

Advocacy for children with epilepsy: Leveraging the WHA resolution. Advocacy Task Force, Commission of Pediatrics, International League Against Epilepsy

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SUMMARY

In May 2015 the World Health Assembly (WHA) approved the Resolution on the Global Burden of Epilepsy. This report addresses how the Resolution can be leveraged to improve the care of children with epilepsy worldwide. Children with epilepsy have unique needs and face unique challenges from stigma at all levels of society. Children lack a voice to lobby for their own needs, including their right to have access to education. Effective leadership and governance should be enhanced through the support of stakeholders empowered to counsel, advise, and lobby for appropriate care. National health care plans should integrate primary and specialist care, and they need to be adapted to local specificities. Antiepileptic medicines should be widely accessible in appropriate, sustained, and affordable ways. Public awareness initiatives are needed to improve the inclusion of affected children in society and to reduce stigma. Cost-effective interventions are also needed to address preventable causes of epilepsy. Without greater investment in research, evidence-based interventions cannot be implemented. Through all of this, civil society must be engaged to ensure that the multivariate dimensions from the clinic to the community are addressed to fulfil the needs of children with epilepsy.

KEY WORDS: Seizures, Treatment gap, Education, Training, Advocacy.

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The World Health Organization (WHO) has defined health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”¹ The Dartington Social Research Unit identified 5 different “lenses” for children’s well-being, namely needs: assessing the needs of children and families within specific communities, eradicating poverty (with a focus on child poverty), improving the quality of life of children (through a range of initiatives such as having safe places to play), promoting social and emotional learning in school, and addressing social exclusion, and, finally, children’s rights.² The first 4 areas, or “lenses” are reasonably well delineated, but the area of children’s rights is less clearly defined.

In May 2015 the World Health Assembly (WHA) approved the WHO Resolution on the Global Burden of Epilepsy.³ The Resolution addresses the need for coordinated action against epilepsy at a country level to address

KEY POINTS

- The Global Burden of Epilepsy Resolution can be used to improve the care of children with epilepsy worldwide
- Children with epilepsy have unique needs and face unique challenges from stigma at all levels of society
- Cost-effective interventions are needed to address preventable causes of epilepsy
- Civil society must ensure that the multivariate dimensions, from clinic to community, address the needs of children with epilepsy

implications for health, social, and public knowledge. The Resolution was facilitated by collaboration between WHO, the International League Against Epilepsy (ILAE), the International Bureau for Epilepsy (IBE), and other professional societies, including the World Federation of Neurology (WFN).⁴

Eight key areas are highlighted: (1) strengthen *effective leadership and governance*; (2) introduce and implement *national health care plans*; (3) integrate epilepsy management into *primary health care*; (4) improve *accessibility to antiepileptic medicines*; (5) ensure *public awareness of and education about epilepsy*; (6) promote actions to prevent causes of epilepsy; (7) improve investment in *epilepsy research*; and (8) engage with *civil society*.

This report addresses how these actions relate to the care of children with epilepsy worldwide.

STRENGTHEN EFFECTIVE LEADERSHIP AND GOVERNANCE

To address the specific needs of children with epilepsy and make resources available for evidence-based plans and actions, key stakeholders must be identified that are well positioned to influence regional and national attitudes, lobby for care, and implement recommendations. The successful submission of legislation in Argentina and Colombia that led to effective action for people with epilepsy are impressive examples of this process occurring.⁵

The preparation of methodologically sound guidelines should include representation of all relevant stakeholders, to ensure that the policies to be developed are viable, effective, and truly reflect the needs of the target population.^{6,7}

In particular, representation of skilled personnel in governance and leadership positions, such as national Departments of Health (DOHs), is an essential requirement. In addition, those in leadership positions should have access to counseling and advice from regional key experts. The report by the Epilepsy Advocacy Europe Task Force of the ILAE eloquently documented how an expert working group could

draw up an effective strategic plan to advocate for the needs of people with epilepsy.⁸

Ensuring that the needs of children are adequately met is often a challenge, because children have a unique list of vulnerabilities.⁹ For guidelines to be accepted and successfully acted upon, it is critical to involve those institutions that can provide the infrastructure for the project. These are usually governmental bodies, namely the DOH or Ministry of Health (MOH). ILAE and IBE chapters are well placed to liaise with DOH/MOHs to support this process, to assist with the identification of key experts to be involved in committees, and to provide access to high-quality guidelines. A multilayered approach involving DOH/MOHs and early engagement of all stakeholders, including health practitioners, should ensure that resources are available to implement appropriate interventions.

INTRODUCE AND IMPLEMENT NATIONAL HEALTH CARE PLANS

National healthcare plans aimed at overcoming inequalities and inequities in epilepsy management must be viable and relevant to the local context. Although guidelines should be a major component of national health care plans, many existing “guidelines” do not have a strong evidence base and their development did not incorporate a sound methodological approach, such as compliance with the AGREE principles. These documents, therefore, reflect more expert opinion than evidence-based medicine.¹⁰

A recent systematic review of epilepsy guidelines identified substantial gaps in the covered topics (with only 22% of reports focused on children), and considerable methodological heterogeneity, highlighting the limitations in the quality of existing recommendations.¹¹

To implement and adapt epilepsy guidelines (or recommendations), local resources and needs must be understood, including an assessment of locally prevailing causative factors and barriers to care. National health care plans will not be viable if implementation does not include local adaptation.^{12–14} Examples of guidelines that are well developed and constantly reviewed and adapted are those produced by the National Institute for Health and Care Excellence (NICE) in the United Kingdom,^{15,16} the practice parameters of the American Academy of Neurology (AAN) and the American Academy of Pediatrics (AAP) in the United States,^{13,14,17,18} and the updated 2016 WHO guideline Pediatric Emergency Triage Assessment and Treatment (ETAT).¹⁹ Ensuring access to effective epilepsy surgery programs should also be a component of any epilepsy care guidelines and national health care plans.

When developing guidelines and recommendations there needs to be a balance of the reality of the local capacity with a clear statement of the specific services that any child with epilepsy, regardless of location, should be able to access,

without neglecting issues related to social and educational environment. In some regions, access to even the most basic skills in diagnosing epilepsy and a sustained supply of antiepileptic drugs (AEDs) are lacking. This situation violates the rights of the child who is unwittingly born into this setting. Including in the recommendations a standard approach to care is important to enable local settings to improve their services.

INTEGRATE EPILEPSY MANAGEMENT INTO PRIMARY HEALTH CARE

In most parts of the world, children with epilepsy are not managed by child neurologists, let alone pediatric epilepsy specialists. Integrating epilepsy management into primary health care is an essential step to reduce the treatment gap and requires effective training programs.²⁰ These programs should be aimed at training nonspecialist health care providers, and at empowering people with epilepsy and their caregivers for greater use of self- and home-care programs.^{12,21}

The treatment gap is 48.9% across Africa, 64.3% across Asia, and 55.4% across Latin America, with worldwide figures of figures of 46.8% in urban settings and 73.3% in rural settings.²² Up to 89% of children in one region in rural Kenya were not diagnosed or treated for their epilepsy.²³ The treatment gap is associated with, and exacerbated by, lack of manpower, incorrect cultural beliefs about epilepsy, and poor access to AEDs.²⁴ In low- and middle-income countries (LAMICs), children are typically first assessed by a traditional healer or a primary health care worker. Chronic care is often by an adult physician or a psychiatrist.²⁵ In these settings, for developing effective and practical education programs the appropriate groups is essential.²⁶ An example is the “Paediatric Epilepsy Training” (PET) program developed by the British Paediatric Neurology Association, now being adapted to reach resource-limited settings in Asia, Africa, and Latin America (<https://www.bpna.org.uk/pet/>). These concise courses can reach a wide field of health care workers and provide practical tools for and effective management of children with epilepsy. In Latin America, the Pan American Health Organization (PAHO), in collaboration with ILAE and IBE, has also implemented a series of projects.⁵ Examples include epidemiological research on epilepsy to design interventions to reduce the treatment gap, the creation of specialized health care clinics in Mexico, development of the E-Jaguar website in Brazil to educate the general public in order to improve health care and quality of life for people with epilepsy, and the organization of workshops in Uruguay to raise awareness and change practice.⁵ The demonstration project in China rolled out under the auspices of the Global Campaign Against Epilepsy, illustrated that this community-based intervention was able to reduce the burden of epilepsy through increased

access to phenobarbital.²⁷ Other effective training programs include ILAE-supported on-line courses, such as those organized within the setting of the Virtual Epilepsy Academy (VIREPA). ILAE is also acting to address key gaps present in some geographical areas, including the lack of skilled staff in neurophysiology, nursing, neuropsychology, and neurosurgery.

IMPROVE ACCESSIBILITY TO AND AFFORDABILITY OF QUALITY-ASSURED ANTIEPILEPTIC MEDICINES

The developing brain may show an increased vulnerability to the adverse effects of AEDs.²⁸ Worldwide, phenobarbital (Pb) is the most common agent prescribed to children.²⁹ Concerns about its impact on neurodevelopment were raised by an early study in which its use as prophylaxis for febrile seizures (a now obsolete indication) was associated with a mean drop of 8 points in intelligence quotient (IQ) scores over 2 years, which did not completely resolve after withdrawal of the drug.^{30,31} Other studies, however, have not confirmed such detrimental effects.³² For example, in a randomized comparison of Pb (maximum dose 3 mg/kg/day) to phenytoin (maximum dose 5 mg/kg/day) in 94 children with epilepsy from rural India, no significant differences in parental reported behavioral side-effects or efficacy were found.³³ In a cohort of 1780 children and adults from China, in which Pb was used in one-half of the cases, 25% of those treated with Pb became seizure-free and 23% had adverse events leading to withdrawal of the drug.³⁴ In a systematic review that included 20 studies evaluating the effects of Pb, the authors identified methodological problems across studies, but also evidence that the agent is associated with higher withdrawal rates for adverse events compared to valproate, carbamazepine, and phenytoin.³⁴

The WHO has devised the Essential Medicines List (EML) to promote access to effective medications (Table 1).³⁵ The EML is intended as a guide for the development of national and institutional essential medicine lists. Although the list was not designed as a global standard, there is general acceptance that it is a powerful tool to promote health equity. However, being on the EML does not ensure access to a drug in the local market. There are countries, including some high-income countries, where low-priced drugs such as Pb have been withdrawn, and other countries, with India as a notable example, where ethosuximide is not available.^{36,37} Especially in LAMICs, AEDs that are formally approved but poorly profitable may not be readily available at clinics or pharmacies, resulting in the paradox that the most affordable drugs are often the least accessible. In the case of Pb, which has the lowest cost, accessibility is further hampered by its classification as a controlled substance, subject to acquisitions and dispensation requirements, which represent a disincentive to making it accessible.³⁸ The

EML does not include some newer generation AEDs, such as vigabatrin (a first-line treatment for infantile spasms), topiramate, and levetiracetam. As evidence develops to support targeted use of these newer drugs, a strong case should be made for the inclusion of these agents.

Use of low-cost generic AEDs can facilitate interventions to reduce the treatment gap, but concerns have been expressed on their comparative safety. Although there are reports of adverse outcomes associated with the use of generic AEDs, a review of the overall evidence from studies in high-income countries does not suggest an association between loss of seizure control and generic substitution.^{39,40} In fact, many observational studies that reported worsening of seizures or appearance of side effects with the use of generic AEDs are likely to have been affected by reporting bias, and by the misperception (often fueled by manufacturers of brand products) that many patients and physicians have about the quality of generic drugs.⁴⁰ At least 3 recent rigorous prospective studies conducted in the United States with lamotrigine, a drug frequently subject to reports of adverse outcomes from generic switching, failed to provide any evidence that use of generics was harmful.^{41–43} These findings, however, may not be applicable to geographical settings where regulatory control over the quality of generic drugs is less stringent than in Europe or the United States. Indeed, there is evidence that the quality of some medications available in certain LAMICs is grossly substandard.⁴⁴ The preliminary data from the quality of AEDs in Africa (Quaeda) study in Kenya and Gabon, found that in most settings AEDs met required standards; however, 5% of supplied AEDs were found to be fake drugs.⁴⁵ This problem affected particularly phenobarbital and phenytoin. As such, the challenge is not so much generic switching, as access to good quality AEDs. This crucial issue needs to be addressed in close collaboration with governmental institutions of those countries.

ENSURE PUBLIC AWARENESS OF AND EDUCATION ABOUT EPILEPSY

Stigma in people with epilepsy is associated with low quality of life and poor psychosocial health outcomes, and

Table 1. The 2017 Essential Medicine List of AEDs for children with epilepsy.³⁵

Carbamazepine (oral)
Diazepam (gel or solution for rectal)
Lamotrigine (oral)
Lorazepam (injection only)
Midazolam (oromucosal only)
Phenobarbital (oral and injection)
Phenytoin (oral and injection)
Valproic acid (oral)
<i>Complementary list</i>
Ethosuximide (oral)
Valproic acid (injection)

its effects may be particularly felt by adolescents, who are already dealing with the challenges of developing self-identity and self-esteem.^{46,47} Epilepsy stigma has 3 different levels; internalization, interpersonal, and institutional. Internalization often relates to the emotion of shame suffered by the affected parties. Parental, teacher, and health care worker reactions can further negatively influence this. The interpersonal level relates to the negative responses where the child with epilepsy is regarded as spiritually possessed or cursed, mentally ill, or infective. At an institutional level, epilepsy support groups need to challenge the current social concept of epilepsy with regard to disability and stigma.

Faced with the prospect of stigma, children with epilepsy and their parents adopt varying disclosure management strategies, from concealment to voluntary disclosure.⁴⁸ Barriers to disclosure include fear of stigmatization and rejection. Factors that support disclosure include willingness by others to engage with and learn about epilepsy.

Although epilepsy-associated stigma is prevalent in all settings, its expression is highly influenced by the cultural context. In sub-Saharan Africa, particularly in rural regions, close family ties, communal living situations, and traditional belief systems influence the expression of stigma.⁴⁹ Many children with epilepsy in this region, which has a high treatment gap, experience seizures in locations where severe burns, drowning, and fractures may result.⁵⁰ Burn scars are seen as a mark of intractable epilepsy. Many people in sub-Saharan Africa believe seizures to be contagious, and spread by saliva and other body fluids expelled during a convulsion. The fear of contagion results in isolation and unwillingness of bystanders to intervene and prevent injury. Supernatural beliefs, such as witchcraft, are frequently cited as causing seizures.⁵¹ Misdiagnosis and poor management are common; for example, children with malaria-induced febrile seizures may have deferred medical intervention as parents visit traditional healers rather than seek immediate medical treatments from local clinics. Families may not be able to afford to educate all children in the family, and parents may choose not to invest in a child with epilepsy whose employment options are limited. Parents may also remove a child from school to avoid the embarrassment that might occur should the child have a seizure. In some regions teachers expel children with epilepsy from school because of misbeliefs related to the child's disorder.⁵² Children with epilepsy may be hidden from visitors, physically segregated, and even removed to remote areas.⁵³ In these settings, most primary health care providers receive little training in neurological care, and some of these medical practitioners attribute seizures to supernatural causes.^{12,51,54,55} Traditional healers are key figures in mediating stigma and may profit from stigmatizing beliefs about witchcraft causing epilepsy.

Stigma stems largely from ignorance and lack of adequate information. In a survey of 1167 adults in Moscow,

Russia, about 60% of the survey participants believed that epilepsy was a type of mental retardation, 34% of respondents were afraid of staying close to a person with epilepsy, and almost half stated that they would object to their child playing or studying with a boy or girl who had epilepsy.⁵⁶ The survey illustrated the importance of public education in reducing the stigma of epilepsy.

In all settings, education is key in fighting stigma and its consequences. Youth with epilepsy have 3 themes, which fall under medical, educational, and social challenges,⁵⁷ and these need to be addressed through improvements in public awareness and changes in public policy. In a US study, differences in the attitude toward mental health care and epilepsy-related stigma between Hispanic and Caucasian mothers resolved after they read a brochure on the neurobehavioral comorbidities of epilepsy.⁵⁸ Educational interventions are particularly effective when targeted to school children and their teachers. In a cohort of Czech children, use of a video led to reduced stigma.⁵⁹ In a randomized Canadian study that enrolled 783 grade 5 students (9–11 years), implementation of an epilepsy education program was associated after 1 month with a significant increase in epilepsy knowledge and positive attitudes in the intervention group 1 month later compared with the control group.⁶⁰ In an Italian study, education of primary school teachers improved the management of a child during a seizure, but the belief that epilepsy was a source of social disadvantage remained unaffected by the educational intervention.⁶¹ The study suggested that the education program addressed readily the lack of knowledge, but stronger intervention would be needed to counteract stigmatizing behaviors. In a study from Germany, an intervention with preschool teachers succeeded in training them to administer anticonvulsant rescue medication, which allowed for an increase in their level of self-confidence with regard to children with epilepsy.⁶²

PROMOTE EVIDENCE-BASED INTERVENTIONS TO ADDRESS PREVENTABLE CAUSES OF EPILEPSY

The WHO estimates that children in LAMICs are 16 times more likely to die before 5 years of age compared to children in high-income countries.⁶³ Almost 75% of these childhood deaths are attributable to 6 preventable conditions: neonatal causes (preterm birth, asphyxia and infections), pneumonia, diarrhea, malaria, human immunodeficiency virus (HIV), and measles.

In these countries, one-third of childhood epilepsies are related to perinatal insults, whereas parasitic infections account for one-third of epilepsy cases in adults.⁶⁴

Maternal ill-health inclusive of chronic infections (eg, HIV, tuberculosis), toxin exposure (eg, alcohol and

substance abuse), and poor nutrition (including iron deficiency), as well as poor access to obstetric services, are major risk factors for having a neurologically compromised child.⁶⁵ In resource-poor settings most babies are delivered at home without access to skilled birth attendance services.^{66,67} Among those infants surviving delivery, the number with neurodisability related to prematurity, birth asphyxia, and infections is far higher in LAMIC than in high-income countries.

The environment where a child grows up in may influence his/her health status. Some regions of Africa, Asia, and Latin America are endemic for neurocysticercosis, malaria, rabies, and tuberculosis. Overlying these issues is the genetic make-up of the child which, whilst influenced by environmental factors, contributes to the clinical phenotype. Most studies on the influence of genetic factors were conducted in resource-rich countries, and it is unclear whether the same factors are similarly expressed in other parts of the world, and especially in LAMICs.⁶⁸ At the end of 2014 there were an estimated 2.6 million children younger than 15 years of age worldwide living with HIV infection, with approximately 88% living in sub-Saharan Africa.⁶⁹ Neurological disease is common in infected children due to primary HIV infection, secondary or opportunistic infection, and from treatment-related complications. In LAMICs, only one-third of children requiring antiretroviral therapy receive it.⁷⁰ Seizures are common, and epilepsy occurs in up to 14% of affected children.^{71,72}

Twenty-three percent of neonates who survive meningitis in LAMICs have moderate to severe neurological sequelae.⁷³ Tuberculous meningitis affects around 1% of all people with tuberculosis, and results in death or severe disability in about 50% of cases.⁷⁴ Children with cerebral malaria often present with acute convulsive seizures, a factor associated with a poor prognosis.⁶⁴ Neurocysticercosis is also endemic in many LAMICs, due to poor pig management practices and sanitation, and is a leading cause of epilepsy in these regions.⁷⁵

Traumatic brain injury in children living in LAMICs is an often-avoidable complication related to easy access to busy roads that lack barriers or traveling unrestrained in vehicles.⁷⁶

A large proportion of cases of childhood death, neurodisability, and epilepsy worldwide could be prevented with better obstetric and neonatal care, effective vaccination programs, use of mosquito repellents and bed nets for malaria, measures to reduce mother to child transmission programs and early antiretroviral therapy (ART) intervention for HIV and avoidance of Zika virus in endemic regions by pregnant women. Inclusion of epilepsy prevention and care in WHO activities related to child and maternal health (communicable and noncommunicable disorders) should also promote early recognition of seizures and epilepsy in these at-risk groups.

INVEST IN EPILEPSY RESEARCH AND INCREASE RESEARCH CAPACITY

Historically, there has been a paucity of well-designed studies evaluating the efficacy and safety of AEDs in children, with very few or no studies conducted in rare epilepsy syndromes of infancy and childhood.^{77,78}

As a result, there is a poor evidence base for the use of many medications in pediatric age, and the fact that many AEDs are not licensed for use in children or for epilepsies occurring predominantly in infancy and childhood results in frequent off-label prescribing in the younger age groups.⁷⁹

Exclusion of pediatric populations from AED trials has also hampered the development of better treatments for children with epilepsy.⁸⁰

Although for some epilepsy syndromes, such as focal epilepsies, efficacy data can be reasonably extrapolated from adults to children within a specified age range, the same does not necessarily apply to tolerability and safety.¹⁰ Moreover, specific studies are needed to evaluate efficacy and safety in syndromes that occur exclusively or predominantly in the pediatric age group.⁸⁰

In recent years the European Union and the United States have enacted legislative and regulatory changes to encourage pharmaceutical companies to invest in research involving children. The international forum of standards for research with children (<http://www.ifsrc.org/>) has led to an increased number of studies being conducted. Partly because of these efforts, in the last decade there has been an increase in investment of industry into the development of medications for pediatric orphan indications such as Dravet syndrome and Lennox-Gastaut syndrome.^{81,82} An area that still is in need of improvement, however, is the issue of including clinically meaningful endpoints in clinical trials. Regulatory endpoints such as 50% seizure reduction are of little clinical relevance, and improved study designs are needed to permit a more comprehensive evaluation of treatment effects by prioritizing measures, such as sustained seizure freedom and cognitive outcomes, that are of greater relevance to the child's quality of life.

How focused research could improve the future of children with epilepsy has been addressed in a recent publication.⁸³ The areas identified as priorities were patient outcomes, especially seizure control but also behavioral, academic, and social functioning; early and accurate diagnosis and optimal control of seizures; role and involvement of parents in communication and shared decision-making; as well as integration of school and community organizations with epilepsy care delivery. Emphasis was placed on the need for a proactive approach rather than reactive, for example, by focusing on preventing a crisis in management at the time of established pharmacoresistance. Identified barriers to care included inadequate evidence about many

aspects of diagnosis and management, and suboptimal access to specialized care for epilepsy and its comorbidities.

Similar research priorities have been highlighted in high-quality guidelines for children with epilepsy,^{11,83} and in the report of the ILAE European Advocacy Task Force.⁸

ENGAGE WITH CIVIL SOCIETY AND OTHER STAKEHOLDERS

It is essential that epilepsy is brought “out of the shadows.” This requires engagement of civil society to dispel misconceptions and ensure tolerance, support, and understanding for children with epilepsy. In the United States, the Epilepsy Foundation of America, supported by the Centers for Disease Control and Prevention, conducts annual multifaceted public education and awareness campaigns that target the broad population as well as specific subgroups, including adolescents, young adults, minority ethnic groups, and people with epilepsy and their caregivers.⁸⁴ Campaign channels have included traditional media, social media, and community opinion leaders and celebrity spokespersons.

Related effective engagement methods include the annual International Epilepsy Day events run by ILAE and IBE Chapters,⁸⁵ nongovernmental organization (NGO)-driven “Epilepsy Weeks,” radio and television programs reaching out to the general population, awareness campaigns involving sport champions such as the ILAE, “Stand up for Epilepsy” initiative (<https://www.ilae.org/about-ilae/public-policy-and-advocacy/epilepsy-and-sport-project-stand-up-for-epilepsy>), and recruitment as “epilepsy ambassadors” of sports and media celebrities who have epilepsy. There is a powerful message in these ambassadors showing how their condition did not preclude them from living a fulfilling life and making great achievements.

CONCLUSION

The WHA Resolution on the Burden of Epilepsy provides a unique opportunity to establish multiple layers of improved care for children with epilepsy. An important priority is in the area of prevention, without disregarding the need to establish services for early recognition and intervention. For these actions to occur, improved education across all sectors of society are needed. Access to care is a right for any child with epilepsy and should include access to health care providers who understand the condition and are empowered to deliver appropriate management. Interventions should be based wherever possible on evidence-based data, and research efforts must be stepped up in areas where adequate evidence is lacking. Successful actions will only be possible through engagement of parents, civil society, and governmental institutions. All stakeholders that supported and made the Resolution possible should be in the

frontline in ensuring that these priorities are addressed in a timely and effective way.

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DISCLOSURE OF CONFLICT OF INTEREST

JW is an associate editor for the journal *Epilepsia*. AG has nothing to disclose. MS has nothing to disclose. JHC has acted as advisory board member and/or speaker for Eisai, GW Pharma, Nutricia, Shire, UCB Pharma, Zogenix, and Takeda, for which remuneration was made to her department. She has been investigator for clinical trials for Vitaflor, Zogenix, and GW Pharma. EP received speaker and consultancy fees from Eisai, Biopharm Solutions, GW Pharma, LivaNova, Mylan, Sanofi, Sandoz, Shire, Sun Pharma, Takeda, and UCB Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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