JPPT | Letter to the Editor

Correspondence on "Gabapentin for Delirium in Infants in the Neonatal Intensive Care Unit"

To the Editor—Members of the Johns Hopkins University School of Medicine Neuroscience Intensive Care Nursery Program would like to raise concerns regarding the paper, "Gabapentin for Delirium in Infants in the Neonatal Intensive Care Unit" by Chang et al.[1] Our concerns are focused on the scientific bases, diagnostic assessments, and treatment protocol proposed in the article.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, defines delirium as an acute disturbance of attention, awareness, and cognition due to an underlying medical condition or exposure, but not due to an underlying neurocognitive disorder.[2] Attention, awareness, and cognition are based on brain development, and milestones for these skills have only been established in healthy neonates. However, neonates in the neonatal intensive care unit (NICU) have many risk factors for atypical development, including prematurity, medical comorbidities, brain injury, prolonged hospitalization, and an altered sensory environment. They also have a medically and developmentally limited repertoire of neurobehavioral skills. Establishing a neurocognitive baseline can, therefore, be challenging and, in many cases, is not feasible, limiting our ability to detect acute neurobehavioral changes in NICU patients.

Currently, there is no clear definition of neonatal delirium nor a gold standard diagnosis for validation of standardized assessments. The Cornell Assessment of Pediatric Delirium (CAPD) scale has been used in children below 2 years of age but has only been validated in the PICU population.[3,4] Most of the studies using the CAPD scale have included a strikingly low number of infants and neonates.[3,5] To allow for more effective and safer treatment interventions, the ideal neonatal assessment must distinguish delirium from not only other disorders with similar neurobehavioral symptoms, such as pain, agitation, overstimulation, and withdrawal, but also from neurodevelopmental impairment from perinatal brain injury or underlying prenatal brain maldevelopment. We have previously expressed our concerns regarding the underlying neurobiology of delirium and how the anatomical and biochemical substrates may not exist at this stage of development.[6] We continue to recommend more robust preclinical and clinical research regarding neonatal delirium.

Of particular concern is the use of medications with unclear safety and efficacy data in neonates for indications not well-defined in the NICU population. This study's delirium protocol includes the initiation of antipsychotic medications in Step 3. There is currently almost no safety data for the use of antipsychotics in neonates, and the current clinical data are limited to case reports and small case series. In contrast, gabapentin use in neonates has steadily increased over the past 2 decades.[7] Several studies report efficacy in neonatal pain, agitation, withdrawal, and visceral hyperalgesia, all common conditions mimicking delirium in the NICU.[8] Furthermore, gabapentin has a favorable side effect profile compared with other drugs typically used for these indications and is well tolerated in most cases.[9] Thus, for neonates with refractory agitation or inability to wean sedation, gabapentin is our preferred agent after implementation of maximal nonpharmacological interventions, which should always be first-line treatment.[7] The effectiveness of gabapentin in the management of refractory agitation is corroborated in this series by the lack of patients requiring step 3 escalation after gabapentin initiation and the improvement of agitation scores. Our team discourages the use of antipsychotics in this population for reasons discussed previously.[6]

We must also recognize mechanistic concerns regarding gabapentin use in neonates. While gabapentin is a structural analog of GABA, it does not bind GABAa or GABAb receptors. Gabapentin interacts with and changes the function of voltage-gated Ca2+ channels, limiting the release of excitatory neurotransmitters. Specifically, the α2δ-1 subunit of the voltage-dependent calcium channels is a binding site for gabapentin and thus contributes to the effects on excitation/inhibition balance in developing neural networks.[10] On the other hand, preclinical data suggest gabapentin may attenuate GABAergic deficits following neonatal hypoxic-ischemic brain insults, which may be neuroprotective.[10–13] Thus, we acknowledge that rigorous safety data regarding developmental outcomes are still urgently needed for the use of gabapentin in neonates.

This article concludes that gabapentin initiation improved measures of neonatal pain/agitation and withdrawal, consistent with prior reports, but not CAPD scores. However, the title implies that gabapentin was used to treat delirium, and the authors' conclusion does not explicitly contradict this interpretation, which may lead to misunderstanding and misapplication of this study's data. The authors should have clearly stated that there was no evidence in their study that gabapentin treats delirium.

In conclusion, delirium as a clinical entity in the neonatal population remains controversial. We agree with the use of gabapentin for behavioral changes in neonates and young infants in the appropriate clinical context. We also encourage further research into the neurodevelopmental safety of gabapentin. We recommend against the use of antipsychotics for neonatal behavioral changes until robust preclinical and clinical data are available regarding the safety of these medications on the immature injured brain.

April N. Sharp, MD; Raul Chavez-Valdez, MD; Vera Joanna Burton, MD, PhD; Michele Hilberg, CRNP; Gwendolyn Gerner, PsyD; Dawn B. Lammert, MD, PhD; Joseph Scafidi, DO; Lauren L. Jantzie, PhD; Shenandoah Robinson, MD; Maureen Gilmore, MD; Charlamaine Parkinson, RN; Carl E. Stafstrom, MD, PhD; Marilee C. Allen, MD; Frances J. Northington, MD; and Sapna Kudchadkar, MD, PhD

Article Information

Affiliations. Departments of Neurology, Division of Pediatric Neurology (ANS, VJB, DBL, JS, CES), Pediatrics, Division of Neonatology (RCV, LLJ, MG, MCA, CP, FJN), Neurosurgery (SR), and Anesthesiology (SK), Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology and Developmental Medicine (ANS, VJB, MH, GG, JS), Kennedy Krieger Institute, Baltimore, MD.

Correspondence. April Sharp, MD; asharp7@jhmi.edu

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References

1. Chang E, Parman A, Johnson PN, et al. Gabapentin for delirium in infants in the neonatal intensive care unit. *J Pediatr Pharmacol Ther*. 2024;29(5):487–493
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th edition. Washington, DC: American Psychiatric Association Publishing; 2022.
3. Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. *Crit Care Med*. 2014;42(3):656–663.
4. Silver G, Kearney J, Traube C, Hertzig M. Delirium screening anchored in child development: the Cornell Assessment for Pediatric Delirium. *Palliat Support Care*. 2015;13(4):1005–1011.
5. Silver G, Traube C, Kearney J, et al. Detecting pediatric delirium: development of a rapid observational assessment tool. *Intensive Care Med*. 2012;38(6):1025–1031.
6. Chavez-Valdez R, Northington FJ, Sharp A, et al. Correspondence on "recognition and management of delirium in the neonatal intensive care unit: case series from a single-center level iv intensive care unit." *J Child Neurol*. 2024;39(7-8):292–295.
7. McPherson C. Gabapentin in infants: critical evaluation of a novel sedative/analgesic medication. *Neonatal Netw*. 2021;40(4):267–272.
8. Sacha GL, Foreman MG, Kyllonen K, Rodriguez RJ. The use of gabapentin for pain and agitation in neonates and infants in a neonatal ICU. *J Pediatr Pharmacol Ther*. 2017;22(3):207–211.
9. Fleser L, Tibbetts E, Hanson A, et al. Evaluating gabapentin dosing, efficacy and safety in infants. *J Pediatr Pharmacol Ther*. 2024;29(2):159–168.
10. Wu T, Chen SR, Pan HL, Luo Y. The α2δ-1-NMDA receptor complex and its potential as a therapeutic target for ischemic stroke. *Front Neurol*. 2023;14:1148697.
11. Spahic H, Parmar P, Miller S, et al. Dysregulation of ErbB4 signaling pathway in the dorsal hippocampus after neonatal hypoxia-ischemia and late deficits in PV+ interneurons, synaptic plasticity and working memory. *Int J Mol Sci*. 2022;24(1):508.
12. Parmar P, Spahic H, Lechner C, et al. Neonatal hypoxia-ischemia alters the events governing the hippocampal critical period of postnatal synaptic plasticity leading to deficits in working memory in mice. *Neurobiol Dis*. 2024;202:106722.
13. Chavez-Valdez R, Emerson P, Goffigan-Holmes J, et al. Delayed injury of hippocampal interneurons after neonatal hypoxia-ischemia and therapeutic hypothermia in a murine model. *Hippocampus*. 2018;28(8):617–630.

AUTHOR'S RESPONSE: We appreciate the Letter to the Editor from Sharp et al[1] regarding our article entitled "Gabapentin for delirium in infants in the neonatal intensive care unit".[2] We agree with some of the concerns raised about diagnosis and treatment of delirium in the neonatal intensive care unit (NICU) due to limited study of the Cornell Assessment of Pediatric Delirium (CAPD) scale in this setting, and the relative lack of efficacy and safety data with gabapentin use in this population and, would like to respond to a few of the specific concerns raised.

First, the concern raised about using the CAPD scale in the NICU population. It is true that the CAPD scale has not be validated in the NICU setting; however, it should be noted that it was validated in the pediatric intensive care unit (PICU) setting and developmental anchor points have been established for patients <2 years of age and specifically include anchor points for newborns, and patients at 4 weeks, 6 weeks, 28 weeks, 1 year, and 2 years of age.[3,4] Siegel et al[5] used the CAPD scale to assess the prevalence of delirium in their NICU, since the CAPD scale was previously validated in term infants or in preterm infants corrected to term based on postmenstrual age. Therefore, there is

evidence that the use of the CAPD scale is occurring in the NICU setting. It is also important to note that the median postnatal age of patients in our study at the time of gabapentin initiation was 111 days (median postmenstrual age of 43.5 weeks). These patients had prolonged NICU admissions, and all received mechanical ventilator support, with a median duration of 92 days prior to gabapentin initiation. This is important to mention because the term "neonatal delirium" or "neonates" is mentioned. Although they are patients in the NICU, these patients are infants and could be similar in characteristics to infants in the PICU. And despite the lack of studies assessing the validity of delirium scoring in infants <6 months of age, the 2022 Society of Critical Care Medicine's pain, agitation, neuromuscular blockade and delirium (PANDEM) guidelines recommend routine screening for all pediatric patients in the PICU.[6]

Second, the concern raised about the delirium protocol implemented at the institution. We agree with the concern about antipsychotic medications being used in neonates but would expand this to include young infants as well. This delirium protocol was developed based on previous reports of the treatment of delirium in the NICU and PICU to provide guidance for our providers for order of initiation of agents.[6–8] Therefore, the study was conducted to explore how gabapentin was being prescribed by providers based on the protocol and to determine if any NICU patient would require escalation to step 3 (antipsychotics) of the protocol. In the development of the protocol, our hope was that gabapentin and/or melatonin would be effective in mitigating symptoms, and we would not need to progress past step 2. Based on our findings, either gabapentin or gabapentin plus melatonin was effective for all patients in the study and no patient required escalation to need for initiation of antipsychotic agents. In fact, since the publication of this project, no patient has been initiated on antipsychotic agents in our NICU, as we share the concerns presented by Sharp et al.[1]

Third, the concern raised about the conclusions of the study. We agree that gabapentin improved scoring on pain scales and withdrawal assessments but did not show benefit for improvement of delirium scoring. We note that this was an oversight in the conclusion section of the article, and we did not mention the lack of benefit on delirium scoring. Unfortunately, so few patients had documented CAPD scores prior to or after gabapentin initiation, so this significantly limited our ability to analyze this information and make a strong conclusion due to risk for a Type 2 error. However, as mentioned previously, it is encouraging that no patients required initiation of antipsychotic agents; this would imply that CAPD scores were not continuing to rise after initiation of gabapentin. Regarding the title of the article, we still believe that delirium should be included in the title because the use of gabapentin was associated with the institution's delirium protocol. Therefore, it would have been disingenuous to remove delirium from the title because we did not have significant study results related to CAPD scores.

In conclusion, we appreciate the opportunity to respond to the letter by Sharp et al[1] to clarify a few points. We do agree with the conclusions that they emphasize in the final paragraph of their letter. Identification and diagnosis of patients in the NICU is difficult, specifically if those patients are neonates at <28 days of life. We believe that gabapentin can be useful for some infants in the NICU, but further research on efficacy, safety, and long-term neurodevelopmental outcomes is needed. Last, we also agree that antipsychotic agents should be avoided in this population if possible. If antipsychotic agents are used, it should be used in a research setting with strict monitoring of clinical and neurodevelopmental outcomes.

Eugenie Chang, PharmD; Avery Parman, PharmD; Peter N. Johnson, PharmD; Katy Stephens, PharmD; Stephen Neely, MPH; Nalini Dasari, MD; Netsanet Kassa, MD; and Jamie L. Miller, PharmD

Article Information

Affiliations. Department of Pharmacy (EC), Bethany Children's Health Center, Oklahoma City, OK; Department of Pharmacy: Clinical and Administrative Sciences (JLM, SBN, PNJ), College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Pharmacy (AP, KS), Oklahoma Children's Hospital at OU Health, Oklahoma City, OK; Department of Pediatrics (ND, NK), College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Correspondence. Jamie L. Miller, PharmD; jamie-miller@ouhsc.edu

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References

1. Sharp AN, Chavez-Valdez R, Burton VJ, et al. Correspondence on "gabapentin for delirium in infants in the neonatal intensive care unit". *J Pediatr Pharmacol Ther*. 2025.
2. Chang E, Parman A, Johnson PN, et al. Gabapentin for delirium in infants in the neonatal intensive care unit. *J Pediatr Pharmacol Ther*. 2024;29(5):487–493.

3. Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. *Crit Care Med*. 2014;42(3):656–663.
4. Silver G, Kearney J, Traube C, Hertzig M. Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium. *Palliat Support Care*. 2015;13(4):1005–1011.
5. Siegel EJ, Groves AM, Silver G, et al. Delirium in the NICU: a point prevalence study. *Hosp Pediatr.* 2021;11(11):e321–e325.
6. Smith HAB, Berkenbosch JW, Betters KA, et al. 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockage, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Ped Crit Care Med*. 2022;23(2):e74–e110.
7. Capino AC, Thomas AN, Baylor S, et al. Antipsychotic use in the prevention and treatment of critically ill infants and children with delirium. *J Pediatr Pharmacol Ther*. 2020;25(2):81–95.
8. Sacha GL, Foreman MG, Kyllonen K, Rodriguez RJ. The use of gabapentin for pain and agitation in neonates and infants in a neonatal ICU. *J Pediatr Pharmacol Ther*. 2017;22(3):207–211.