Epilepsy is a major chronic noncommunicable neurologic disorder. Although a simple, safe, efficacious, and low-cost treatment has been available for nearly 100 years, the treatment gap remains disturbingly high in many low- and middle-income countries (LMICs). Treatment gap is generally defined as a “difference between the number of people with active epilepsy and the number being appropriately treated.” There are many reasons for this treatment gap; one important reason is an overly restrictive regulation on barbiturates such as phenobarbital (PB). These restrictive regulations deserve a wider and open discussion, even though epileptologists and others are intensely engaged on reducing the epilepsy treatment gap. With this article, we provide our viewpoint with an aim of raising an extremely important issue: undue regulatory restriction on phenobarbital, an essential lifesaving antiepileptic drug (AED).

**TEXT AND EVIDENCE**

**Essential drug status versus controlled substance status**

In many LMICs, PB is the first-line AED. This is because of its satisfactory efficacy, broad coverage for multiple seizure types, convenient use, low cost, and good tolerability. Countries where large-scale primary-care epilepsy treatment programs are ongoing have shown not only clinical improvements with PB, but also lower costs and long-term benefits for the patients. Although PB is an “essential” medicine on most essential drugs lists in LMICs, it is also listed with other barbiturates as a “controlled substance.” There is not any particular rationale or specific reason that PB has been listed as a scheduled substance other than that it is a barbiturate and therefore has a potential to be a drug of abuse. In China, where large demonstration project and national epilepsy programs have taken place, there have been no major negative impact on cognitive function of people with convulsive seizures treated with PB, but instead cognitive gains have been observed as a result of PB treatment. Treatment guidelines call for controlled substances such as AEDs to be readily available, but this has not been the case in many LMICs. As noted by the World Health Organization (WHO), international drug-control conventions provide the basic framework for national drug-control legislation (Box 1).

**Restrictions function at two levels**

Regulatory restrictions may function at two levels—international and national. First, restrictions posed by international agencies may restrict a country’s ability to meet its own drug requirements. For instance in Lao People’s Democratic Republic, the International Narcotics Control Board (INCB) delivers an annual quota of 25 kg of raw PB to Laos’s Food and Drug Department. This allows the production of 245,000 PB tablets per year, equivalent to 671 annual adult treatments. But Laos has >40,000 people with epilepsy (PWE) who need access to treatment, so the policy is contrary to what is required and what INCB declared in its recent annual report: “One of the fundamental objectives of the international drug control treaties is to ensure the availability of narcotic drugs and psychotropic substances for medical and scientific purposes and to promote access to and rational use of narcotic drugs and psychotropic substances.” Second, countries may introduce additional...
Role of pharmaceutical companies

By increasing production of PB, manufacturers may play an important role in increasing PB access and reducing the epilepsy treatment gap. However, it is likely that too many regulatory controls discourage pharmaceutical companies from engaging in active production of PB; as a result possibly affecting treatment coverage. Moreover, some countries have shown to have withdrawn PB with little notice. Ghana Health Ministry has recognized the importance of public-private partnership with pharmaceutical manufacturers in order to increase access to PB.

Potential cons of PB

Although PB is often viewed more as a drug of abuse than as a medication, PB in fact has low abuse potential. Abusing PB, for instance for suicide, should also be looked individually for each country, since there may be exceptions, such as Cambodia. In addition, almost all black market barbiturates are diverted from legitimate medical practice/sources. Therefore, use of security barcodes on the packets of AEDs (and other controlled substances) and specific registration numbers may be of help in reducing diversion to illicit market to some extent. This step could be feasible, since according to the WHO, just five countries—the U.S.A., Japan, Germany, France, and United Kingdom account for two-thirds of the value of all medicines produced worldwide. Moreover, in large studies conducted in LMICs, PB is not found to have a major cognitive neurotoxicity and in fact renders some cognitive gains to the patients treated with PB. Despite its numerous advantages and wider use, PB is not the ideal AED, but is just like any other AED. Coadministration of this or other enzyme-inducing AEDs and antiretroviral drugs can possibly result in virologic failure, breakthrough seizures, or AED or antiviral toxicity. The teratogenic risk of PB in pregnancy may be higher than that of some other AEDs. But for the moment, LMICs are often presented with either having a treatment with PB or having no treatment at all. Therefore, any barriers to its use in countries needing it should be reduced.

Finally, to conclude, the millennium development goal 8E (see Key Messages) requires that the access to essential medicines, including for people with epilepsy, should be ensured. Medicines that are life-saving, essential, and, more so, effective and safe, cannot be withheld from the health care systems purely on the grounds that they are listed in the international drug conventions. We urge international agencies such as WHO and the International League Against Epilepsy (ILAE) to initiate a wider and open debate on this important subject.

Acknowledgment

None.
GRAY MATTERS

Key Messages

1. PB is an essential first-line and life-saving drug for many PWEs in most LMICs.
2. Although it is not an ideal AED, the cost–benefit ratio supports its widespread use for epilepsy in LMICs.
3. Each country should self-help for determining negative consequences (e.g., suicidal tendency) attributed to PB exclusively, instead of adopting a generalized opinion, since exceptions to this have been shown to exist in LMICs.
4. Phenobarbital should not be withheld from the health care systems just because it is listed in the international drug conventions. Such an action will prevent the achievement of the millennium development goal 8E.

Millennium Development Goal 8E: In cooperation with pharmaceutical companies, provide access to affordable essential medicines in developing countries.

LMICs, low- and middle-income countries; PB, phenobarbital; PWE, people with epilepsy.

Disclosure

None of the authors has any conflict of interest to disclose. 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.

References

Recruitment of patients with both epilepsy and intellectual disability

To the Editors:

With great interest we took notice of the recent paper entitled “Genetic testing preferences in families containing multiple individuals with epilepsy” by Okeke et al. 1 In this study on 143 individuals with epilepsy and 165 relatives without epilepsy they found that interest in genetic testing in families with epilepsy may be high, especially when testing has implications for improving clinical care.

We would like to add additional data that show that the other way around, a low interest when there is no benefit, is also true, at least for patients with both epilepsy and intellectual disability (ID). Our observation is that the inclusion of patients with both epilepsy and ID is the role of the legal guardian. To give consent for a person you care for might, especially when there is no benefit to be expected, be even more difficult than when it would be for yourself.

We conclude that in genetic studies on patients with both epilepsy and ID, the absence of direct clinical relevance, will negatively influence the inclusion rate for that study. Genetic studies are important because they could improve knowledge about underlying mutations, which may provide insight into the natural course, effective antiepileptic treatments, recurrence risk, or comorbidity and enables specific anticipation on these topics. Therefore, it is important to explain explicitly the added value of a genetic diagnosis to improve participating and to move forward.

Disclosure

The authors declare no conflicts of interest in this work. 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.

Petra van Mierlo1
mierlop@kempenhaeghe.nl
Francesca M. Snoeijen-Schouwenaars2
Monique J. B. M. Veendrick2
In Y. Tan2
Marjolein H. Willemsen3,4
H. Jurgen Schelhaas1
Bert U. Kleine1

1Department of Neurology, Academic Center for Epileptology, Kempenhaeghe, Heeze, The Netherlands; 2Department of Residential Care, Kempenhaeghe, Heeze, The Netherlands; 3Department of Human Genetics, Radboudumc, Nijmegen, The Netherlands; and
Department of Clinical Genetics, Academic Center for Epileptology, Maastricht University Medical Center, Maastricht, The Netherlands.

REFERENCES

ANNOUNCEMENTS

31st International Epilepsy Congress
5–9 September, 2015; Istanbul, Turkey.
Please see the congress website: www.epilepsyistanbul2015.org.

Regional Congresses

12th European Congress on Epileptology
11–15 September, 2016; The Prague Congress Centre, Czech Republic.
Website: www.epilepsyprague2016.org.

Upcoming Chapter Congresses

The Annual Emirates league epilepsy meeting
22–23 May, 2015; Dubai, UAE.

5th SEIN Course on Clinical Epileptology
8–19 June, 2015; Stichting Epilepsie Instellingen Nederland (SEIN), the Netherlands.
The course objective is to improve diagnosis and treatment of epilepsy in the student’s own clinical setting by offering young doctors the opportunity to follow a short, yet comprehensive and practically oriented training in clinical epileptology in both lectures and interactive workshops/discussion sessions.
Application Deadline: 24 October, 2014. Information: cmorton@sein.nl.

Brazilian Epilepsy Congress
9–11 June, 2016; Recife, Brazil.

Other Congresses

2nd International Residential Course on Drug Resistant Epilepsies in Tagliacozzo
3–9 May, 2015, Tagliacozzo, Italy.
Topics: semiologic characteristics of different types of epileptic seizures, utilization of Video-EEG, notions of antiepileptic drug pharmacodynamics and kinetics, alternative treatments, role of epilepsy surgery, and more.
Announcement

Antiepileptic Drug Trials XIII Conference

XXIV European Stroke Conference (ESC) 2015
13–15 May, 2015; Vienna, Austria.
Website: http://www.eurostroke.org/default.html

5th SEIN Course on Clinical Epileptology
8–19 June, 2015; Stichting Epilepsie Instellingen Nederland (SEIN), the Netherlands.
The course objective is to improve diagnosis and treatment of epilepsy in the student’s own clinical setting by offering young doctors the opportunity to follow a short, yet comprehensive and practically oriented training in clinical epileptology in both lectures and interactive workshops/discussion sessions.
Application Deadline: 24 October, 2014. Information: cmorton@sein.nl.
1st Congress of the European Academy of Neurology (EAN)
20–23 June, 2015; Berlin, Germany.
Congress website: http://www.eaneurology.org/berlin2015/

GLUT1-Deficiency Annual Conference
6–8 July, 2015; Orlando, Florida.
Information: www.g1dfoundation.org

International advanced course on Seizures and Epilepsies in Childhood: Management, co-morbidities, and adaptation of guidelines
19–31 July 2015; ISNV, Venice International University, San Servolo, Venice, Italy.
Course directors: Jo Wilmshurst (South Africa) and Marilena Vecchi (Italy).
Announcement
For more information: epilepsysummercourse@univiu.org.

3rd International Summer School for Neuropathology and Epilepsy Surgery (INES 2015)
26–30 July, 2015; State University of Campinas – UNICAMP, Brazil.
Information | Past INES meetings | Contact: blue-mcke@uk-erlangen.de

9th Baltic Sea Summer School on Epilepsy (BSSSE 9)
2–7 August, 2015; Sigulda, Latvia.
Improve your level in epileptology by studying in a setting of young international peers with a group of dedicated and experienced tutors!
Information | Past BSSSE Schools
Contact: petra.novotny@wolfstiftung.org | www.epilepsiestiftung-wolf.de

Epileptology Mechanisms, Models, Prediction and Control: 7th International Workshop on Seizure Prediction (IWSP7)
3–6 August, 2015; University of Melbourne, Australia.

XIII Workshop on Neurobiology of Epilepsy (WONOEP) 2015
31 August – 4 September, 2015.
Heybeliada Island, Turkey.
About WONOEP: http://www.ilae.org/Visitors/Congress/Ed-WONOEP.cfm
For more information, email: decurtis@istituto-besta.it.

2nd International Epilepsy Symposium
4–5 September, 2015; Bielefeld-Bethel, Germany.
Main topics: Epilepsy, cognition, autoimmunity and surgical therapy.
Organizers: Epilepsy Centers Bethel and Berlin-Brandenburg.
Information: bbs2015@mara.de.

International Symposium on Benign Infantile Seizures (ISBIS)
25–26 September, 2015; Chiyoda-ku, Tokyo, Japan.
Information | Website

15th European Congress on Clinical Neurophysiology
30 September–4 October, 2015; Brno, Czech Republic.
Congress website: http://www.eccn2015.eu/

6th Eilat International Educational Course on the Pharmacological Treatment of Epilepsy (6thEilat Edu)
12–16 October, 2015; Jerusalem, Israel.