

Phenobarbital: missing in action

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Epilepsy affects more than 60 million people worldwide, and over 80% of them live in resource-poor countries.¹ Approximately 85% of these people do not receive appropriate treatment² because of economic, cultural, social and legislative barriers, compounded by little interest on the part of pharmaceutical companies because drug distribution is not lucrative. Left untreated, people with epilepsy face devastating social consequences, including stigma and discrimination, and can even die from seizures. The morbidity and premature mortality associated with epilepsy and the large economic burden the disease imposes on health-care systems can only be mitigated by making effective antiepileptic treatment widely available.

Phenobarbital, an effective anti-epileptic drug, has been used since the early twentieth century.³ Its relatively low cost and favourable cost–efficacy ratio, which is lower than that of any other anti-epileptic drug in current use,⁴ makes the drug affordable and suitable for use in low- and middle-income countries, where cost-effectiveness often supersedes other priorities. In addition, the drug's half-life allows for the use of a single daily dose, which is convenient. The World Health Organization (WHO) recommends phenobarbital as a first-line treatment for convulsive seizures in resource-poor countries⁵ and includes it in its Model Lists of Essential Medicines. Accordingly, a continuous supply of phenobarbital of assured quality in appropriate dosage forms should be available in all of WHO's Member States, duly accompanied by information on its use.

Phenobarbital controls seizures effectively.³ In an observational study in rural Mali, the drug prevented seizures in about 80% of individuals and reduced the frequency of seizures in 16%.⁶ A more recent study from Mali found that almost 60% of the people who took phenobarbital were seizure-free at the last follow-up.⁷ In an interventional study in rural China, 68% of the 1897 patients who completed 12 months' treatment with phenobarbital experienced a substantial reduction

in seizure frequency and 34% stopped having seizures altogether.⁸ Subsequent research into the costs of treatment in two of the communities in rural China showed that phenobarbital treatment significantly reduced each patient's total expenditure over the course of one year.⁹

Despite the advantages of phenobarbital, the epilepsy treatment gap is large. A survey of pharmacies in Zambia revealed that almost half of them did not stock any anti-epileptic drugs at all and that only one fifth stocked phenobarbital. Participating pharmacists attributed this to excessive regulations surrounding the ordering and tracking of this drug.¹⁰ Phenobarbital, which is listed as a psychotropic substance by the International Narcotics Control Board,¹¹ is subject to strong international control and to stringent regulations that pharmacies in Zambia, and probably in other low- and middle-income countries, find obstructive. Fear that inadequate records or discrepancies in record keeping could lead to punitive consequences is a common barrier to more extended use of phenobarbital.¹⁰

Phenobarbital's adverse effects, especially capacity to alter mood and neurocognitive function, have generated concern. A recent study, however, showed no significant difference between treatment and control subjects in cognitive and mood test scores. Treated subjects even experienced some cognitive gains, perhaps as a result of improved seizure control.¹² In a randomized controlled trial involving 94 children with epilepsy, behaviour rating scores on the Conners parent rating scale and the preschool behaviour screening questionnaire did not differ significantly between those who were treated with phenobarbital and those who received phenytoin.¹³

In the study in rural Mali,⁶ some patients on phenobarbital experienced minor, transient side-effects, such as dizziness and drowsiness, but at one year only three of 96 participants were experiencing side-effects and none of them withdrew from treatment. Furthermore, the clinical benefits of

phenobarbital have been noted in people with epilepsy who have never been treated and in more rudimentary medical settings, which suggests that the drug is suitable for use in poorer countries. In rural China, treatment retention was 84% after one year among the 2455 individuals who received phenobarbital.⁸

An effective method of epilepsy control is clearly needed to fill the epilepsy treatment gap worldwide. Phenobarbital is efficacious, convenient to use and cost-effective with side-effects which are frequently tolerable. As some have noted, in low-resource countries “the choice is not between phenobarbital and a new medicament, but between phenobarbital and no treatment at all”.⁶ To make this drug more widely available and more attractive to physicians, its efficacy, tolerability and potential effects on cognition should be more comprehensively studied, together with the barriers hampering its wider use. In efforts to fill the treatment gap, the commercial sector will play a crucial role and active collaboration among different stakeholders, such as public health bodies, patient support groups and academia, will be essential. ■

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