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Phenobarbital for childhood epilepsy: systematic review

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Abstract

Introduction—Against a background of concern about the safety of new pharmaceutical products, there has been renewed interest in one of the oldest antiepileptic drugs (AEDs), phenobarbital. Although still in widespread use in developing countries, its popularity has slipped in Western countries over the past century, partly because of controversy about its adverse effect profile. This critical review examines the evidence supporting its effectiveness and its associated behavioural adverse effects for febrile convulsions and childhood epilepsy.

Methods—Relevant randomised controlled trials (RCTs) of phenobarbital vs other antiepileptic drugs or placebo between 1970-2005 were identified through a comprehensive manual and computer database search of the world biomedical literature. Eleven RCTs of febrile convulsions and nine RCTs of childhood epilepsy were systematically reviewed against a conventional set of quality criteria.

Results—With a few exceptions, the overall quality of clinical trial methodology, especially in the early studies conducted in the 1970s and 1980s, was poor. There is no evidence for a difference in antiepileptic efficacy between phenobarbital and any other compared AED, yet no evidence for absolute efficacy. No convincing evidence exists for an excess of behavioural adverse effects, over other AEDs, attributable to phenobarbital. Masked studies of phenobarbital in childhood epilepsy have shown no significant differences in behavioural or cognitive adverse effects compared to other AEDs. This is in contrast to the excess of such adverse effects reported in studies open to observer bias. However, the one finding of reduction in cognitive ability associated with phenobarbital treatment for febrile convulsions remains a concern. Future areas of clinical and genetic epidemiological research are outlined.

Keywords

phenobarbital; systematic review; randomised controlled trial; efficacy; adverse effects; childhood; epilepsy; febrile convulsion

Introduction

There has been a resurgence of clinical interest in the role of phenobarbital (PB) for treating childhood epilepsy in Western countries. In 1912, PB became one of the first agents used against epilepsy[1] and is now the most widely used anti-epileptic drug (AED) in the world. Its low cost and accepted use for a wide range of seizure types has led to its position as the World Health Organization's first-line AED in developing countries.

In Western countries, PB has been in and out of favour as an AED. Although widely used as a prophylactic against febrile seizures in the 1960s and 1970s, concerns about its neurobehavioural adverse effect profile[2] led to a decline in its use for all seizure disorders.

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More than a decade after it was in vogue, a meta-analysis of its effectiveness as a febrile seizure prophylactic concluded no advantage over placebo[3]. The pooled odds ratio (OR) of British clinical trials demonstrated no significant protection from either phenobarbital OR 0.8 (CI 0.53–1.20) or sodium valproate OR 1.42 (CI 0.85–2.36).

A flurry of uncontrolled observational studies from the 1970s and 1980s, claiming excessive behavioural adverse effects, had a strongly negative effect on prescribing behaviour, even in research circles. For example, in the MRC Anticonvulsant Trial started around 1980[4], PB was withdrawn from the children's trial arm as a result of perceived adverse behavioural effects and because it was believed that inclusion of PB was hampering recruitment. The evidence for PB's excessive adverse effects was never examined in critical detail. Thus PB's role in the antiepileptic armamentarium remains controversial. Now, approaching its centenary, PB has once again been hailed as an AED of promise[5].

The reasons for renewed interest in this tried and tested “old” drug arise mainly from doubts about the safety of newly licensed pharmaceuticals, and public disquiet over the unsatisfactory regulatory framework for preclinical evaluation of new medicines, particularly for children[6]. Financial settlements to patients harmed by COX-2 inhibitors[7], and of course the controversies about risk-benefit profiles associated with felbamate[8] and vigabatrin[9], are stimulating clinicians to take a more conservative approach toward new treatments, and to re-evaluate older drugs that have suffered from “commercial neglect”[10]. Cost of treatment may also be a consideration: carbamazepine costs around ten times, and lamotrigine almost forty times as much as the equivalent dose of PB[11].

Now that prescribing fashion is turning back towards PB, it is an opportune moment to reevaluate the original controversy surrounding PB, and be sure that today PB is prescribed in accordance with the evidence for its efficacy and tolerability. In this paper therefore, we ask: (i) to what extent the original concerns about PB were justified; (ii) given the current understanding of PB's neurobehavioural adverse effect profile, what are the most promising areas for its use in wealthy and poor societies; and (iii) what research questions need to be addressed to realise more of its commercial potential?

Methods

The methodology of a systematic review has been used to evaluate pertinent studies. Systematic reviews are a useful way to weigh research evidence, especially when there are conflicting results, when there is possible heterogeneity in the study parameters, and when no single trial is adequately designed to define best clinical practice. Randomised controlled trials (RCTs) have been chosen as the basis for this systematic review because observational studies are limited by bias and uncontrolled confounding factors. RCTs provide the best quality of evidence for clinical decision-making. RCTs of PB for childhood epilepsy or febrile convulsions were identified by the Cochrane search strategy[12]. These trials were systematically assessed on criteria of design and reporting quality (meeting or not meeting criteria, or unclear). Criterion referenced assessment is commonplace in meta-analysis and systematic reviews[13]. Studies including both afebrile and febrile seizures were included in the review because many of the conclusions about paediatric tolerability were made from studies of PB in febrile seizures.

Study selection criteria

All RCTs of AEDs involving phenobarbital as continuous (maintenance) oral monotherapy versus placebo, no treatment or other active drugs were included. Quasi-randomised studies, e.g. treatment assigned on the basis of day of admission or birth date, were excluded because of the possibility of selection bias. Subjects had to include young people or children, as defined

by the authors, with clinically diagnosed generalised tonic-clonic or focal epilepsy or febrile convulsions. Papers reporting the use of PB for seizures in the context of infectious illness were not included[14]. Behavioural problems were defined variously by the authors to include parental reports of hyperactivity, "hyperagility", overactivity, hyperkinesia, listlessness, irritability, aggressiveness, emotional instability, "unpleasant behaviour", temper tantrums, fussiness, paradoxical excitation and agitation. Only a few studies used validated behavioural instruments to measure outcome.

Search strategy

Papers were identified through the Cochrane Epilepsy Group Register of Clinical Trials in Epilepsy; the Cochrane Library; computer database search of MEDLINE, EMBASE, SCISEARCH, PSYCHLIT between 1969 and 2005 in all languages, using keywords and strategies developed by the Cochrane Epilepsy Group; review articles; chapters in books; citation search; reference lists of all papers identified by the search; lastly, certain authors were approached for knowledge of unpublished trials. Abstracts of potential studies were reviewed for inclusion. Very few RCTs of AEDs were carried out before 1970[15] and therefore this period was not included. Data were extracted from published studies using the proforma in Tables 1 and 2.

Quality criteria

Trials were judged according to the reporting of treatment assignment, blinding, follow-up completeness, and method of analysis. Similar criteria have been used in other systematic reviews, with the rationale that poorly designed or conducted clinical trials are open to bias, random error and confounding and therefore should be interpreted with caution[16].

Results – febrile convulsions

Febrile convulsions are a mainly benign group of seizures, common (5%) in early childhood. Associated with febrile illnesses, most children who have one febrile seizure have only the one or two (infrequently more) febrile convulsions in the first six years of life. Up to 10% may later have afebrile seizures, but there is no evidence that treating febrile convulsions with AEDs prevents later epilepsy. In the 1960s and 1970s there was a vogue for prophylactic treatment of febrile convulsions with AEDs, principally PB. This practice was more common in the US than in Europe.

Sixteen trials were identified, of which five did not meet entry criteria because of non-random treatment assignment[17-21]. Fourteen reports from the 11 remaining trials are summarised in Table 1. Of these 11 trials, five used masked assessments and six were unmasked. Four of the five masked trials studied behavioural side-effects and showed no differences compared to placebo or intermittent diazepam. The fifth showed an important long term deficit in cognitive outcome in the PB group[22]. Four of the six unmasked trials studied behavioural side-effects: two showed an excess of behavioural side effects with PB compared to either valproate or no treatment[23-25] and two showed no difference compared with phenytoin or rectal diazepam[26,27]. The studies are described below.

Wolf et al. compared three regimens: continuous PB, intermittent PB or no treatment in children with febrile seizures. The results for seizure recurrence, behavioural effects and cognitive function were reported separately and have had a considerable influence on subsequent clinical practice both regarding the use of PB and prophylaxis of febrile convulsions[23,24,28]. The main study randomised 355 children into three groups and followed them up over a mean period of 28 months (m). The design allowed children on no treatment to convert to the active treatment group. Seven of 106 (7%) in the continuous PB group had a seizure recurrence during one year

of follow up compared to 20/249 (8%) in the intermittent and no treatment groups. After adjusting for duration of follow-up, this difference was reported to be significant although neither point estimate nor confidence intervals for this difference were given, and durations of follow-up were not reported for each group.

The study also reported 46/109 (42%) of treated children developing behavioural problems compared to 21/120 (18%) in the no-treatment group[24]. Sixteen per cent of those on continuous treatment dropped out early because of hyperactivity but no data were presented on the proportions in the other groups dropping out, so it was difficult to assess if dropout was related to treatment group. Behaviour was assessed only by parental report and neither parent nor physician was blind to treatment status. It was also notable that there was resistance from parents to accept continuous PB treatment, some refusing to enter that arm of the study because of knowledge of side effects. This obviously raises the question of bias in assessing outcome. Also, the effect of tablet administration alone on child behaviour was not adequately measured by the nil treatment group, and it was not clear whether results were presented for all subjects who had entered the trial or if only completers were studied. Interestingly, the only significant predictor of behavioural problems in both treatment arms was the existence of preexisting behavioural problems.

In a subsequent study, Wolf et al. compared cognitive function in 25 children completing the study on PB to 25 not on treatment[28]. It was not clear how these subjects had been selected from the larger group. There were no differences in IQ by the Wechsler Preschool Inventory (WPPSI) scale either just before stopping or three months after stopping therapy. However, the study had selected children who completed the trial, and who would be less likely to have neurobehavioural side effects, and more likely to come from well-motivated families. Both factors would not have been revealed by baseline comparison and would have biased the results by diminishing differences between treatment and control groups. Also there was no baseline comparison of IQ, so it was possible that the groups were not comparable to begin with. In summary, Wolf et al.'s studies were seriously affected by bias from not using an intention to treat analysis, by lack of blinding, by the absence of a placebo group, by not reporting follow-up in control groups, and by non-random selection of children for cognitive testing. Neither protection against recurrent febrile convulsions nor excessive serious behavioural effects of PB can be concluded from these studies.

Camfield conducted a double-blind, placebo controlled comparison of PB and placebo for febrile convulsions[29]. Follow-up was over 12 m with 70% of 65 subjects completing that period. Outcome was assessed by parental report of behaviour and standardised psychological testing. There were no physician or parent reported episodes of hyperactivity, and no significant differences in emotional state or cognitive function between the two groups at outcome. Subgroup analysis suggested a reduction in the memory subscale for children on PB, and for a fall in comprehension between 8 m and 12 m testing, but the confidence intervals for this reduction were not reported. A follow-up report of 79 children showed that 5.1% of the PB group had recurrence compared with 25% of those treated with placebo[30].

Ngwane and Bower compared the efficacy of PB and sodium valproate for the prevention of simple febrile convulsions[31]. Allocation of active treatments was randomised but a no treatment group was created by default through parental or physician refusal to enter the trial, introducing selection bias. Treatment status was double-blind over 12 m, with four drop-outs owing to side effects equally distributed between the treatment groups. Analysis was by χ^2 test between the three groups, showing fewer seizure recurrences in active compared to no treatment groups, but no difference in recurrences between the two active treatments. Since the control group was not randomly selected, and did not receive placebo treatment, it was not valid to conclude a preventive effect for either drug.

Bacon et al. investigated the efficacy of PB and phenytoin against placebo[26]. Allocation was randomised but blinding failed because phenytoin could not be administered successfully as a capsule, whilst PB and placebo were given as capsules. After 12 m, 69 of 207 had dropped out but no information was given relating to dropout and initial treatment allocation, introducing possible selection bias into the assessment of outcome. There were no differences in recurrence rates. However, the authors claimed a significant protective effect against seizure recurrence in a subgroup (those with PB salivary levels > 8 mg/l) of a subgroup (children < 14 m) – a total of 10 children. This type of subgroup analysis of compliers is neither convincing nor does it have clinically useful implications. In a parallel study, the authors compared behavioural side effects of 56 children in the three study groups and found no differences in incidence of behavioural problems between the study arms[26]. However, they used an unvalidated questionnaire which might not have been sensitive enough to detect clinically important differences.

McKinlay and Newton compared the efficacy of PB and sodium valproate for preventing recurrence in children at increased risk of recurrent febrile convulsions[25]. Subjects were randomised to continuous treatments or intermittent rectal diazepam. 151 children were followed for an average of two years, 13% dropped out. The trial, which was analysed on an intention to treat basis, found no significant reduction in recurrence from any intervention. The odds ratio of effect for sodium valproate was 2.19 (95% CI: 0.96–5.0) and for PB was 1.36 (95% CI: 0.55–3.34) relative to the diazepam group. Eight of 41 children had their PB stopped by parents because of side effects, compared to three of 50 in the valproate group.

Lee and Melchior compared efficacy of PB and sodium valproate after a first febrile seizure[32]. A group of children whose parents refused treatment was selected as controls. The trial was not blinded and the primary outcome of seizure recurrence was examined at 12 m by comparing compliers only by χ^2 test using one sided p values. The authors concluded a beneficial effect for sodium valproate over the no treatment group, but this was not justified since compliers were being compared to a selected control group. They also concluded PB to be ineffective in preventing recurrence and for sodium valproate to be significantly more effective. However, no confidence intervals were presented, and if the analysis was repeated using conventional two-sided *P* values and intention to treat data, then the difference between the two active treatments would not be significant at the 5% level.

Anthony and Hawke randomised children with recurrent febrile seizures to PB or carbamazepine to study their relative efficacy[33]. Almost half of their subjects were excluded from analysis because of loss to follow-up, low AED levels or side effects. The investigators were supposedly blind to the treatments although the treating clinician was not blinded and the tablets were readily identifiable by parents. The method of assessing side effects was not given. With so many subjects lost to follow-up, and only analysing compliers, it was impossible to endorse the authors' conclusion that PB was more effective than carbamazepine in preventing febrile convulsions. Neither was it valid to comment on side effects when blinding was not effective.

Mamelle et al. compared sodium valproate, PB and placebo in 67 subjects randomised to treatment for an average of 24 m[34]. In all, there was one recurrence in the valproate group of 22 subjects (4.5%), 4/21 in the PB group (19%) and 14/26 (35%) in the placebo group. Monitoring was by a doctor aware of treatment status. Parents however, were unaware of the name of the medication. There were five children reported to have agitation on PB, and no side effects with either valproate or placebo were reported. The relation of side effects to dropout was unknown, there being one in the valproate and placebo group and two in the PB group.

Garcia et al. conducted a study similar in design to that of McKinlay, comparing continuous PB with intermittent rectal diazepam[27]. One hundred children, randomised to either treatment, were followed up over 18 m for seizure recurrence and side effects. 10% of the PB treated children had a recurrence compared with 8% of the diazepam group. Side effects were similar, the authors reporting three (6%) poorly tolerating PB because of hyperactivity (necessitating change to sodium valproate) compared to five (10%) with drowsiness in the diazepam group.

Farwell et al. conducted a large randomised, placebo controlled, double-blind study of PB for febrile seizures[22]. 80% of 217 subjects completed two year follow up. The primary outcomes were seizure recurrence and IQ assessment by the Stanford-Binet scale. Cox multiple regression was used, controlling for baseline variables, and using intention to treat analysis, and this showed an eight point deficit on the Stanford-Binet scale after two years of treatment, a deficit persisting for 6 m after discontinuation of therapy[22]. There was no significant decrease in the recurrence rate of febrile seizures on treatment compared to placebo. Parents of children on PB reported more behavioural problems in the first six weeks, but there were no differences compared to the placebo group after two years. A small difference might have been diluted by crossover of 25% of the placebo group to PB by the end of the study.

Hirtz et al. investigated sleep disturbance in a double blind, randomised, placebo controlled, crossover study of PB versus placebo[35]. They demonstrated no increase in sleep disturbance in toddlers treated with PB for the prevention of febrile seizures, except in those infants who had exhibited sleep disturbances at the start of treatment. The authors suggested an interaction between PB treatment and an intrinsic vulnerability for behavioural (sleep) disturbance.

Summary

As well as lack of evidence for efficacy in preventing febrile seizures, the clinical trials above show a lack of conclusive evidence for an excess of behavioural adverse effects associated with PB.

Results – childhood epilepsy

Nine clinical trials were identified using the above strategy and all were included for review (Table 2). Of the nine, six were in Western countries, and three were from developing countries. Four trials used masked assessments, and none of these showed significant clinical differences in side effects, although numbers were small. Three trials did not use masked assessments: one claimed intolerable side effects[4], another was too poorly designed and analysed to allow interpretation[36], and the third showed no difference in IQ testing at outcome to other treatment groups[37]. None of the trials in developing countries showed a significant difference in side effects between PB and other active treatments. No trial showed any difference in relative efficacy. All nine trials are described below in chronological order.

Ozdirim et al. investigated behavioural problems in children with newly diagnosed epilepsy[36]. Sixty three children were randomised to PB, phenytoin or placebo. After 3 m, their scores on four standardised psychological tests and a custom made behaviour questionnaire were compared by analysis of variance. No details were given of randomisation procedure or baseline details to verify the efficacy of randomisation. Treatment and assessment were not blinded and the duration of follow-up was very short. The PB group showed no improvement in one of three cognitive tests, and children in this group were also reported to have more behavioural problems. However, there were no differences in performance on other tests of adaptation and non-verbal performance. This one difference, which was not quantified, might have been the result of multiple significance testing. The behaviour rating scale was unvalidated and open to observer bias. The analysis did not allow for the effect of confounding variables such as age or sex. These flaws make the study results uninterpretable.

Young et al. compared the behavioural side effects of PB and mephobarbital[38]. They used a randomised, double-blind, crossover design with eight subjects over a period of 3 m. Behaviour was measured by the Conners Parent Rating Scale and the two groups compared by analysis of variance. No significant deterioration after treatment or difference of behaviour between treatments was demonstrated. However, with only eight children, assuming that 40% of PB treated children developed behavioural side effects, the study had a mere 1% power to demonstrate a risk ratio of 4.0.

Mitchell and Chavez compared the behaviour, cognition and seizure control of 33 non-retarded children with focal seizures randomised to either PB or carbamazepine[39]. Cognitive performance was measured by standard psychological instruments but behaviour was assessed using an unvalidated, custom made instrument. Parents and the evaluating psychologist were blind to treatment status. There was no significant difference in seizure control, and no difference in behaviour or cognitive function between the groups. However, only 19 children completed the 12 month trial and the power of the study to detect real differences was therefore quite low.

Vining et al. compared the efficacy and side effects of PB and valproic acid in a double-blind crossover study of 21 children of normal intelligence with mild seizure disorders, treated for 6 months with each drug[40]. Vigilance and attention were measured by a neuropsychological test battery, and behavioural problems assessed using the Conners Parent and Teacher Rating Scales[41]. Parents and assessors were both blind to treatment status. Seven children dropped out, four reportedly because of behavioural problems on PB. Each arm lasted six months and was analysed, for completers only, by significance testing and analysis of variance between treatment groups. The drugs were thought to be equally effective in seizure control.

No differences in side effects were noticed in routine clinical assessment but the authors noticed a tendency for better performance on testing with valproic acid. There were at least 17 tests of significance used to demonstrate differences on subscales of the Conners Scale and Wechsler Intelligence Scale for Children. However, there were no preset hypotheses concerning the subscales expected to be important, and differences in favour of valproic acid could have occurred by chance either as a result of multiple testing, or due to type I error owing to the small sample size. Additionally, these differences were not supported by clinical report. This trial did not therefore show clinically meaningful differences in side effects.

De Silva et al. compared the efficacy of PB, phenytoin, carbamazepine and sodium valproate in a randomised pragmatic trial of newly diagnosed childhood epilepsy[4]. Both parents and physicians knew the identity of the drug after randomisation. There were no significant differences with regard to efficacy after three years of follow up, 73% achieving one year remission. Six of ten children randomised to PB were withdrawn because of reported behavioural side effects. Only four children remained on PB for the duration of the trial. A total of 15 (9%) of the original sample withdrew because of side effects. The strong possibility of observer bias limited conclusions about the possible excess of side effects of PB in this study.

Feksi et al. conducted a clinical trial of adults and children with epilepsy in Kenya, using PB and carbamazepine[42]. They showed no difference in efficacy: 52–54% of subjects on either drug achieving seizure remission at one year and 65% experiencing an improvement in seizure control. In all, 302 subjects were randomised to either drug, and 82% completed follow-up over a year. There were similar numbers of withdrawals (26 *vs* 27) and unacceptable side effects reported to the clinic psychiatrist or visiting health worker (carbamazepine 8, PB 5) in each group.

Placencia et al. conducted a similar randomised study in a community epilepsy control programme in Ecuador[43]. 192 adults and children were randomised to PB or carbamazepine. After 12 m follow-up, 54% of the PB group and 47% of the carbamazepine group achieved seizure freedom, and there was no difference in the proportions with reduced seizure frequency between the two groups (60% *vs* 68%). Side effects were monitored with a checklist throughout the study, only 5 subjects dropping out because of overt side effects. There were no differences in the proportion of completers reporting side effects in each treatment arm.

Chen et al. compared cognitive function of newly diagnosed children with epilepsy randomised to PB, sodium valproate or carbamazepine[37]. Seventy-six children, with no pre-existing behaviour problems, were followed up for 12 m measuring outcome with the Chinese version of the Wechsler Intelligence Scale for Children-Revised and Bender-Gestalt test, as well as neurophysiological performance in response to auditory tones. No differences were found in IQ testing at outcome between the groups, but children in the PB group had longer latencies of electro-physiological response at 6 and 12 m, a finding of uncertain clinical significance.

Pal et al. conducted a RCT of PB vs phenytoin in children aged 2 to 18 yr[44]. The authors recruited a population-based sample of untreated children with epilepsy in rural India. 94 children were randomised, using the technique of minimisation to stratify for age group and cerebral impairments. 62 children (66%) remained on treatment after 12 m, but 82 (87%) of the original cohort had behavioural outcomes recorded. Intervention was framed in a community-based rehabilitation setting, including home visits by disability workers. Seizure outcomes were measured as actuarial (time to first seizure) events, as well as proportion seizure free at quarterly intervals. Behavioural problems were measured using validated instruments such as the Conners Scale (CPRS-48), the investigator blinded to treatment status. There were no differences in efficacy between the two drugs (Hazard ratio: 0.51, 95% CI: 0.16–1.59). 65% were seizure-free in the final quarter. There were no significant differences in objectively assessed behavioural problems in either treatment arm, even when adjusted for confounding variables. There were no significant differences in parent-reported adverse effects.

Summary

None of the nine masked clinical trials of PB, for either the prevention of febrile seizures or of epilepsy, has shown an excess of behavioural adverse effects over placebo or active treatment. In comparison, three of 11 unmasked clinical trials have attributed significant behavioural adverse effects to PB. The quality of evidence from these trials is discussed below.

Discussion

The overall design quality and statistical methodology of clinical trials in this area is poor, especially for those trials conducted in the 1970s and 1980s. Coatsworth reached similar conclusions in reviewing the efficacy of AEDs for the era up to 1970[15]. Small sample size and multiple significance testing may have resulted in missed or false associations, respectively. Control groups receiving no treatment introduce bias because of the absence of the placebo effect, exaggerating the magnitude of treatment and side effects. Inadequate randomisation and the absence of blinding also make selection and observer bias a distinct possibility, leading to misleading inferences regarding effectiveness and toxicity. Blinding is more feasible in trials that include only one or two active treatments. Substantial losses to follow-up and the inability to demonstrate lack of bias in these losses relative to those retained, further reduce the validity of results. Lastly, the analysis of compliers invalidates the general-isability of findings to the general population and misses the whole point of randomising to eliminate confounding from other factors related to staying in treatment[45].

To what extent were the original concerns about PB justified?

The early concerns about PB's adverse effects were largely based on its use in preventing febrile convulsions in preschool aged infants and children. As shown, careful evaluation of the RCTs from that era does not provide convincing evidence for an excess of behavioural adverse effects, over other AEDs, attributable to PB. Overall, masked studies of childhood epilepsy have shown no significant differences in behavioural or cognitive side effects for PB compared with other AEDs. This is in contrast to the excess of such side effects reported in studies that are open to observer bias, i.e. unmasked. An important lesson from this review is the vastly different conclusions that can be inferred from different classes or quality of evidence. Findings from febrile convulsion trials are consistent with childhood epilepsy trials, with one important difference: a significant reduction in learning ability among children treated with PB was demonstrated[22]. So far this result has not been replicated or examined in children with childhood epilepsy, but nevertheless remains a concern. The question remains open whether cognitive ability is impaired only in children with febrile convulsions, only in preschool children, or whether there are other important interactions involved. Until this question is investigated in detail, it is doubtful that PB will be chosen as a first-line agent for childhood epilepsy in situations where an economically viable alternative exists.

No study has shown a difference in antiepileptic efficacy between PB and other first-line AEDs, either in Western or developing countries, yet absolute efficacy for epilepsy has not been proven. There is conflicting evidence about absolute efficacy of PB in preventing febrile convulsions, but this is a moot finding because prophylactic AEDs have hardly been used in the clinical management of febrile seizures since the 1970s.

As a general finding, the proportion of behavioural (and other) side effects leading to dropout from treatment has been lower in developing countries compared to Western studies of antiepileptic drugs. There may be many explanations for this. Some are simple and related to study design, e.g. studies may have contained a mixture of adult and child subjects; or varying dosing schedules may have been used. Behavioural “problems” in children are socio-culturally defined: most measuring instruments rely on parental or teacher proxy reports of behaviour, rather than on intrinsic measures of individual's neurophysiological functioning; thus their prevalence varies considerably both across and within countries. Parents in different countries may have different thresholds for labelling behaviour as problematic, or may be more or less inclined to attribute such behaviours to extrinsic agents like drugs.

Within cultures, behavioural problems have a multifactorial basis, with important biological and socio-cultural risk and protective factors[46]. Biological factors include age, the peak onset for attention deficit/hyperactivity disorder being in the preschool years; central neurological deficit is also a strong risk factor[47]. However, more recent studies of child behaviour problems have examined potent risk factors from the environment, including parenting style, social support etc[46,48,49]. This new perspective replaces an earlier view in which behavioural problems in children with epilepsy were explained solely on the basis of seizure and treatment variables. Nevertheless, many of the interactions between biological and environmental factors are incompletely understood, especially in children with pre-existing neurological disorders. The large list of variables that need to be taken into consideration as possible confounding variables necessitates caution on the part of investigators who are designing or analysing studies in this area. Few clinical trials for example, except those completed in the last decade, have stratified or otherwise adjusted for these variables. Despite the lower prevalence of behavioural problems reported in developing country trials, there is no evidence for an excess of behavioural problems in children with epilepsy treated with PB.

Given the current understanding of PB's neurobehavioural adverse effect profile, what are the most promising areas for its use in wealthy and poor societies?

In Western countries, cost is not generally an issue to the end-user, partly because there is not a huge difference in cost between PB and some of the older alternatives. Efficacy and tolerability generally outweigh economic considerations, and a much broader range of treatment options is available. Realistically, PB is unlikely to return as a first-line AED. However, PB continues to be employed as a tertiary adjunctive therapy in patients who do not achieve seizure remission on monotherapy. This is most likely the area in which PB's use will be increasingly considered. PB's story resembles that of felbamate: initially viewed as a useful first line AED, withdrawn because of (fatal rare) adverse effects, and now reinstated as a treatment for intractable epilepsy. Two other indications that are not considered in this review include infantile epilepsies and convulsive status epilepticus. PB has an established role in these clinical scenarios.

The decision matrix for treating epilepsy in poor sectors of developing countries is vastly different to that in affluent sectors of Western countries. In developing countries, the overwhelming priority is to retain the patient in treatment through a reasonably long period. This mandates low-cost and accessible treatment[50]. PB is without doubt the most widely available and cheapest AED in the world, and clinical trials above, as well as those conducted in adults, show it is well tolerated in developing country contexts. Long term safety, in terms of cognitive performance, cannot be judged on the available evidence. However, this potential disadvantage may be considered an acceptable trade-off against the option of helping a person with epilepsy integrate more fully into the social and economic life of their community. Balancing these kinds of quality-of-life issues is difficult to translate for Western audiences because of the enormous differences in context. PB is therefore likely to maintain its lead as a first-line AED in developing countries, at least until other AEDs reach a similar standard of cost, distribution and familiarity amongst primary care providers. At present, newer AEDs are not widely available in developing countries, although clearly there is a need for a choice of treatment options.

What research questions need to be addressed to release more of its commercial potential?

There is not much impetus for research into established, out-of-patent antiepileptic drugs in Western countries, except when indicated for status epilepticus and for intractable epilepsies. While a head to head monotherapy clinical trial of PB against newer drugs, using appropriate outcome measures and well defined childhood epilepsy syndromes, would be logical, there would likely be much resistance to recruitment in Western countries. Nevertheless, there are some interesting questions that could be addressed in low cost clinical epidemiological studies that could prove helpful in focusing the optimum clinical indications for PB.

(a) Most pressing of these is the possibility of cognitive impairment in children with epilepsy treated with PB monotherapy. Does cognitive impairment only occur in children with epilepsy treated with PB? If so, what age groups are most vulnerable? Is it reversible after treatment ceases? Is there interaction with central neurological deficit? Which domains of intellect are most affected? Can the impact be mitigated by educational intervention? Is there a dose effect? Does the gain in cognitive function expected in children with more severe epilepsy successfully controlled with PB outweigh the deficit from treatment? In other words, how does the cost-benefit of PB vary according to the specific clinical scenario? This body of research would be most valuable for developing country markets.

(b) In Western countries, while the same questions are relevant, molecular diagnostics might in the near future be useful in assessing prior risk of adverse effects. Recent studies have put forward the possibility that allelic variants at pharmacologically relevant genes may increase

prediction of maximum doses for AEDs, and possibly for so-called “drug resistance” or toxicity[51,52]. This field of research may well lead to panels of alleles that could be simultaneously tested against a patient's DNA to predict the risk of adverse effects. This could potentially lead to a new lease of life for PB and many other pharmacologically active agents that have been on the shelf for many years. However, the sample sizes required for such allelic association studies would be very large.

Conclusions

Early studies, of questionable quality, on the use of PB in febrile convulsions led to widespread concern amongst paediatricians and neurologists about its toxicity. This concern became generalised to PB in its use as an *anti-epileptic* agent and was accompanied by a flurry of poorly designed, seemingly confirmatory studies. Despite better quality recent trials showing no evidence of excessive behavioural problems using PB for epilepsy, the debate over the routine use of PB in Western countries was superseded by the advent of new generations of AEDs. However, public concern over the safety of newer AEDs, and newer pharmacological agents in general, has prompted a re-evaluation of tried and tested older agents. Although this pendulum may soon swing back in the opposite direction, there is a real prospect of molecular biological advances permitting tailored prescribing of both new and older agents with lower risks of adverse effects. It is important to remember though, that large scale clinical studies will still be necessary to associate genotypes with toxicity and other outcome phenotypes.

The extreme contrast of health care accessibility for and social attitudes towards epilepsy in developing countries is often hard to comprehend in Western countries. These differences greatly influence the trade-offs between seizure control and toxicity that are accepted by patients, their families and their health care providers. Added to this are potential differences in biological, and more importantly, environmental factors that bear upon the behavioural and cognitive outcomes that we have selected as the topic of this review. In these contexts, cost is king, and PB retains the crown of antiepileptic drugs. PB will remain largely unchallenged until newer AEDs become more accessible. Interestingly though, the kind of clinical epidemiological studies suggested above for optimising PB's indications may simultaneously be valuable in developing molecular biological diagnostics for wealthier markets.

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Table 1

Clinical trials of phenobarbital in febrile convulsions

Reference	**53**	**24**	**28**	**29, 30**	**31**	**32**	**26**	**26**	**33**	**27**	**34**	**25**	**22**	**35**
Country	USA	USA	USA	Canada	UK	Singapore	UK	UK	Australia	Spain	France	UK	USA	USA
Type of trial	Simple	Simple	Not trial	Simple	Non-random	Simple	Stratified	Stratified	Simple	Simple	Simple	Simple	Stratified	—
Compared with	PB itmt Nil	PB itmt Nil	Nil	Placebo	SV Nil	SV	PHT Placebo	PHT Placebo	CBZ	DZM	SV Placebo	SV DZM	Placebo	Placebo
Sample size	355	395	50	65	64/3	101	161	138	72	100	73	151	217	217
Assignment														
Method	ID numbers	ID numbers	None	U	U	—	U	U	Pharmacy	U	Yes	U	Yes	Yes
Concealment	No	No	—	U	Yes	U	U	U	Yes	U	No	U	Yes	Yes
Baseline comparison	Yes	Yes	No	U	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding														
Method	No	No	N/A	Yes	Yes	No	No	No	No	No	Yes	No	—	—
Subject aware	Yes	Yes		No	No	—	Yes	Yes	Yes	Yes	No	Yes	No	No
Clinician aware	Yes	Yes		No	No	—	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Assessor aware	Yes	Yes		No	No	—	Yes	Yes	No	U	Yes	Yes	No	No
Analysis blind	U	U		U	No	—	U	U	Yes	U	U	No	Yes	Yes
Follow up														
Duration (m)	28	>18	35	12	12	12	12	12	53	18	21	24	24	30
% followed up	73%	?	Retro	69%	94%	90%	39%	66%	56%	100%	95%	87%	80%	80%
Reasons for dropout	PB group only	—	—	—	Yes	No	No	Yes	No	—	Yes	No	Yes	Yes
Analysis														
Primary outcome	Rec	ADRs	WISC	Rec; ADRs	Rec	Rec	ADRs	Rec	Rec	Rec	Rec	Rec	Rec; IQ	Sleep
Statistical method	ANCOVA	Sig tests	Sig tests	Sig tests	Sig tests	Sig tests	Sig tests	Sig tests	Regression	Sig tests	Sig tests	OR	Cox	GLM
Intention to treat	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes
Confidence intervals	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No
Exact p values	No	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes
Caution with subgroups	No	No	No	No	—	No	No	Yes	—	Yes	—	Yes	No	Yes
Inferences														
Efficacy	PB better	—	—	PB better	PB=SV>nil	SV>PB	—	PB better	PB better	ND	SV>PB>Placebo	Nil	Nil	—
Behaviour	—	PB worse	—	ND	—	—	ND	—	—	ND	—	—	ND	ND
Cognition	—	—	ND	ND	—	—	—	—	—	—	—	—	PB↓IQ	—

ANCOVA=analysis of covariance; CBZ=carbamazepine; Cox=Cox regression model; DZM=diazepam; GLM=general linear regression model; itmt=intermittent; ND=no difference; PB=phenobarbital; PHT=phenytoin; Rec=recurrence; Retro=retrospective; Sig tests=significance tests; SV=sodium valproate; U=unclear; WISC=Wechsler IQ Scale

Table 2

Clinical trials of phenobarbital in children with epilepsy

Reference	**36**	**38**	**39**	**40**	**42**	**43**	**4**	**37**	**44**
Country	Turkey	USA	USA	USA	Kenya	Ecuador	UK	Taiwan	India
Type of trial	Simple	Crossover	Crossover	Crossover	Simple	Simple	Simple	Simple	Simple
Compared with	PHT Placebo	MB	CBZ	SV	CBZ	CBZ	PHT SV;CBZ	CBZ	PHT
Sample size	63	8	33	21	302	192	167	76	94
Assignment									
Method	U	U	Balanced	U	Number list	Number list	Cards	Block	Minimised
Concealment	U	Yes	U	Yes	U	U	Yes	U	Yes
Baseline comparison	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding									
Method	U	No	U	Yes	No	No	No	No	No
Subject aware	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Clinician aware	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Assessor aware	U	No	No	No	Yes	Yes	Yes	Yes	No
Analysis blind	U	U	U	U	U	U	U	U	Yes
Follow up									
Duration (m)	3	3	12	6	12	12	44	12	12
% followed up	—	100%	—	—	82%	73%	—	96%	66–81%
Reasons for dropout	No	—	No	Yes	Yes	Yes	Yes	Yes	Yes
Analysis									
Primary outcome	5 tests	Behaviour	Behaviour	Behaviour	Seizure free	Seizure free	Recurrence	IQ and EEG	Behaviour
Statistical method	ANOVA	ANOVA	Sig tests	Sig tests	Sig tests	Sig tests	Cox model	Sig test	Regression
Intention to treat	No	—	—	No	No	No	Yes	No	Yes
Confidence intervals	No	No	No	—	No	No	Yes	Yes	Yes
Exact p values	No	Yes	No	—	No	No	Yes	Yes	Yes
Caution with subgroups	No	No	No	No	Yes	Yes	Yes	No	Yes
Inferences									
Efficacy	—	Same	Same	Same	Same	Same	Same	—	Same
Side effects	PB worse	ND	ND	PB worse	ND	ND	PB worse	ND	ND

ANOVA=analysis of variance; CBZ=carbamazepine; MB=mephobarbital; ND=no difference; PB=phenobarbital; PHT=phenytoin; SV=sodium valproate; Sig tests=significance tests; U=unclear