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The medical treatment of seizures in newborn babies has remained unchanged for decades. In the past decade, experts in neurology, neonatology, and epilepsy have met on several occasions to discuss the urgent need to study novel anti-seizure agents in newborns;^{1,2} however, since 1999, despite many recommendations, no group has been able to successfully undertake an efficacy trial to assess treatment of electrographic seizures in neonates.

In *The Lancet Neurology*, Ronit Pressler and members of the Treatment of NEonatal seizures with Medication Off-patent (NEMO) consortium³ report the results of a dose-finding and feasibility trial to assess the safety and efficacy of bumetanide (a loop diuretic with anti-convulsant effects in pre-clinical trials) in full-term neonates with hypoxic ischaemic encephalopathy and seizures not responding to a loading dose of phenobarbital. 14 neonates were enrolled (of 24 planned); the trial was terminated early because of a concern for possible increased risk of hearing loss and failure to achieve the a priori outcome for seizure control.

Two crucial questions arise from this trial; first, should bumetanide be studied again (perhaps with a different dosing schedule or a different study design)? How does the NEMO experience inform future neonatal seizure drug trials? Whether to study bumetanide again raises issues of safety and efficacy. Three (27%) of 11 newborn babies had hearing loss. Although there is no obvious comparison group to measure hearing loss in neonates with refractory seizures due to hypoxic ischaemic encephalopathy and receiving aminoglycosides, the rate in neonates receiving bumetanide is higher than the 4–7% reported in trials of hypothermia in neonates with hypoxic ischaemic encephalopathy,⁴ and higher than the 3–4% the investigators report from their own previous data. Although the study design does not offer proof of ototoxicity, the data were suggestive enough to stop the study, and warrant careful thought before new trials are started. As for efficacy, two (14%) of 14 children had the a priori outcome measure of more than 80% reduction in seizure burden (when compared with baseline, 2 h before administration of study drug), without need for additional rescue seizure drug. However, five children had no seizures during the baseline period, so were de facto treatment failures. Researchers note “fluctuations

[in seizure burden] make the study of electrographic seizures as a primary outcome measure problematic if too short a period is used for comparison.”

Nonetheless, this well-done study by experienced investigators has great use to inform future trials for seizure drugs in neonates. The study design was a Bayesian sequential dose escalation design, in which each child received active drug. Although compelling in that it might offer a quicker answer regarding efficacy, the design is problematic because it makes it difficult to adequately measure side-effects, and to assess for efficacy endpoints that fall short of a pre-determined rate of seizure resolution or reduction. Inclusion of a control group would permit more accurate measurement of side-effects and better understanding of fluctuations in seizure burden, and allows for comparisons of seizure burden measured as a continuous variable. The a priori outcome, an 80% reduction in seizures without need for rescue medication in at least 50% of participants is similar to what has been suggested elsewhere.^{1,2} However, this stringent outcome measure risks overlooking drugs that have a better safety profile than standard drugs, such as phenobarbital, with similar or marginally better efficacy. Additionally, investigators have debated whether neonatal seizure trials should include measurement of developmental outcomes and epilepsy, or whether higher efficacy for seizure termination is necessary before studying longer-term outcomes.⁵ Phenobarbital and phenytoin, common first-line and second-line drugs, harm the developing brain in animal studies, whereas newer agents such as levetiracetam and topiramate do not.⁵⁻⁷

Future neonatal drug trials need to enroll sufficient participants (preferably randomised with a control group) to account for expected fluctuations in seizure burden. The choice of outcome measure needs to be carefully weighed, and less stringent measures considered, especially in drugs that are expected to have lower side effect profile than standard care. The investigators appropriately conclude by offering caution in the use of off-label drugs in newborn babies before safety assessment in controlled trials. Use of unstudied agents like levetiracetam is widespread⁸ and is probably increasing, despite limited data about their safety and efficacy.

There is an urgent need to study novel agents in neonates with seizures. The NEMO consortium has taken

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a big step toward improving the treatment of seizures in neonates and will hopefully take lessons learned from this study into their next trial.

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Tackling diagnostic delays in ALS

Delays in the diagnosis of amyotrophic lateral sclerosis (ALS), which depends on the identification of concomitant upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction, are a huge challenge in the management of the disorder. Better methods are urgently needed to detect early symptoms and enable timely referral and intervention. In *The Lancet Neurology*, Parvathi Menon and colleagues¹ present promising results of a large, prospective study of threshold tracking transcranial magnetic stimulation (TMS) for the diagnosis of ALS.

The idea that ALS originates in the cortical motor neurons, with consequent demise of bulbar and spinal motor neurons by anterograde transneuronal degeneration (the dying forward or corticomotoneuronal hypothesis), was first suggested more than 20 years ago.² This hypothesis has been supported by findings from TMS, which can identify UMN dysfunction early in the disease course.³ Hand muscles are frequently affected first in ALS; their specific, highly fractionated movement depends on the monosynaptic corticomotoneuronal pathway, which supports the idea of preferential initial involvement of the large cortical motor neurons.² However, despite widespread evidence from TMS studies that UMN dysfunction is affected early,³ some results with the same technique are contradictory.⁴ Some investigators claim that the disease results from retrograde transneuronal motor neuron damage due to reduced concentrations of neurotrophic factors in the terminal axonal branches.

Findings from studies in humans with ALS⁵ and in animals⁶ show very early changes in the endplate region, with disturbed neuromuscular transmission. Finally, the disease could affect the UMN and LMN independently, although the fact that the most atrophic side of the body shows marked signs of UMN involvement suggests otherwise.⁴

Findings from TMS studies show that the most relevant early indicator of UMN abnormality is cortical hyperexcitability, which can be shown with the short-inhibitory cortical interval.³ Intelligent application of the threshold tracking method (originally developed to test axonal excitability) to brain stimulation has enabled this abnormality in ALS to be explored, with publication of a large set of data.^{1,3} Cortical excitability is increased in other neurodegenerative disorders, such as Alzheimer's⁷ and Parkinson's⁸ diseases, which suggests that loss of cortical inhibitory interneurons is common in neurodegeneration.

Menon and colleagues¹ now show that threshold tracking TMS in ALS is sensitive and specific for diagnosis of the disorder, enabling detection of early signs of UMN dysfunction when LMN involvement is not severe enough to reduce peripheral motor responses to amplitudes lower than 1 mV. Additionally, the technique is useful in differential diagnosis between ALS and other neuromuscular conditions, as shown by Menon and colleagues,¹ and could support early interventions and inclusion in clinical trials. The technique has been used persistently and systematically by this group of



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