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

Devender Bhalla^{1,2,3}, Hasan Aziz⁴, Donna Bergen⁵, Gretchen L. Birbeck^{6,7}, Arturo Carpio⁸, Esper Cavalheiro⁹, Phetvongsinh Chivorakoun^{1,2,10}, J. Helen Cross¹¹, Dismand Houinato^{1,2,12}, Charles R. Newton^{11,13,14}, Peter Odermatt^{15,16}, Sangeeta Ravat¹⁷, Erich Schmutzhard¹⁸, Pierre-Marie Preux^{1,2,3}

¹Tropical Neuroepidemiology, INSERM UMR 1094, Limoges, France ²University Limoges, School of Medicine, Institute of Neuroepidemiology and Tropical Neurology, CNRS FR 3503 GEIST, Limoges, France ³University Hospital Center, Limoges, France ⁴Department of Neurology, Jinnah Postgraduate Medical Center, Karachi, Pakistan ⁵Department of Neurosurgery, Rush University Medical Center, Chicago, Illinois, U.S.A. ⁶Department of Neurology, University of Rochester, Rochester, New York, U.S.A. ⁷Epilepsy Care Team, Chikankata Hospital, Mazabuka, Zambia ⁸Research Department, University of Cuenca, Cuenca, Ecuador ⁹Department of Neurology and Neurosurgery, Federal University of São Paulo, São Paulo, Brazil ¹⁰Francophone Institute of Tropical Medicine, Vientiane, Lao PDR, Laos ¹¹UCL Institute of Child Health & Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom ¹²University of Abomey-Calavi, School of Medicine, Cotonou, Benin ¹³Kenya Medical Research Institute, Center for Geographic Medicine Research Coast, Kilifi, Kenya ¹⁴Department of Psychiatry, University of Oxford, Oxford, United Kingdom ¹⁵Swiss Tropical and Public Health Institute, Basel, Switzerland ¹⁶University of Basel, Basel, Switzerland ¹⁷Seth G.S. Medical College & K.E.M. Hospital, Mumbai, India ¹⁸Department of Neurology, NICU, Medical University Innsbruck, Innsbruck, Austria

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).

Preux@unilim.fr.

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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).

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 (personal 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.

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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

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.