One of the most challenging questions in the neonatal intensive care unit (NICU) is how neonatal seizures should be treated. Currently used drugs work approximately half the time – good news for some patients but not for others (1). Medications designed for a physiologically older age group (i.e., non-neonates) may be less effective in neonates due to differences (compared with older patients) in pharmacokinetics (e.g., absorption and elimination). Just as important, the role played by GABA (traditionally considered to be an inhibitory neurotransmitter) is less clear in neonates (2). At the same time, drugs currently used to treat seizures in neonates may carry a risk of adverse effects in the developing brain, including cell death and abnormal behavior and development (3, 4). These effects need to be considered against the risks of ongoing seizure activity. In general, the longer the exposure to a drug, the greater the risk of adverse reactions. But can one dose of a medication make much of a difference? Forcelli et al. explore this question and conclude that even a single exposure to certain seizure medications can have a prolonged adverse effect. There may however, be safer alternatives.

Forcelli et al. studied electrophysiological and morphologic changes in medium spiny neurons (MSNs) from the striatum of rat pups after exposure to seizure drugs on postnatal day 7 (P7) or P10. The authors chose this cell population because of their prior work showing neurons in this region are susceptible to cell death after seizure drug exposure (3). MSNs receive input from both excitatory glutamatergic and inhibitory GABAergic neurons and integrate both cortical and subcortical signals before producing activity that impacts motor function, including motor learning and memory (5).

OBJECTIVE: Drug exposure during critical periods of brain development may adversely affect nervous system function, posing a challenge for treating infants. This is of particular concern for treating neonatal seizures, as early life exposure to drugs such as phenobarbital is associated with adverse neurological outcomes in patients and induction of neuronal apoptosis in animal models. The functional significance of the preclinical neurotoxicity has been questioned due to the absence of evidence for functional impairment associated with drug-induced developmental apoptosis.

METHODS: We used patch-clamp recordings to examine functional synaptic maturation in striatal medium spiny neurons from neonatal rats exposed to antiepileptic drugs with proapoptotic action (phenobarbital, phenytoin, lamotrigine) and without proapoptotic action (levetiracetam). Phenobarbital-exposed rats were also assessed for reversal learning at weaning.

RESULTS: Recordings from control animals revealed increased inhibitory and excitatory synaptic connectivity between postnatal day (P)10 and P18. This maturation was absent in rats exposed at P7 to a single dose of phenobarbital, phenytoin, or lamotrigine. Additionally, phenobarbital exposure impaired striatal-mediated behavior on P25. Neuroprotective pretreatment with melatonin, which prevents drug-induced neurodevelopmental apoptosis, prevented the drug-induced disruption in maturation. Levetiracetam was found not to disrupt synaptic development.

INTERPRETATION: Our results provide the first evidence that exposure to antiepileptic drugs during a sensitive postnatal period impairs physiological maturation of synapses in neurons that survive the initial drug insult. These findings suggest a mechanism by which early life exposure to antiepileptic drugs can impact cognitive and behavioral outcomes, underscoring the need to identify therapies that control seizures without compromising synaptic maturation.
Seizure Medications in Neonates

A number of clinically relevant questions follow from these findings. Would similar effects be noted if there was only a single exposure of medication at doses more commonly used in the NICU? Because phenobarbital is not typically prescribed to infants who do not have some evidence of neurological illness, would potential benefits outweigh the risks in the setting of hypoxic ischemic injury or neonatal encephalopathy? Both questions were addressed in another study showing that CD1 mice treated with phenobarbital (30 mg/kg) after unilateral carotid ligation and hypoxia (at P12) have fewer seizures and a lower volume of brain atrophy, as well as a resumption of normal exploratory behavior, compared to control mice (10). Similar to the present study, higher doses of phenobarbital (60 mg/kg) afforded no benefit and may have been deleterious. Another question is whether adjunctive therapy used for neonatal encephalopathy (i.e., cooling, erythropoietin, bumetanide) alters outcomes in neonates exposed to phenobarbital. Compared with cooling alone, cooling and adjunctive phenobarbital (40 mg/kg) were associated with improved functional and pathological outcomes in rat pups that underwent a carotid ligation/hypoxia injury at P7 (i.e., the same time as those in Forcelli et al.) (11). Thus, combination therapies may act synergistically, at least in the context of neonatal encephalopathy. Finally, does drug-induced apoptosis (or other forms of cell death with potential benefit, such as autophagy) provide a “quality control” function (i.e., by eliminating dysfunctional neurons) that might be missing if non-apoptosis-inducing medications are used? Careful studies should be able to provide an answer. Confirmation of the current findings in neocortical and hippocampal neurons (i.e., other regions known to show short- or long-term pathology after neonatal insults) also would be useful to study in the paradigms used in these studies.

In the NICU, potential benefits must outweigh the risks of treatment. Given the lack of large, high-quality clinical trials to guide medication choice, as well as the ethical difficulty of performing randomized studies of adverse effects, clinicians depend to a certain degree on preclinical studies. The findings of Forcelli et al. raise awareness of the potential dangers of using some of the most commonly used medications for neonatal seizures. The value of this study is that the risk:benefit ratio of phenobarbital should be reconsidered, particularly in infants without encephalopathy or significant injury (i.e., neonatal seizures without a clear underlying cause). Other data (discussed previously) suggest infants with neonatal encephalopathy may benefit from modest doses of phenobarbital. One additional caveat is that all these data have been generated in rodent models, not humans, and important translational differences may not have been appreciated yet. Until additional clinical data regarding its adverse effects on the brain become available, the use of phenobarbital for treating neonatal seizures likely will continue worldwide because less detrimental alternatives (e.g., levetiracetam) have not been studied as thoroughly as phenobarbital. Alternative medications also may not be as available as phenobarbital in developing economies. Nonetheless, Forcelli et al. remind us to maintain a healthy skepticism about treatments we use and suggest alternatives that may make our practice safer.

by Adam L. Hartman, MD
Seizure Medications in Neonates

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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2. First Name  Adam     Last Name Hartman  Degree MD

3. Are you the Main Assigned Author?  ☒ Yes  ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title: Primum non nocere: Are Seizure Medicines Safe in Neonates?

5. Journal Issue you are submitting for:  13.4

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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<th>Money to Your Institution*</th>
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