nonpharmacologic care. Per protocol, morphine 0.04 – 0.1 mg/kg/dose was given orally every three hours with the initial dosing dependent upon Finnegan scores at therapy initiation. Morphine was typically increased by 0.02 mg/kg/dose for infants with three scores ≥8 or two scores ≥12 in a 24-hour period. When infants reach the maximum dose of morphine (typically 1 mg/kg/day), clonidine could be added at a dose of 1 mcg/kg/dose every 3 hours. Clonidine may also be initiated by the attending neonatologist if the infant demonstrated an intolerance of morphine weans; intolerance was defined as three Finnegan scores ≥8 or two scores ≥12 in any 24-hour period following a wean of pharmacotherapy. Clonidine dosing was increased by 1 mcg/kg/dose as needed based on Finnegan scores as previously described to a maximum dose of 5 mcg/kg/dose every 3 hours, or 40 mcg/kg/day. Once Finnegan scores were stable (<8 or down trending) for 12–24 hours, morphine could be weaned by 10 – 20% of the maximum dose every 24 to 48 hours to a minimum dose of 0.04 mg every three hours before discontinuation. After discontinuation of morphine, clonidine was weaned by 1 mcg/kg/dose every 24 to 48 hours for consistent Finnegan scores <8 to a minimum of 1 mcg/kg/dose every 3 hours before discontinuation. Patients were observed for a minimum of 48 hours after discontinuation of any pharmacologic agent prior to discharge.

Gabapentin Usage. The decision to add gabapentin was at the discretion of the attending neonatologist. The standard gabapentin dosing strategy used included a stepwise titration starting at 5 mg/kg daily for one day, followed by 5 mg/kg twice daily for one day, and then 5 mg/kg three times daily. Doses were further increased by 5 mg/kg/day as needed to a typical maximum dose of 30 mg/kg/day divided three times daily.

Data Collection. Data points recorded were maternal characteristics including tobacco or reported drug use; infant demographic information including sex, gestational age, and birth weight; medication information including the starting and maximum daily dose and days of therapy for morphine, clonidine, phenobarbital, and gabapentin, day after birth each medication was started; wean information for morphine and clonidine including the time to successful morphine wean, duration of therapy until morphine and clonidine discontinuation, and the number of failed morphine wean attempts; feeding regimen; days spent in the NICU; and if the patient was discharged on clonidine and/or gabapentin. A successful morphine wean was defined as the first morphine dose reduction that did not subsequently require dose escalation. Medical records were also reviewed for potential adverse events within 24 hours of gabapentin initiation or titration, including somnolence, bradycardia, tachycardia, increased emesis, and increased irritability.[12] This study was approved by the Institutional Review Board at Washington University in St. Louis.

Case Series. A total of 191 infants were admitted with a diagnosis of NOWS during the study period. Seven patients met all inclusion criteria including a NOWS diagnosis and treatment with morphine, clonidine, and gabapentin in our NICU during the study period. One patient was excluded as gabapentin was initiated after morphine discontinuation. Six patients were included in the final case series. Patient cases are summarized in Table 1 and a detailed description of each case is included below.

Case 1. Infant 1 is a 39-week gestational age male infant born weighing 2.59 kg. He was exposed to 220 mg of methadone daily in utero with unknown tobacco exposure. Infant 1 received a maximum morphine dose 0.96 mg/kg/day and a maximum clonidine dose of 24.1 mcg/kg/day. He was successfully weaned to 0.1 mg/kg/day of morphine but failed three further attempts to wean morphine before gabapentin was

Table 1. Summary of patients receiving gabapentin for NOWS

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Male	Female	Male	Female	Male
Gestational age (completed weeks)	39	37	41	39	35	38
Birth weight (kg)	2.59	2.67	3.24	3	3.1	2.79
Morphine duration (days)	35	64	40	50	48	50
Maximum morphine dose (mg/kg/day)	0.96	1.38	1.23	3.2	0.42	1
Time to wean off morphine after gabapentin initiation (days)	4	31	22	17	4	35
Clonidine duration (days)	40	72	35	52	26	48
Maximum clonidine dose (mcg/kg/day)	24.1	41	16	8	16	15
Inpatient gabapentin duration (days)	17	43	30	23	12	36
Maximum gabapentin dose (mg/kg/day)	25	42.7	15	24.8	22.5	41.3
Days in neonatal intensive care unit	47	75	52	60	57	51
Discharge medications	Gabapentin	Gabapentin + clonidine	None	Gabapentin	Gabapentin	Gabapentin + clonidine

considered. Infant 1 started on gabapentin after 31 days of morphine at an initial dose of 15 mg/kg/day and titrated to a maximum dose of 25 mg/kg/day over 3 days. Morphine was discontinued 4 days after gabapentin initiation. Clonidine was weaned beginning 8 days after gabapentin initiation and discontinued prior to discharge. The infant received Enfamil Gentlease throughout their admission. In total, infant 1 received 35 days of morphine, 40 days of clonidine, and 17 days of gabapentin during the NICU hospitalization. Infant 1 was discharged home on gabapentin after 47 days in the NICU.

Case 2. Infant 2 is a 37-week gestational age male born weighing 2.67 kg. He was exposed to tetrahydrocannabinol (THC), cocaine, fentanyl, and tobacco in utero. Infant 2 received a maximum morphine dose of 1.38 mg/kg/day and a maximum clonidine dose of 41 mcg/kg/day. The infant received Enfamil formula after birth and was transitioned to Enfamil Gentlease on day 7 after birth. Because of elevated Finnegan scores, infant 2 received phenobarbital for 4 days at a dose of 2 mg/kg/day divided every 12 hours beginning on day 10 after birth. He had two failed morphine wean attempts prior to gabapentin initiation. Infant 2 started on gabapentin after 33 days of morphine treatment with an initial dose of 5 mg/kg/day and titrated to a maximum dose of 42.7 mg/kg/day over 9 days. Infant 2 had his first successful morphine wean 12 days after gabapentin initiation, and discontinued morphine 31 days after gabapentin initiation. Clonidine was weaned beginning

33 days after gabapentin initiation. In total, infant 2 received 64 days of morphine, 72 days of clonidine, and 43 days of gabapentin during NICU hospitalization. Infant 2 was discharged home on clonidine and gabapentin after 75 days in the NICU.

Case 3. Infant 3 is a 41-week gestational age female born weighing 3.24 kg. She was exposed to methadone 65 mg daily, fentanyl, heroin, and tobacco in utero. Infant 3 received a maximum morphine dose of 1.23 mg/kg/day and a maximum clonidine dose of 16 mcg/kg/day. She had 2 failed morphine wean attempts prior to gabapentin initiation. Infant 3 was started on gabapentin after 18 days of morphine with an initial dose of 5 mg/kg/day and titrated to a maximum dose of 15 mg/kg/day over 2 days. Infant 3 had her first successful morphine wean 15 days after initiating gabapentin and discontinued morphine 22 days after gabapentin initiation. Clonidine was weaned 25 days after gabapentin initiation and discontinued before discharge. Gabapentin was weaned 25 days after it was started and discontinued after 4 days of weaning. The infant received Enfamil formula throughout their admission. In total, infant 3 received 40 days of morphine, 35 days of clonidine, and 30 days of gabapentin during NICU hospitalization. Infant 3 was discharged home with no NOWS medications after 52 days in the NICU.

Case 4. Infant 4 is a 39-week gestational age male born weighing 3 kg. He was exposed to methadone 300 mg daily, amphetamines, THC, and tobacco in utero. This infant underwent therapeutic hypothermia treatment for suspected hypoxic-ischemic encephalopathy and was initially on a morphine infusion to prevent shivering and discomfort. After therapeutic hypothermia was complete, the infant was converted to oral morphine for treatment of NOWS symptoms. Infant 4 received a maximum morphine dose of 3.2 mg/kg/day and a maximum clonidine dose of 8 mcg/kg/day. He had 4 failed morphine wean attempts prior to gabapentin initiation. Infant 5 was started on gabapentin after 33 days of morphine at an initial dose of 5 mg/kg/day and titrated to a maximum dose of 24.8 mg/kg/day over 12 days. The infant received Enfamil formula initially and was transitioned to Enfamil Gentlease at day 41 after birth. He had his first successful morphine wean 11 days after gabapentin initiation and discontinued morphine 17 days after gabapentin initiation. Clonidine was first successfully weaned 18 days after gabapentin initiation. In total, infant 4 received 50 days of morphine, 52 days of clonidine, and 23 days of gabapentin during NICU hospitalization. Gabapentin was not weaned during the hospital stay and the infant was discharged home to continue gabapentin after 60 days in the NICU.

Case 5. Infant 5 is a 35-week gestational age female born weighing 3.1 kg. She was exposed to buprenorphine 8 mg daily, amphetamine, methamphetamine, heroin, and tobacco in utero. Infant 5 received a maximum morphine dose of 0.42 mg/kg/day and a maximum clonidine dose of 16 mcg/kg/day. She had four failed morphine wean attempts prior to gabapentin initiation. The infant received Enfamil formula initially and was transitioned to Enfamil Gentlease at 42 days after birth. Infant 5 was started on gabapentin after 44 days of morphine at an initial dose of 5 mg/kg/day and titrated to a maximum dose of 22.5 mg/kg/day over 9 days. She had her first successful morphine wean 1 day after gabapentin initiation and discontinued 4 days after gabapentin initiation. Clonidine was weaned 6 days after gabapentin initiation, with escalation of gabapentin for persistent hypertonia after discontinuation of clonidine. Gabapentin was not weaned prior to discharge. In total, infant 5 received 48 days of morphine, 26 days of clonidine, and 12 days of inpatient gabapentin during NICU hospitalization. She was discharged home on gabapentin after 57 days in the NICU.

Case 6. Infant 6 is a 38-week gestational age male born weighing 2.79 kg. He was exposed to buprenorphine 30 mg daily (<1 week), methamphetamine, fentanyl, cocaine, diazepam, and tobacco in utero. Infant 6 received a maximum morphine dose of 1 mg/kg/day and a maximum clonidine dose of 15 mcg/kg/day. He had 3 failed morphine wean attempts prior to gabapentin initiation. Infant 6 was started on gabapentin after 15 days of morphine at an initial dose of 5 mg/kg/day and titrated to a maximum dose of 41.3 mg/kg/day over 31 days. He had his first successful morphine wean 25 days after gabapentin initiation and discontinued morphine 35 days after gabapentin initiation. Clonidine and gabapentin were not weaned as an inpatient. The infant received Enfamil Gentlease throughout their admission. In total, infant 6 received 50 days of morphine, 48 days of clonidine., and 36 days of gabapentin during NICU hospitalization and was discharged on clonidine and gabapentin after 51 days in the NICU.

Discussion

In this report, we describe the largest case series of patients to date who received gabapentin as adjunctive therapy for treatment of NOWS. There are no recommendations or guidelines for potential therapeutic options for infants with NOWS who continue to exhibit symptoms of opioid withdrawal while receiving both an opioid and clonidine. This series describes the pharmacologic approach and outcomes of six challenging cases at a single center, highlighting the need for further research in this subset of patients with NOWS.

Of the six infants included in this report, all were receiving adjunctive clonidine and had repeatedly failed morphine weans before the initiation of gabapentin. Additionally, most infants required higher doses of morphine (≥1 mg/kg/day), although gabapentin was initiated across a wide range of morphine doses (0.1 – 3.2 mg/kg/day). The time from gabapentin initiation to first successful morphine wean varied from one to twenty-five days with all six infants ultimately weaned

off morphine prior to hospital discharge between four and 35 days after initiation of gabapentin. Additionally, four of the six infants were weaned off clonidine prior to discharge. Clonidine for these patients spanned a wide dosing range. This is possibly indicative of two different usage cases for clonidine: higher dosing for patients whose symptoms were not controlled on morphine, and lower doses for patients unable to wean from morphine monotherapy. Although there is no information on gabapentin dosing in NOWS, it is notable that most of our patients started at 5 mg/kg/day and were titrated to a maximum dose of 15–25 mg/kg/day reflective of limited published experience in the treatment of neuropathic pain in infants, although two patients required > 40 mg/kg/day.[12] We did not detect any adverse events commonly associated with gabapentin in this cohort during a 24 hour observation period selected based on the relatively rapid time to peak of 2–3 hours. No patient had their gabapentin dose weaned prior to the discontinuation of morphine and five patients were discharged home on gabapentin.

While failure of initial therapy for NOWS is relatively common, with an incidence of ~25%, the only published data regarding the use of gabapentin for infants with NOWS is a single case report by Brzenski and Greenberg describing an infant unable to wean completely from methadone despite the addition of clonidine. This infant was able to successfully wean from methadone 4 weeks after the initiation of gabapentin.[10] In this case, gabapentin was initiated at 10 mg/kg/day and titrated to 20 mg/kg/day over one week. Like our case series, the patient failed two opioid weans and was receiving clonidine prior to gabapentin initiation; however, most patients in our cohort received higher doses of clonidine (> 15 mcg/kg/day) which may indicate more refractory disease. Despite this, most of the infants we describe were able to wean off opioid therapy in less than 4 weeks, with 4/6 infants weaned off morphine within 22 days of starting gabapentin. This could be due to the differences in the institutional weaning protocols which may also reflect the pharmacokinetic differences between opioid therapies, with more frequent weans attempted in the infants included in our report due to the shorter half-life of morphine as compared to methadone. We also report higher doses and a faster gabapentin dose titration in our case series compared to Brzenski and Greenberg, which may have affected our ability to wean morphine. Finally, the infant in the other case report was discharged on gabapentin, like the infants from our institution. That infant was also discharged on clonidine as were 2/6 infants from our institutional cohort. The case report describes tapering of outpatient clonidine over four weeks followed by gabapentin over two additional weeks; our case series is limited by inconsistent access to outpatient records. With this potential exception, our experience with gabapentin as adjunctive treatment for NOWS resulted in a similar outcome to the infant described by Brzenski and Greenberg.

Phenobarbital has historically been used as a second-line agent for infants with NOWS refractory to opioid therapy. However, there are well-documented neurodevelopmental adverse effects attributed to long-term use of phenobarbital in infants. In one study of patients who received long-term maintenance phenobarbital for seizures, patients had a mean IQ 8.4 points lower than their counterparts who did not receive phenobarbital, and this difference persisted even after phenobarbital had been tapered and discontinued.[13] Additional studies have also supported adverse neurodevelopmental effects related to phenobarbital use in the neonatal period.[14] While our experience does not demonstrate any apparent short term adverse outcomes related to gabapentin use in these infants, we acknowledge that we did not assess long term outcomes associated with its use nor are we aware of robust studies in this domain.

Although our experience demonstrated weaning of morphine after initiation of gabapentin as adjunctive therapy for the treatment of NOWS, our findings are limited by a small sample size and retrospective study design. Additionally, our evaluation lacked a comparator group which is required to determine if the ability to wean morphine was caused by the initiation of gabapentin or if infants would have been able to wean morphine without the use of gabapentin if given more time. However, the latter strategy needs to be balanced with the desire to minimize duration of opioid therapy, reduce the length of hospital stay, and limit long term neurodevelopmental adverse events associated with prolonged opioid therapy.[5,15] We did not include Finnegan scores in our report, which limits our ability to correlate changes in medication therapy to a specific assessment of each infant; however, given that many of our patients were initiated on gabapentin or continued beyond 28 days of age, the utility of the Finnegan score in this patient population is questionable. Additionally, though our institution has a protocol for morphine and clonidine therapy in NOWS, we did not assess compliance with that protocol. Despite these limitations, we believe our experience demonstrates that gabapentin can be safely and successfully used as adjunctive therapy for patients with NOWS who cannot be successfully weaned from morphine even with concurrent clonidine treatment.

Conclusion

Though these results are promising and demonstrate the potential for an association between gabapentin use and successful weans of morphine, they are not sufficient to support a direct causative link. Treatments for NOWS beyond morphine and methadone are understudied in general, and there is even less information related to the utilization of gabapentin in NOWS.

Although there is a clear subset of neonatal patients who experience opioid withdrawal requiring therapy beyond that of an opioid and clonidine, there is very limited published data to guide management. Larger prospective studies evaluating infants with NOWS treated with gabapentin are warranted.

Article Information

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