markers (generally sleep variables) were highlighted.[7] On the risk-benefit front, no consistent difference was found between the Z drugs and benzodiazepines for either effectiveness or safety.[7] On the economic front, since the Z drugs are each several times the cost of older benzodiazepines, without evidence of superior effectiveness, they cannot be considered cost effective.

With the NICE guidance added to the weighty pile of negative evidence and expert opinion on hypnotic agents, do reasonable alternatives exist? Drugs are still important considerations in two main areas. Firstly, some commonly used drugs are well known to disrupt normal sleep—notably alcohol, selective serotonin reuptake inhibitors, drugs for Parkinson's disease, methyxanthines, and diuretics—and should be considered as potential contributors to the insomnia. Secondly, drugs can be effective for causes of secondary insomnia, especially pain and depression. Antidepressant medications are increasingly being prescribed for insomnia[8]; whether they are safe and effective outside of depression-associated insomnia is still controversial. The use of antidepressants, antipsychotics, or anticholinesterase inhibitors for insomnia related to delirium or dementia is also unproved.

No drug has yet been shown to be more effective and safer than placebo in primary insomnia for the type of outcomes that matter, such as quality of life, daytime function, cognition, falls and fractures, or dependency. Placebo itself, as in every domain of therapeutics, has been found to be effective—in this case in improving sleep.[9] The current aim of treatment is less focused on reduction of arousal from sleep and more focused on changing beliefs and attitudes about sleep.[10] Thus NICE's recommendation that long term, non-pharmacological interventions for insomnia should be a primary target for evaluation of cost effectiveness. Although physical exercise shows merit and can be recommended by primary care providers,[11] the current front runner for non-pharmacological treatment is cognitive behaviour therapy,[12 w1 w2 w3] a technique not familiar to providers outside of psychiatry. Trials of different methods of training family doctors in cognitive behaviour therapy are currently under way.

Cognitive behaviour therapy has many elements—stimulus control (your bed is only for sleep), sleep restriction (restrict your time in bed to your usual sleeping time), sleep hygiene, and relaxation therapy. Which of these elements are effective is unclear, but this is worth finding out as more passive interventions, such as audit and feedback to primary care doctors, are not effective.[w4] In the meantime, the newer hypnotics remain with the older hypnotics as prime examples of iatrogenesis imperfecta.

Anne M Holbrook *director*

Division of Clinical Pharmacology, McMaster University, Hamilton, ON, Canada L8N 3Z5
(holbrook@mcmaster.ca)

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Revisiting phenobarbital for epilepsy

Large gaps in knowledge still exist, but we may be underestimating its clinical value

A recent review of phenobarbital for the treatment of epilepsy draws attention to an ethical dilemma and to the many gaps in our knowledge about a drug that has been in use since 1912.[1] Phenobarbital is commonly prescribed in the developing world, but in most developed countries it has fallen into disrepute. The World Health Organization (WHO) recommends it as a first line drug for partial and generalised tonic-clonic seizures in developing countries.[2] Its antiepileptic efficacy is undisputed, but concerns remain about its side effects.[1] If people with epilepsy in Britain are not prescribed phenobarbital because of its toxicity, is it ethical to recommend its use in developing countries? And if the drug is not as toxic as it is believed to be, might it not be used more in the developed world?

Phenobarbital has many favourable features: broad spectrum efficacy against all seizure types other than absences; a starting dose within the clinically effective range; seizure freedom rates comparable to those associated with modern drugs; a very low risk of life threatening adverse effects; linear pharmacokinetics; long half life compatible with once daily dosing; low propensity to be a target for drug interactions (except for the inhibition of its metabolism by valproate); availability of a parenteral formulation, and low cost.[3] The perception that phenobarbital is more commonly associated with withdrawal seizures is not supported by the best available evidence.[4] Documented disadvantages include enzyme induction, which may alter response to co-administered drugs such as oral contraceptives, and adverse cognitive and behavioural effects, particularly in children.[1 3]

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Most of the evidence on phenobarbital comes from observational studies, and controlled trials are scarce and mostly of modest quality. In randomised trials in developed countries, phenobarbital was associated with higher discontinuation rates than carbamazepine and phenytoin,[5 6] but the difference was not huge and was mostly seen in open label trials where management could have been affected by doctor or patient bias.[1] Even in children, in whom phenobarbital is considered to be least well tolerated, evidence for a negative impact on cognition and behaviour is less compelling than generally thought. Although phenobarbital has been repeatedly reported to affect adversely intelligence scores and behaviour in children with febrile seizures (no longer an acceptable indication), results from studies in adults and children with epilepsy did not yield univocal evidence for significant cognitive and behavioural impairment.[1] Most importantly, studies in developing countries did not usually show excess neuropsychological toxicity in comparison with modern antiepileptic drugs.[1 7–10] Admittedly, many of these studies had methodological weaknesses, but their more favourable results might also be related to the use of lower effective doses than in trials conducted in developed countries.[1]

What conclusions can we draw from this evidence? The first is that low cost is not just phenobarbital's greatest asset but also its greatest liability, having led the drug into commercial neglect. Eadie pointed out appropriately that phenobarbital "may be allowed to fade from use, at least in affluent societies, not so much because of its limitations, but because its virtues are no longer promoted," and one cannot avoid wondering what we would be saying about phenobarbital today if it had been licensed in the last decade.[11] Phenobarbital probably does have an inferior tolerability (including subtle neurotoxic effects and, in children, overt behavioural disturbances) compared with some other antiepileptic drugs, but the size of the difference may have been overstated and may not necessarily apply to dosages at the lower end of the effective range.

In affluent societies, phenobarbital is unlikely to represent the best choice for most people with newly diagnosed epilepsy.[1] In the developing world, when the choice is between the cheapest treatment or no treatment at all, phenobarbital should be used, particularly in adults. However, local doctors should not present phenobarbital to patients as the best drug but should inform them about its advantages and disadvantages (and deficiencies in knowledge) compared with alternative treatments. After all, cost is an important consideration in drug selection in developed countries too, and prioritising allocation of health resources is never unethical when done in a fair and transparent way. We also need to remember that making a drug available in a remote part of a developing country involves much more than the price of tablets, and includes the costs of a reliable and uninterrupted transport service and of facilities for storage and dispensing. Such added costs would be similar for all drugs.

Although phenobarbital may be less toxic than generally thought, and might be considered more often to treat patients in developed countries (particularly as second line treatment), gaps in knowledge about this drug (and other antiepileptic agents) remain a major concern. Can dose-response relationships for its efficacy and neurotoxicity be better defined? Do pharmacogenetic differences exist in its tolerability between people from diverse ethnic backgrounds? Are we sure that patients in the developing world are not just tolerating a greater degree of side effects because they are offered little choice in their treatment? Doing high quality research will be expensive and, given the lack of interest of pharmaceutical companies in phenobarbital, difficult to fund.

The International League Against Epilepsy and WHO, which have a series of demonstration projects for epilepsy, have the responsibility of addressing these issues, particularly as they continue to endorse the use of phenobarbital in poor countries. Simply doing more observational studies or non-randomised open trials cannot solve the problem. Only robust evidence will address the gaps in our knowledge and the ethical dilemma of recommending a drug for the developing world but shunning it in the developed world.

Rajendra Kale *assistant editor, BMJ*

(rkale@bmj.com)

Emilio Perucca *professor*

Institute of Neurology IRCCS C. Mondino Foundation, University of Pavia, Via Mondino 2, I-27100 Pavia, Italy

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RK has been a member of the executive committee of the International Bureau for Epilepsy and chaired the Commission for the Developing World of the International League Against Epilepsy. Several of the epilepsy and neurology meetings, especially those organised by these organisations, which RK participated in and gave talks at have been held all over the world and have been funded directly or indirectly by pharmaceutical companies (including Novartis, SmithKlineBeecham, E Merck, Cipla, Sanofi, Pfizer, and others). For more information please see http://bmj.bmjjournals.com/aboutsite/comp_editorial.shtml

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