## LETTER

# Undue regulatory control on phenobarbital—an important yet overlooked reason for the epilepsy treatment gap

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).[1] 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.[2] 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.[3] 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.[4] Treatment guidelines call for controlled substances such as AEDs to be readily available, but this has not been the case in many LMICs.[5,6] As noted by the World Health Organization (WHO), international drug-control conventions provide the basic framework for national drug-control legislation (Box 1).

**Box 1**

Relevant laws and principles

*Single Convention on Narcotic Drugs, Preamble, paragraph 2:* "Recognizing that the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes."[18]

*Convention on Psychotropic Substances, Preamble, paragraph 5:* "Recognizing that the use of psychotropic substances for medical and scientific purposes is indispensable and that their availability for such purposes should not be unduly restricted."[6]

*United Nations Office on Drugs and Crime:* "Ensuring availability of controlled medications for the relief of pain and preventing diversion and abuse - Striking the right balance to achieve the optimal public health outcome."[18]

*Constitution of Cambodia (article 72):* "Right to health, and obligation on the State to provide high-level medical treatment and to give full consideration to disease prevention."[19]

**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.[5] 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."[6] *Second*, countries may introduce additional

drug regulations that go beyond the international conventions, rarely assessing their effect on the accessibility of essential drugs. In Zambia, the Zambian Pharmacy regulatory agency newly enforced regulatory requirements to facilitate proper management of scheduled medications in line with the recommendations of WHO Expert Committee on Drug Dependence. However, these unintended actions have in fact led to a decreased availability of PB, with the consequence that nearly 50% of pharmacies do not have a stock of PB, and pediatric syrups are completely unavailable, therefore, risking the lives of children.[7]

**What reality says**

WHO has also specified that national drug control policies should recognize that controlled medicines are also absolutely necessary for medical and scientific purposes.[6] We conducted an informal survey to determine the regulation, availability, and utilization of PB in different countries. Twenty-five neurologists from 20 LMICs in Asia (n = 3), Africa (n = 12), and Latin America (N = 5) reported PB to be the first-line AED in 60% (n = 12) of their countries (unpublished data, Pierre-Marie Preux, 2013). Fifty-five percent of countries (n = 11) rely solely on imports to meet their PB needs, with 10% (n = 2) relying on both in-country production and importation of PB. In 40% of countries (n = 8), tight regulations exist that restrict the availability of PB. In 12% of countries (n = 3, Burkina Faso, Burundi, and Brazil), specific border restrictions prohibit the importation of PB. In Burundi, PB was not allowed inside the country from the Border Post (perssonal data, Pierre-Marie Preux, 2013) leading to a 3-month interruption in the supply to that country. PB is on the essential drug list in Pakistan, but its listing as a narcotic makes PB unavailable in the market, although it is often available illicitly to those with substance abuse (personal data, Hasan Aziz, 2014).

**Training helps**

WHO has introduced the Mental Health Gap Action Programme (mhGAP) intervention Guide (mhGAP-IG), which includes management of epilepsy, substance abuse, and other disorders in nonspecialist health settings.[8] By training health care providers with such a tool, governments can reduce the risk that controlled substances may be handled inappropriately without ignoring the need to give access to these substances for therapeutic use. In Tanzania, treating epilepsy has been incorporated into the basic tasks and activities of mental health nurses with training in the appropriate use of "controlled substances."[9] Therefore, appropriate training can be a useful mitigating tool to facilitate safer use of scheduled substances such as PB.

**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.[10] Ghana Health Ministry has recognized the importance of public-private partnership with pharmaceutical manufacturers in order to increase access to PB.[11]

**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.[12] Abusing PB, for instance for suicide, should also be looked individually for each country, since there may be exceptions, such as Cambodia.[13] In addition, almost all black market barbiturates are diverted from legitimate medical practice/sources.[14] 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.[15] 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.[4] 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.[16] The teratogenic risk of PB in pregnancy may be higher than that of some other AEDs.[3] But for the moment, LMICs are often presented with either having a treatment with PB or having no treatment at all.[17] 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.

## 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.

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## 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 based on two different cross-sectional studies that attempted to include the complete population of our institutionalized patients with both epilepsy and ID. The first study was an anonymous study concerning genetic risk factor for epilepsy. The blood samples for DNA analysis were acquired together with the annual routine laboratory examinations. There was no benefit to the patient. In this study, 266 subjects were asked to participate: 79 (30%) were included, 66 (25%) refused and 121 (45%) did not respond. The second study focused on the diagnosis and treatment of osteoporosis. This was an invasive study that included measurements of bone density.[2] Treatment was offered when osteoporosis was diagnosed. Of the 260 subjects eligible for the study, 205 subjects (79%) were included, 32 (12%) refused, and 23 (9%) did not respond. In both studies, the patients and their families were informed in a similar manner by the same staff.

In line with the observation of Okeke et al., we found a relatively high inclusion rate in the study that did have implications for clinical care. The low interest in our study on genetic risk factors could potentially also be explained by the fact that, although it was an anonymous study, there still was the fear that the results would have consequences for other family members. This issue was addressed by Dlugos et al.,[3] who looked at the inclusion rate of children in a genetic susceptibility study on the common forms of epilepsy. In their study, they found that patients refused because of the fear of phlebotomy and not because of the fear of genetic testing. An interesting aspect concerning 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.

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# ANNOUNCEMENTS

## 31st International Epilepsy Congress

5–9 September, 2015; Istanbul, Turkey.
Please see the congress website: www.epilepsyistanbul 2015.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

13–15 May, 2015; May 13–15, 2015.
Aventura (North Miami Beach), Florida.
Website: http://www.epilepsy.com/accelerating-new-therapies/antiepileptic-drug-trials-xiii-conference-may-2015

## 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: bluemcke@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
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## Epilepsy Mechanisms, Models, Prediction and Control: 7th International Workshop on Seizure Prediction (IWSP7)

3–6 August, 2015; University of Melbourne, Australia.
Program: http://www.ilae.org/Commission/CAOA/documents/IWSP7_Program-2014.pdf

## XIII Workshop on Neurobiology of Epilepsy (WONOEP) 2015

31 August – 4 September, 2015.
Heybeliada Island, Turkey.
Announcement: http://www.ilae.org/Visitors/Congress/congressinfo/WONOEP_announce15.pdf
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.

Presented by ILAE-CEA, Israeli League Against Epilepsy, and CURE.
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Congress website: www.eilatedu2015.com

## XXII World Congress of Neurology (WCN 2015)

31 October–5 November, 2015; Santiago, Chile.
Website: http://www.wcn-neurology.com/