Pediatric Neurology 97 (2019) 64–70

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Gabapentin Use for Hospitalized Neonates

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ARTICLE INFO

Article history:
Received 6 December 2018
Accepted 12 February 2019
Available online 21 February 2019

Keywords:
Gabapentin
Neonate
Neonatal intensive care unit
Off-label drug use
Irritability
Neonatal abstinence syndrome
Dose

ABSTRACT

Background: Despite some clinician advocacy for the use of gabapentin to treat neonatal irritability of presumed neurological origin, the extent of gabapentin administration to hospitalized neonates is unknown. We aimed to identify trends in gabapentin utilization among infants hospitalized in neonatal intensive care units (NICUs) across the United States and to evaluate the associations between clinical diagnoses and gabapentin treatment.

Methods: We analyzed neonates admitted to the NICU using the Pediatric Health Information System (2005 to 2016) to measure treatment timing, duration, and frequency. We used modified Poisson regression with a robust between-cluster variance estimator to calculate a probability (adjusted relative risk) for gabapentin administration.

Results: Of 278,403 neonates, 374 were administered gabapentin (0.13%). The median treatment duration was 16 days (25th to 75th percentile: 8; 40). Gabapentin use increased from 0% in 2005 to 0.39% in 2016. Treatment was prescribed to neonates at 31 of 48 studied hospitals; 73% of total treated infants localized to five neonatal intensive care units. Term (0.16%) and ≤28 weeks' gestation preterm infants (0.22%) were most likely to receive gabapentin. Varying by gestational age, a diagnosis of chromosomal abnormalities, severe bronchopulmonary dysplasia, hemorrhagic stroke, and neonatal abstinence syndrome were associated with higher treatment with gabapentin. The majority (88.8%) of treated infants did not have a seizure diagnosis.

Conclusion: Gabapentin use in NICU in the United States increased in recent years and varies markedly between institutions. Term infants, ≤28 weeks' gestation preterm infants, and neonates with chronic genetic, neurological, and gastrointestinal diagnoses were more likely to receive gabapentin.

Introduction

Among neonates hospitalized in neonatal intensive care units (NICUs), a sometimes unclear distinction between pain and agitation can lead to the concept of irritability, a poorly defined broad term describing subjective behavioral and physiological indicators such as persistent crying, tense posture and muscle tone, inconsolability, and vital sign changes.[1–4] Nonverbal communication and lack of well-validated pain assessment scales create challenges for clinicians evaluating and treating perceived discomfort.[1,2,5,6] In the NICU, various identifiable causes of neurological compromise include infections, ischemia, hemorrhage, thrombosis, and epileptogenic disorders. However, even in these infants presumed to experience chronic pain with agitation, the use of traditional pharmacologic management—including benzodiazepines and opioids—is varyingly effective.[2,3] Adverse effects often occur, such as sedation, decreased gastrointestinal motility, respiratory depression,[7,8] and the development of dependency and associated withdrawal symptoms after a few days of use.[7,8] Consequently, alternative treatment options including gabapentin have been proposed as potentially less harmful treatment options.[4,9,10]

Gabapentin ([1-(aminomethyl)cyclohexaneacetic acid], or Neurontin[11]), a gamma-aminobutyric acid (GABA) analog,[12] is approved by the US Food and Drug Administration to treat partial

Declarations of interest: The authors report no conflicts of interest.

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https://doi.org/10.1016/j.pediatrneurol.2019.02.012
0887-8994/

epilepsy in children as young as three years of age and postherpetic neuralgia in adults.[13,14] Gabapentin has and continues to be used in neonates with seizures, pain, and irritability[2–4] despite the lack of a formal US Food and Drug Administration-approved indication for neonatal use. Studies are available examining adult use for approved indications and off-label use,[14–16] whereas little research exists regarding gabapentin safety and effectiveness among a neonatal-specific population.[2–4,15] In an era in which clinicians are increasingly prescribing gabapentin despite this knowledge gap,[3] we aimed to examine trends in gabapentin administration among a national cohort of NICU-hospitalized neonates and to determine any associations between clinical diagnoses and increased probability of gabapentin treatment. Our objectives were to identify trends in gabapentin utilization among infants hospitalized in NICUs at US children's hospitals and to evaluate the associations between clinical diagnoses and gabapentin treatment.

Methods

Study source

We conducted our analysis using de-identified data obtained from the Pediatric Health Information System (PHIS), a large administrative database (Children's Hospital Association; Shawnee Mission, Kansas) containing demographic data, daily medication records, procedures, diagnoses, and billing information from 48 NICUs across the United States. This study was reviewed and approved by the Nationwide Children's Institutional Review Board.

Inclusion criteria and variables

Our cohort included neonates discharged between January 2005 and June 2016 with a recorded gestational age (GA) at birth. A Clinical Transaction Classification code was used to identify gabapentin administration (Clinical Transaction Classification code: 116047) and other medications (Supplementary Table 1). Although we anticipate that neonatologists were the most common gabapentin prescribers within the NICU, and that consulting pediatric neurologists and developmental pediatricians may have influenced treatment decisions, we were unable to ascertain the exact specialty of the prescribing clinician. Clinical diagnoses included stages 2 and 3 of necrotizing enterocolitis using x-ray-documented signs of pneumatosis and perforation, chromosomal abnormalities, periventricular leukomalacia, seizures, congenital brain abnormalities, hypoxic-ischemic encephalopathy, ischemic or thrombotic stroke, hemorrhagic stroke, grades 3 and 4 intraventricular hemorrhage (IVH), and neonatal abstinence syndrome. Diagnoses and GA categories (22 to 24, 25 to 28, 29 to 32, 33 to 34, 35 to 36, and ≥37 weeks) were classified as binary variables using *International Statistical Classification of Diseases and Related Health Problems, Ninth* and *Tenth Revisions* diagnostic codes (Supplementary Table 2). Preterm infants born at ≤32 weeks' GA receiving oxygen were identified as having bronchopulmonary dysplasia (BPD) based on the degree of respiratory support at 36 weeks postmenstrual age: infants utilizing oxygen therapy were identified as having moderate BPD, and infants using invasive or noninvasive positive pressure ventilation were identified as having severe BPD.[17]

Statistical analysis

Treatment timing and duration of gabapentin administration was examined using univariate analysis. We estimated adjusted relative risks (adjusted risk ratios) (aRRs) using a robust error variance Poisson regression, controlling for within-hospital clustering to measure any associations between various diagnoses and the probability of receiving gabapentin.[18,19] The aRR is the multivariable adjusted ratio of the probability of gabapentin administration for patients with a measured risk factor (predictor variable) to the probability of gabapentin administration for patients without that same risk factor. Trends over time were evaluated with Cochran-Armitage test. All analyses were conducted using Stata 15.0 (StataCorp, College Station, TX, USA). As the purpose of our article was to explore the prevalence of and factors associated with neonatal gabapentin utilization within specific patient subgroups, we chose not to control for multiple comparisons.[20,21] This should be noted when interpreting our findings.

Results

Patient characteristics

Throughout the study period, 278,403 infants hospitalized in 48 PHIS-participating NICUs fit our inclusion criteria (female: n = 122,384, 44%; ≥37 weeks' GA: n = 138,234, 50%) (Table 1). A total of 374 (0.13%) infants received gabapentin during their hospitalization in the NICU (female: n = 153, 41%; ≥37 weeks' GA: n = 216, 58%). Of those treated with gabapentin, 12.0% (n = 45) had severe BPD and 12% (n = 45) were diagnosed with congenital brain abnormalities, 11.2% (n = 42) with seizures, 10.7% (n = 40) with chromosomal abnormalities, and 6.7% (n = 25) with neonatal abstinence syndrome. Within the treated cohort, 73 (19.5%) received gabapentin within the first 30 days of life and 262 (70.1%) still received gabapentin at discharge. A further breakdown of gabapentin administration and diagnoses by GA is available in Table 2.

Treatment timing and duration

The median age at first administration of gabapentin was 66 postnatal days (twenty-fifth to seventy-fifth percentile: 37 to 125; Table 3). Those born ≥37 weeks' GA had the earliest median age at first dose (47 days; twenty-fifth to seventy-fifth percentile: 30 to 78) and those born ≤28 weeks' GA had the latest (158 days, twenty-fifth to seventy-fifth: 120 to 242; 32 to 74 days after 40 weeks post-term corrected age) (Table 3). The distribution of gabapentin administration by GA was bimodal. The age groups with the highest proportion of infants receiving gabapentin were ≤24 weeks' gestation preterm infants (0.31%) and ≥37 weeks' gestation term infants (0.16%) (Fig 1). Clinical diagnoses and sex had an additional impact on the timing of the first dose of gabapentin. Across most gestational age groups, male infants typically received gabapentin earlier than females (Table 3). Compared with those in the same GA stratum, the median age at first dose was earliest for infants diagnosed with NAS, HIE, chromosomal abnormalities, and IVH.

Overall, the median treatment duration for all treated infants was 16 days (twenty-fifth to seventy-fifth percentile: eight to 36; Table 1). Infants born at ≤32 weeks' gestation had a median duration of 32 days (≤28 weeks: 31; twenty-fifth to seventy-fifth percentile: 14 to 57) (29 to 32 weeks: 32; twenty-fifth to seventy-fifth percentile: 12 to 61) and those born at greater than 32 weeks' gestation had a median duration of 14 days (33 to 36 weeks: 22; twenty-fifth to seventy-fifth percentile: 10 to 65) (≥37 weeks: 12; twenty-fifth to seventy-fifth percentile: seven to 27).

Clinical predictors of gabapentin administration

After accounting for gestational age, sex, and other diagnoses (Table 4), the largest measured predictors of ever receiving

TABLE 1.
Cohort Demographic Characteristics

	Full Sample, N = 278,403	Gabapentin Treated, N = 374
	n (%)*	n (%)
Birth gestation (weeks)		
≤28	32,092 (11.5)	70 (18.7)
29-32	31,546 (11.3)	23 (6.2)
33-36	76,531 (27.5)	65 (17.4)
≥37	138,234 (49.7)	216 (57.8)
Sex		
Female	122,384 (44.0)	153 (41.0)
Male	155,869 (56.0)	220 (59.0)
Diagnoses		
NEC	3,689 (1.3)	16 (4.3)
Chromosomal abnormalities	5,164 (1.9)	40 (10.7)
Periventricular leukomalacia	2,760 (1.0)	14 (3.7)
Moderate BPD†	7,276 (2.6)	8 (2.1)
Severe BPD†	6,524 (2.3)	45 (12.0)
Seizure	11,180 (4.0)	42 (11.2)
Congenital brain abnormalities	10,382 (3.7)	45 (12.0)
HIE	6,487 (2.3)	21 (5.6)
Ischemic or thrombotic stroke	1,334 (0.5)	2 (0.5)
Hemorrhagic stroke	682 (0.2)	3 (0.8)
Intraventricular haemorrhage	6,731 (2.4)	14 (3.7)
NAS	11,725 (4.2)	25 (6.7)
Medications		
Opioids	109,617 (39.4)	365 (97.6)
Benzodiazepine	75,109 (27.0)	343 (91.7)
Nonbenzodiazepine antiepileptics	22,434 (8.1)	100 (26.7)
Dexmedetomidine	6,583 (2.4)	88 (23.5)
Propofol	28,784 (10.3)	155 (41.4)
Ever received gabapentin	374 (0.13)	374 (100)
Early use of gabapentin‡	73 (0.03)	73 (19.5)
Discharged on gabapentin	262 (0.09)	262 (70.1)
Treatment duration (days)§	-	16 (8-40)

Abbreviations:
BPD = Bronchopulmonary dysplasia
HIE = Hypoxic-ischemic encephalopathy
IQR = Interquartile range
NAS = Neonatal abstinence syndrome
NEC = Necrotizing enterocolitis
* Percentages were derived using N as the denominator.
† BPD diagnoses restricted to infants born at ≤32 weeks' gestation.
‡ Received within the first 30 days of life.
§ X (X to X) = median (IQR).

gabapentin among the entire cohort were diagnoses of hemorrhagic stroke, NAS, and severe BPD for infants, differing by GA (Table 4). Neonates with severe BPD had from 5.20 (95% confidence interval [CI]: 3.19, 8.49) to 7.43 (95% CI: 3.23, 17.06) times greater probability of being treated with gabapentin compared with neonates not diagnosed with severe BPD within the same GA categories. Conversely, infants with a diagnosis of IVH born at ≤28 weeks' GA had a 0.61 (95% CI: 0.40, 0.92) times lower likelihood of receiving gabapentin than those within the same GA category that did not have an IVH. A lower probability was also seen among females born between 29 and 32 weeks' GA (aRR: 0.34, 95% CI: 0.15, 0.76). The magnitude of these associations stratified by GA can further be seen in Table 4.

Hospital utilization of gabapentin

The proportion of neonates who received gabapentin increased rapidly throughout the study period, from no use in 2005 to 0.07% in 2010, followed by a steep increase to 0.39% in 2016 (Fig 2). When examining interhospital variation in gabapentin administration, gabapentin was prescribed in 31 of 48 studied hospitals and 72.5% of infants ever treated with gabapentin were hospitalized at five centers (Fig 3).

Other medications

Over 90% of gabapentin-treated neonates received benzodiazepines or opioids during at least one service day of their NICU time (Fig 4). A total of 370 (98.9%) infants were prescribed other opioid or anxiolytic sedative medications in conjunction with gabapentin, and 217 (58%) received these other medications concurrently at the time of gabapentin initiation.

Discussion

We observed a significant, rapid increase in national neonatal gabapentin administration throughout our 11-year study period despite a lack of high-quality safety and efficacy evidence.[2–4,15,23] Clinical diagnoses were associated with both increased and decreased probabilities of receiving gabapentin. We unexpectedly observed a high likelihood of gabapentin treatment for infants with severe BPD. At present, there are no proven mechanisms or disorders supporting a neuropathic origin of pain in BPD. Furthermore, 58% of our treated cohort received opioid or sedative medications on the initial day of gabapentin administration. Our findings of large institutional variability in gabapentin prescription rates in a setting of limited effectiveness or safety data may be reflective of subjectivity in both pain assessment measures and treatment decisions, resulting in inconsistent management.[6] Gabapentin is used as an analgesic for cases of chronic pain,[24] but the prolonged effects of both gabapentin and pain on the early, active processes of neonatal neurodevelopment are unknown. Thus physicians must weigh symptom alleviation with long-term effects of the underlying diagnosis.

Metabolically, gabapentin does not bind to and affect $GABA_A$ receptor function despite a structural similarity to GABA.[25,26] GABA acts as an inhibitory neurotransmitter in adults but contrastingly creates an excitatory effect in the neonatal brain.[27–29] This resulting neuronal membrane depolarization is a hypothesized critical component of early cortical development.[27–29] Gabapentin has been shown in rodent models and human-based *in vitro* systems to selectively inhibit the alpha-2 delta-1 ($\alpha_2\delta$-1) subunit of voltage-gated calcium channels encoded by the CACNA2D1 gene,[30] thereby alleviating neuropathic pain. Further investigation is warranted to determine whether treatment in neonates causes increased GABA levels or $\alpha_2\delta$-1 inhibition.

Emerging concern exists regarding possible neonatal gabapentin withdrawal[31] after several studies contend a possibility of fetal retention following maternal exposure.[32-34] Huybrechts et al.[35] reported that *in utero* co-exposure to opioids and gabapentin was associated with both an increased risk of neonatal withdrawal and more severe withdrawal symptoms compared with opioid exposure alone, a worrisome finding given 58% of our treated cohort were concomitantly prescribed opioid or sedative medications and gabapentin. Moreover, two case reports[31,34] featuring neonates withdrawing from *in utero* gabapentin exposure reported symptom improvement following reintroduction to gabapentin. In an era of rising co-prescription rates of gabapentin, opioids, and benzodiazepines[36] and gabapentin misuse among adults,[13,37] the weighing of perceived benefits against real dependency risks is imperative.[2–4,15]

TABLE 2.
Gabapentin-Treated Cohort Characteristics by Gestational Age Categories

Birth Gestation (weeks)	Gabapentin Treated, N = 374			
	≤28, N = 70 n (%)*	29-32, N = 23 n (%)	33-36, N = 65 n (%)	≥37, N = 216 n (%)
Sex				
Female	27 (38.6)	5 (21.7)	28 (43.1)	93 (43.1)
Male	43 (61.4)	18 (78.3)	37 (56.9)	122 (56.7)
Diagnoses				
NEC	11 (15.37)	1 (4.4)	1 (1.5)	3 (1.4)
Chromosomal abnormalities	1 (1.4)	3 (13.0)	11 (16.9)	25 (11.6)
Periventricular leukomalacia	8 (11.4)	2 (8.7)	1 (1.5)	3 (1.4)
Moderate BPD†	6 (8.6)	2 (8.7)	-	-
Severe BPD†	36 (51.4)	9 (39.1)	-	-
Seizure	10 (14.3)	-	11 (16.9)	21 (9.7)
Congenital brain abnormalities	4 (5.7)	5 (21.7)	11 (16.9)	25 (11.6)
HIE	-	1 (4.4)	8 (12.3)	12 (5.6)
Ischemic or thrombotic stroke	-	-	-	2 (0.9)
Hemorrhagic stroke	-	2 (8.7)	-	1 (0.5)
Intraventricular haemorrhage	11 (15.7)	1 (4.4)	1 (1.5)	1 (0.5)
NAS	3 (4.3)	4 (17.4)	1 (1.5)	17 (7.9)
Medications				
Opioids	70 (100)	21 (91.3)	63 (96.9)	211 (97.7)
Benzodiazepine	66 (94.3)	19 (82.6)	60 (92.3)	198 (91.7)
Nonbenzodiazepine antiepileptics	25 (35.7)	7 (30.4)	18 (27.7)	50 (23.2)
Dexmedetomidine	15 (21.4)	9 (39.1)	20 (30.8)	44 (20.4)
Propofol	25 (35.7)	11 (47.8)	40 (61.5)	79 (36.6)
Early use of gabapentin‡	-	1 (4.4)	9 (13.9)	63 (29.2)
Discharged on gabapentin	47 (67.1)	19 (82.6)	39 (60)	157 (72.7)
Treatment duration (d)§	31 (14-57)	32 (12-61)	22 (10-65)	12 (7-27)

Abbreviations:
BPD = Bronchopulmonary dysplasia
HIE = Hypoxic-ischemic encephalopathy
IQR =Interquartile range
NAS = Neonatal abstinence syndrome
NEC = Necrotizing enterocolitis
* Percentages were derived using N as the denominator.
† BPD diagnoses restricted to infants born at ≤32 weeks' gestation.
‡ Received within the first 30 days of life.
§ X (X to X) = median (IQR).

Few published studies indicate that gabapentin is an effective treatment for refractory pain and irritability.[3,4] Edwards et al.[3] reported improved feeding tolerance and decreased irritability among a sample of 11 gabapentin-treated neonates with "visceral hyperalgesia." However, no quantitative or physiologic measurement was used to establish the initial diagnosis prompting

TABLE 3.
Median Postnatal Age at First Gabapentin Administration by Gestational Age

	Median Age at First Dose* Postnatal Days (Twenty-Fifth to Seventy-Fifth Percentile)				
	Full Cohort	≤28 weeks' GA	29-32 weeks' GA	33-36 weeks' GA	≥37 weeks' GA
All treated patients	66 (37-125)	158 (120-242)	101 (78-155)	74 (47-121)	47 (30-78)
Diagnoses					
NEC	144 (110-228)	170 (120-235)	278 (278-278)	115 (115-115)	96 (69-116)
Chromosomal abnormalities	64 (42-92)	115 (115-115)	100 (71-101)	92 (47-171)	53 (41-77)
Periventricular leukomalacia	107 (90-148)	146 (105-241)	111 (90-131)	106 (106-106)	59 (27-96)
Moderate BPD†	140 (113-155)	140 (124-154)	128 (101-155)	-	-
Severe BPD†	144 (107-182)	157 (121-202)	100 (74-144)	-	-
Seizures	71 (32-141)	172 (148-253)	-	81 (35-125)	38 (29-70)
Congenital brain abnormalities	75 (35-125)	137 (114-335)	134 (101-144)	81 (56-125)	41 (32-76)
HIE	30 (13-49)	-	27 (27-27)	51 (23-60)	25 (13-39)
Ischemic or thrombotic stroke	42 (39-45)	-	-	-	42 (39-45)
Hemorrhagic stroke	145 (100-155)	-	128 (100-155)	-	145 (145-145)
Intraventricular haemorrhage	141 (91-170)	166 (127-235)	134 (134-134)	59 (59-59)	22 (22-22)
NAS	32 (26-71)	103 (80-172)	62 (43-175)	20 (20-20)	29 (22-38)
Sex					
Female	71 (42-120)	170 (120-260)	155 (84-157)	66 (43-103)	55 (38-77)
Male	61 (33-129)	148 (117-231)	101 (78-134)	81 (49-139)	38 (27-60)

Abbreviations:
BPD = Bronchopulmonary dysplasia
HIE = Hypoxic-ischemic encephalopathy
NAS = Neonatal abstinence syndrome
NEC = Necrotizing enterocolitis
* See Table 2 for patient n included in each calculation.
† BPD diagnoses restricted to infants born at ≤32 weeks' gestation.

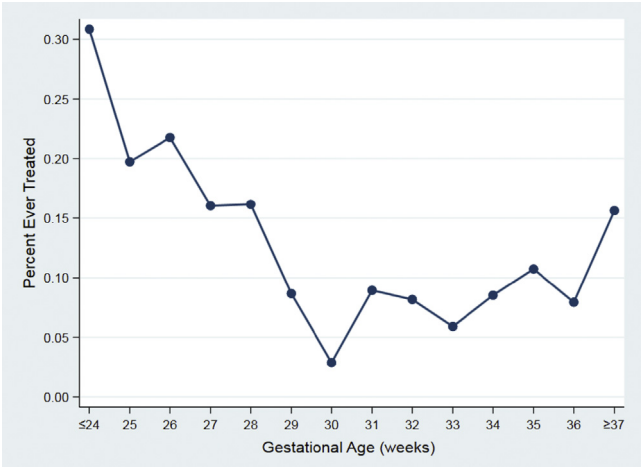

FIGURE 1. Gabapentin utilization by gestational age at birth. The color version of this figure is available in the online edition.

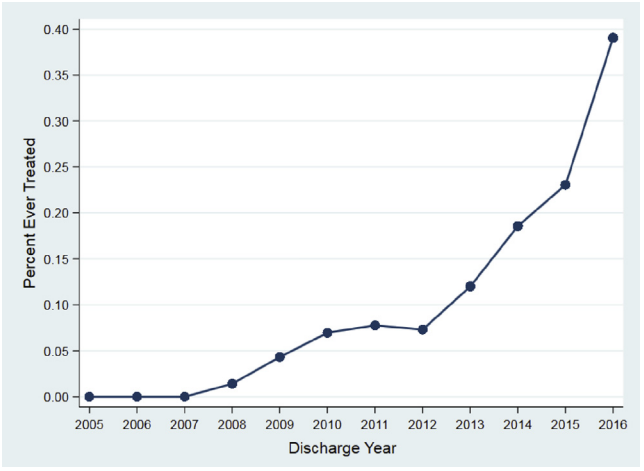

FIGURE 2. Gabapentin utilization by discharge year. The color version of this figure is available in the online edition.

drug usage. Adverse events were recorded in five neonates: three experienced tachycardia, emesis, and irritability as a result of abrupt discontinuation of gabapentin and two experienced bradycardia resolved with a lower dose of gabapentin. Most recently, Sacha et al.[5] published similar findings for 22 NICU-admitted neonates given gabapentin therapy for pain and agitation. Neonatal Pain, Agitation and Sedation Scale scores[1] improved and administration of other analgesic and sedative medications decreased. One patient experienced nystagmus. Despite these studies' small samples, they reflect gabapentin's seeming ability to improve pain-attributed symptoms among a neonatal population.

Our study is primarily strengthened by including a large sample size that enabled us to measure gabapentin utilization and examine associations between clinical diagnoses and gabapentin treatment, aspects that have not been evaluated to this scale in the few similar studies available. Conversely, the use of a large administrative database is inherently prone to errors of coding, misclassification, and underreporting, but the effect may be minimized by internal PHIS database quality checks.[38] We

TABLE 4.
Multivariable Adjusted Probability of Receiving Gabapentin

Birth Gestation	aRR* (95% CI)			
	≤28 weeks	29-32 weeks	33-36 weeks	≥37 weeks
Diagnoses				
NEC	**1.96 (1.13, 3.43)**	0.81 (0.08, 8.25)	1.63 (0.24, 11.07)	**3.74 (1.48, 9.46)**
Chromosomal abnormalities	1.80 (0.39, 8.37)	**3.70 (1.06, 12.93)**	**6.42 (3.21, 12.83)**	**4.77 (2.50, 9.11)**
Periventricular leukomalacia	1.70 (0.85, 3.41)	1.89 (0.34, 10.45)	1.68 (0.20, 14.05)	**4.16 (1.14, 15.23)**
Moderate BPD†	0.90 (0.17, 4.91)	1.81 (0.42, 7.77)	-	-
Severe BPD†	**5.20 (3.18, 8.48)**	**7.43 (3.23, 17.06)**	-	-
Seizure	**3.61 (1.42, 9.21)**	-	**3.98 (1.90, 8.36)**	1.48 (0.85, 2.57)
Congenital brain abnormalities	0.73 (0.31, 1.69)	**4.75 (1.62, 13.94)**	**2.91 (1.03, 8.23)**	2.37 (0.93, 6.04)
HIE	-	**4.07 (1.03, 16.08)**	**4.03 (1.79, 9.07)**	1.42 (0.48, 4.21)
Ischemic or thrombotic stroke	-	-	-	0.95 (0.33, 2.79)
Hemorrhagic stroke	-	**15.52 (1.23, 195.14)**	-	1.58 (0.18, 13.73)
Intraventricular hemorrhage	**0.61 (0.40, 0.92)**	0.68 (0.05, 9.09)	0.97 (0.14, 6.95)	0.95 (0.11, 8.02)
NAS	1.96 (0.98, 3.94)	**8.53 (2.97, 24.50)**	0.45 (0.06, 3.60)	1.63 (0.55, 1.13)
Sex				
Female	0.81 (0.49, 1.35)	**0.34 (0.15, 0.76)**	0.91 (0.55, 1.50)	0.95 (0.79, 1.13)
ICC‡ = 0.09 (0.06, 0.13)				

Abbreviations:
aRR = Adjusted relative risk
BPD = Bronchopulmonary dysplasia
CI = Confidence interval
HIE = Hypoxic-ischemic encephalopathy
ICC = Intraclass coefficient
NAS = Neonatal abstinence syndrome
NEC = Necrotizing enterocolitis
P-value <0.05 are in bold.

* See Table 2 for patient n included in each calculation.

† BPD diagnoses restricted to infants born at ≤32 weeks' gestation.

‡ The ICC, the proportion of total variance in gabapentin use due to variation between hospitals,[22] indicated that clustering by hospital was a significant component of the overall variation in the frequency of gabapentin treatment.

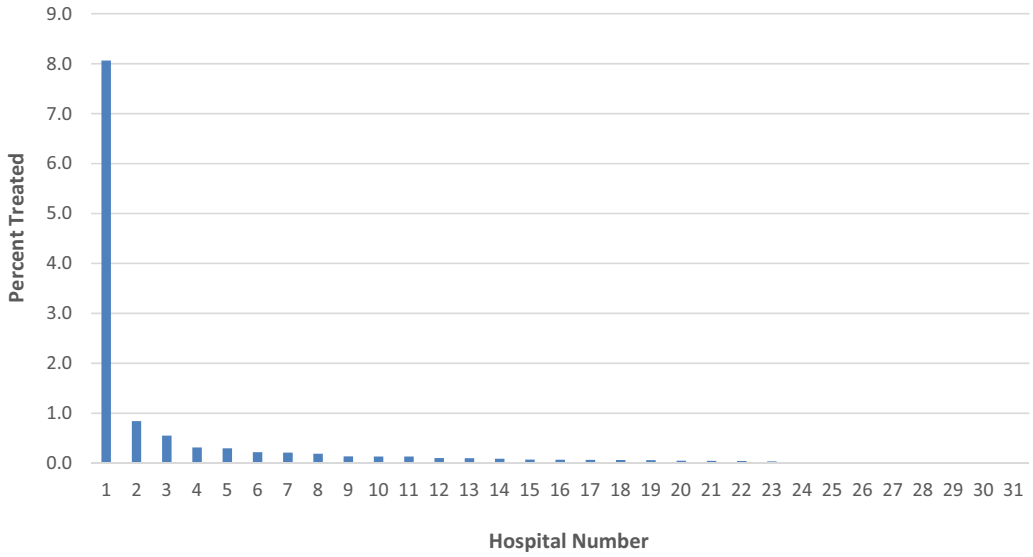

FIGURE 3. Interhospital variation of gabapentin treatment among NICU-admitted neonates. NICU, neonatal intensive care unit. The color version of this figure is available in the online edition.

were unable to evaluate nonrecorded clinical signs that may have provoked gabapentin treatment, analyze follow-up data post-discharge, and examine for adverse effects post-treatment given that we relied on PHIS discharge diagnoses and not direct medical records. Moreover, gabapentin prescription was subjective based on physician and institutional preferences. This may affect the ability to generalize our results. However, it importantly highlights the lack of a national or global consensus on neonatal gabapentin treatment, presumably due to a lack of evidence on safety or effectiveness.

Conclusion

Our data demonstrate an increasing frequency of gabapentin use in US NICUs. The majority of treated infants were not diagnosed with seizures, and based on their concurrent diagnoses and previous reports,[2–5] it is possible that they were instead treated for neonatal irritability and agitation of unproven origin. Neonates diagnosed with chromosomal abnormalities, necrotizing enterocolitis, periventricular leukomalacia, congenital brain abnormalities, BPD, and seizures had higher likelihood of receiving

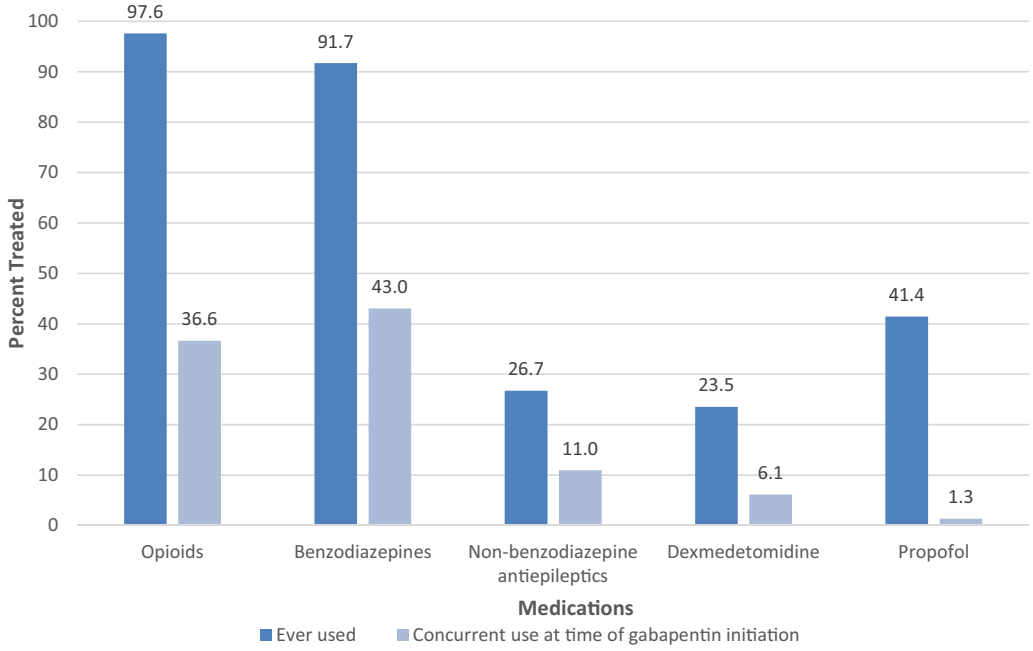

FIGURE 4. Percent of gabapentin-treated infants ever treated with or concurrently taking other medications. The color version of this figure is available in the online edition.

gabapentin. Prescription rates varied greatly between institutions, highlighting a lack of cohesive guidelines. Given the concerns for effectiveness, safety, long-term effects, and potential dependence, further rigorous prospective investigations within the neonatal population are urgently needed.

Acknowledgment

This work was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (K08HL121182 to Dr. Slaughter). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.02.012.

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