Review article

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Side effects of phenobarbital in epilepsy: a systematic review

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ABSTRACT – *Aim*. In recent years, phenobarbital, as an antiepileptic drug, has become less popular based on adverse events, especially cognitive and behavioural side effects. Despite the development of better tolerated new generation AEDs, phenobarbital is still widely used particularly in developing countries because of its low cost. The purpose of this review was to: *(i)* investigate whether phenobarbital can be safely used as an antiepileptic drug and *(ii)* determine the questions which need to be addressed in order to comprehensively and adequately evaluate the safety of phenobarbital for the treatment of epilepsy. *Methods*. The literature was searched using the Cochrane Central Register of randomised controlled trials (1800-2009), Medline (1966-2009), Embase (1966-2009) and three Chinese databases. *Results*. Twenty studies were finally included in this systematic review. The determination of adverse effects of combined antiepileptic drugs (AEDs) from different studies was complicated by numerous factors including study design, different descriptions of adverse events and a lack of standardised data collection. These factors may also have been responsible for the heterogeneity present in the meta-analysis. The data did not demonstrate any evidence of association between phenobarbital and a higher risk of adverse events. However, phenobarbital appeared to be associated with a higher rate of adverse drug reaction related withdrawal (ADR-related withdraw), compared to carbamazepine, valproic acid and phenytoin. This may have been due to a concern for possible adverse effects of phenobarbital. *Conclusions*. Phenobarbital was associated with a higher rate of drug withdrawal although there was no evidence to suggest that phenobarbital caused more adverse events compared to carbamazepine, valproic acid or phenytoin. However, in the case of pregnant women, it is important for clinicians to evaluate the benefits and risks of phenobarbital administration before making a final recommendation. Furthermore, unified scales for the assessment of cognitive function should be applied for future studies particularly in children.

Key words: phenobarbital, side effects, systematic review

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Epilepsy is a chronic disorder of the brain which affects approximately 50 million people world-wide, of whom 40 million are estimated to live in developing countries (WHO, 2004). Studies in both developed and developing countries have shown that up to 70% of newly diagnosed children and adults with epilepsy may lead normal lives if properly treated (WHO, 2009). Unfortunately, 85% of epilepsy patients living in the

developing world do not receive any treatment because of the cost of treatment, superstition and the unavailability of drugs (Kale, 2002; Muba *et al*., 2008).
Phenobarbital (PB) has been a widely used AED due to its low cost and broad indication. Despite the development of new AEDs, phenobarbital is recommended by the World Health Organization (WHO) as a first-line drug in developing countries (WHO, 1990). Several studies suggested there is little difference in antiepileptic efficacy between phenobarbital and other established AEDs (Tudur Smith *et al*., 2003; Kwan and Brodie, 2004; Mattson *et al*., 1985). However, concern for adverse effects has resulted in a decline of use for seizure disorders. Phenobarbital is reported to be associated with a higher rate of side effects and was even withdrawn from a trial arm in a previous study, as a result of perceived adverse behavioural effects (de Silva *et al*., 1996). In some other studies, however, no difference was found between phenobarbital and other AEDs with respect to tolerance (Pal *et al*., 1998). Based on the studies reported to date, a consensus on the safety of phenobarbital has not been possible. Hence, it is necessary to re-evaluate the original controversial issues concerning phenobarbital and systematically reassess its safety for the treatment of epilepsy.

Methods

Search strategy

We searched the Cochrane Central Register of randomised controlled trials (RCTs) (1800-2009), Medline (1966-2009), Embase (1966-2009) and three Chinese databases; VIP (1989-2009), CNKI (1979-20), CBM (1978-2009), using "epilepsy", "seizure", "phenobarbital", "phenobarbitone", "anticonvulsant" and "anticonvulsive agent". We performed an independent search for major congenital malformation using "pregnancy", "prenatal exposure delayed effects", "abnormalities", "teratogens", "congenital defect", "congenital malformation", "birth defect" and "dysmorph". Language was restricted to English and Chinese. The reference lists of relevant publications returned by the above searches were examined.

Study selection criteria

We selected the trials that met each of the following criteria:
– RCTs, double-blind or open-label, performed in patients with partial or generalised epilepsy. There was no restriction on the age of patients. Prospective cohort studies performed in women with epilepsy treated with AEDs were included for "major congenital malformation" assessment.
– Parallel or cross-over design studies were included but the minimum duration of each treatment was eight weeks.
– Studies of monotherapy which compared the administration of phenobarbital by oral route with carbamazepine, valproic acid and phenytoin.
– Studies in which the absolute number of adverse effects (AEs) was reported or could be calculated.

Outcome measures

The classification and definition of AEs were as follows, as previously documented (Aronson *et al*., 2006; Zaccara *et al*., 2008):
– total withdrawal rate;
– ADR-related withdrawal;
– nervous system AEs;
– psychological and psychiatric AEs;
– major congenital malformation.
AEs of the nervous system were divided into three broad classes: those affecting vigilance, those affecting the brain stem and vestibulo-cerebellar system, and those affecting the motor system *(table 1)*.
Psychological and psychiatric AEs included anxiety, depression, dissociation, hallucination, cognitive impairment and behavioural disturbances. Since objective measures for most of these complaints were not used, an analysis of all the psychological and psychiatric AEs as a whole could be misleading. We, therefore, focused on cognitive dysfunction and behavioural disturbances which were frequently rated as the most worrisome adverse event of phenobarbital and usually assessed by measuring scales in original studies. However, since the scales used in different studies varied, data could not be combined and thus a descriptive analysis was performed to assess the cognitive and behavioural effect of phenobarbital.

Table 1. Classification of nervous system adverse events.

Classification	Description
Affecting vigilance	Somnolence
Affecting brain stem and vestibulo-cerebellar system	Dizziness/Vertigo Diplopia Nystagmus Blurred vision Ataxia
Affecting motor system	Chorea and dystonia Tremor

Table 2. Outcome of quality assessment of randomized controlled trials.

Study ID	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Mattson *et al*., 1985	U	U	Y	Y	U	U
Mitchell and Chavez, 1987	U	U	Y	N	Y	U
Vining *et al*., 1987	U	U	Y	Y	Y	U
Meador *et al*., 1990	U	U	Y	Y	Y	U
Feksi *et al*., 1991	Y	U	U	Y	Y	Y
Heller *et al*., 1995	Y	Y	U	Y	Y	Y
Thilothammal *et al*., 1996	Y	U	Y	Y	Y	Y
de Silva *et al*., 1996	U	N	N	N	Y	N
Chen *et al*., 1996	Y	U	Y	Y	Y	Y
Pal *et al*., 1998	Y	Y	Y	Y	Y	Y
Banu *et al*., 2007	Y	Y	Y	N	Y	Y

The quality assessment criteria was based the Cochrane collaboration's "Risk of bias" tool. Y (yes) indicates a low risk of bias, N (no) indicates a high risk of bias and U (unclear) indicates insufficient information to permit judgement of "yes" or "no".

Major congenital malformations were defined as structural abnormalities with surgical, medical, or cosmetic importance (Tomson *et al*., 2007). Minor malformations, not included in most published malformation rate data, were not considered. Major malformation was categorised into nine broad classes according to organs and systems affected: nervous system, eye, ear, face and neck, circulatory system, respiratory system, digestive system, genital organs, urinary system, musculoskeletal system, and other syndromes such as Smith-Lemli-Opitz syndrome and chromosomal abnormalities.

Quality assessment

The quality of RCTs and cross-over studies was assessed based on the following aspects: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome data and other potential threats to validity (Wells *et al*., 2008; Higgins and Green, 2009). The quality of prospective cohort studies was judged by the Newcastle-Ottawa quality assessment scale.

Data collection

Standardised data collection approach

The characteristics of each study, all participants and interventions used were extracted. For the collection of AEs, we proceeded as follows: first, we identified all AEs which had been included in our outcome measures from the AE reporting tables of included studies; second, for each study, the number of patients complaining of AEs and the total number of patients were extracted. We included all studies which were performed with phenobarbital even though some AEs were not observed. Since AEs may not have been considered as such in some trials, there was a potential underestimation of AEs. For cross-over studies, data was extracted from all periods as a whole, when washout period was assessed to be long enough.

Data analysis

Statistical analysis was undertaken following the guidelines of the Handbook of the Cochrane Collaboration 5.0. Related risk for dichotomous data was calculated using the random-effects model in Review Manager 5.0. Heterogeneity between trials was calculated using the Chi square test and was considered to be heterogeneous when $p \leq 0.1$. I^2 values of no more than 25%, 26% to 74% and no less than 75% were considered as "low", "moderate" and "high" heterogeneity, respectively. We considered associations to be statistically significant at $p < 0.05$. A descriptive analysis was considered for the assessment of congenital and behavioural disturbance, as scales implemented varied among original studies. A sensitivity analysis was performed for the study design in which only randomised controlled parallel trials were included.

Table 3. Outcome of quality assessment of observational studies*.

Study ID	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
van der Pol *et al.*, 1991	★	★	★	★	-	★	★	★	★★★★★★★
Lindhout *et al.*, 1992	★	★	★	-	★	-	★	-	★★★★★
Tanganelli and Regesta, 1992	-	★	★	★	★	-	★	-	★★★★★
Waters *et al.*, 1994	★	★	★	★	-	★	★	-	★★★★★★
Samrén *et al.*, 1997	★	★	★	★	-	★	★	-	★★★★★★
Canger *et al.*, 1999	★	★	★	★	-	★	★	★	★★★★★★★
Kaneko *et al.*, 1999	★	★	★	-	-	★	★	★	★★★★★★
Holmes *et al.*, 2001	★	★	★	★	★	★	★	★	★★★★★★★★
Burja *et al.*, 2006	★	★	★	★	-	★	★	-	★★★★★★

* The quality assessment criteria was based on the Newcastle-Ottawa Quality Scale for Cohort Studies. A study was awarded a maximum of one star for each item within the selection and exposure categories. A maximum of two stars was given for comparability. The number of stars represents the quality of study; the quality of study being directly proportional to the number of stars.

Results

Description of studies

The literature search yielded 2,722 and 2,230 citations for congenital malformation and other AEs, respectively. After screening, nine prospective cohort studies were included for analysis of congenital malformation (van der Pol *et al*., 1991; Lindhout *et al*., 1992; Waters *et al*., 1994; Samrén *et al*., 1997; Tanganelli and Regesta, 1992; Canger *et al*., 1999; Kaneko *et al*., 1999; Holmes *et al*., 2001; Burja *et al*., 2006) and eleven randomised trials were included for the analysis of other AEs (Mattson *et al*., 1985; Mitchell and Chavez, 1987; Vining *et al*., 1987; Meador *et al*., 1990; Feksi *et al*., 1991; Heller *et al*., 1995; Thilothammal *et al*., 1996; de Silva *et al*., 1996; Chen *et al*., 1996; Pal *et al*., 1998; Banu *et al*., 2007).

Two cross-over trials were included (Vining *et al*., 1987; Meador *et al*., 1990). In the trial of Vining *et al*. (1987), the wash-out period between two six-month treatment periods was one month. In the trial of Meador *et al*. (1990), no exact wash-out period was reported but the authors mentioned that at the beginning of each phase, subjects were tapered off their pre-existing medication and were started on gradually increasing doses of the drug for that treatment phase. Additionally, all cognitive tests in the trial of Meador *et al*. were performed at the end of each three-month treatment phase.

Of the twenty studies, 13 were from developed countries, and seven from developing countries. Most of them were carried out in a single centre (12/20) and had limited sample size. Only one prospective cohort study (Samrén *et al*., 1997) and one clinical trial (Mattson *et al*., 1985) had a sample size of more than 500. The characteristics of included studies are shown in *appendix 1* and *2*.

Quality of included studies

Among eleven experimental studies *(table 2)* only six (Feksi *et al.,* 1991; Thilothammal *et al.,* 1996; Chen *et al.,* 1996; Heller *et al.,* 1995; Pal *et al.,* 1998; Banu *et al.,* 2007) described sequence generation, of which only three (Heller *et al.,* 1995; Pal *et al.,* 1998; Banu *et al.,* 2007) conducted allocation concealment. Blinding was not performed in three studies (de Silva *et al.,* 1996; Feksi *et al.,* 1991; Heller *et al.,* 1995). In the study of de Silva *et al*. (1996), enrolment to the phenobarbital arm was terminated due to drug-related adverse effects, after randomising only 10 children to this drug.This early termination may be a source of potential threat to validity.

Among the observational studies *(table 3)*, a lack of comparability between cohorts and no description of subjects lost to follow-up were two factors which limited the quality of observational studies. The main reason was that for all included prospective cohort studies, women exposed to AEDs were considered as part of the "exposed cohort" and women without AED treatment or healthy women were considered as part of the "non-exposed cohort", thus the baseline was compared between two cohorts as a whole and failed to report the comparability between different AED treatment groups. Likely, lost to follow-up in each AED treatment group were not reported in most studies although the follow-up of cohorts was reported as a whole. In addition, although sample size was balanced between experimental and control groups in all RCTs, this was not the case for most of the observational studies (Lindhout *et al*., 1992; Tanganelli and Regesta, 1992; Samrén *et al*., 1997; Canger *et al*., 1999; Kaneko *et al*., 1999; Burja *et al*., 2006).

Outcomes

Total withdrawal (figure 1)

Phenobarbital *vs* valproic acid. Total withdrawal information was available for 159 individuals in two trials. The common estimated risk ratio was 1.85 (95% CI: 0.77-4.41), favouring valproic acid but without statistical significance (p=0.17).

Phenobarbital *vs* carbamazepine. Four studies, including 651 participants, reported total withdrawal information. The common estimated risk ratio was 1.23 (95% CI: 0.99-1.53), favouring carbamazepine but without statistical significance (p=0.07).

Phenobarbital *vs* phenytoin. Data comparing the total withdrawal rate between phenobarbital and phenytoin was available in three studies, including 404 individuals. The common estimated risk ratio was 1.20 (95% CI: 0.94-1.52), favouring phenytoin but without statistical significance (p=0.14).

Conclusion. No significant difference was shown between phenobarbital and other AEDs with respect to total withdrawal rate.

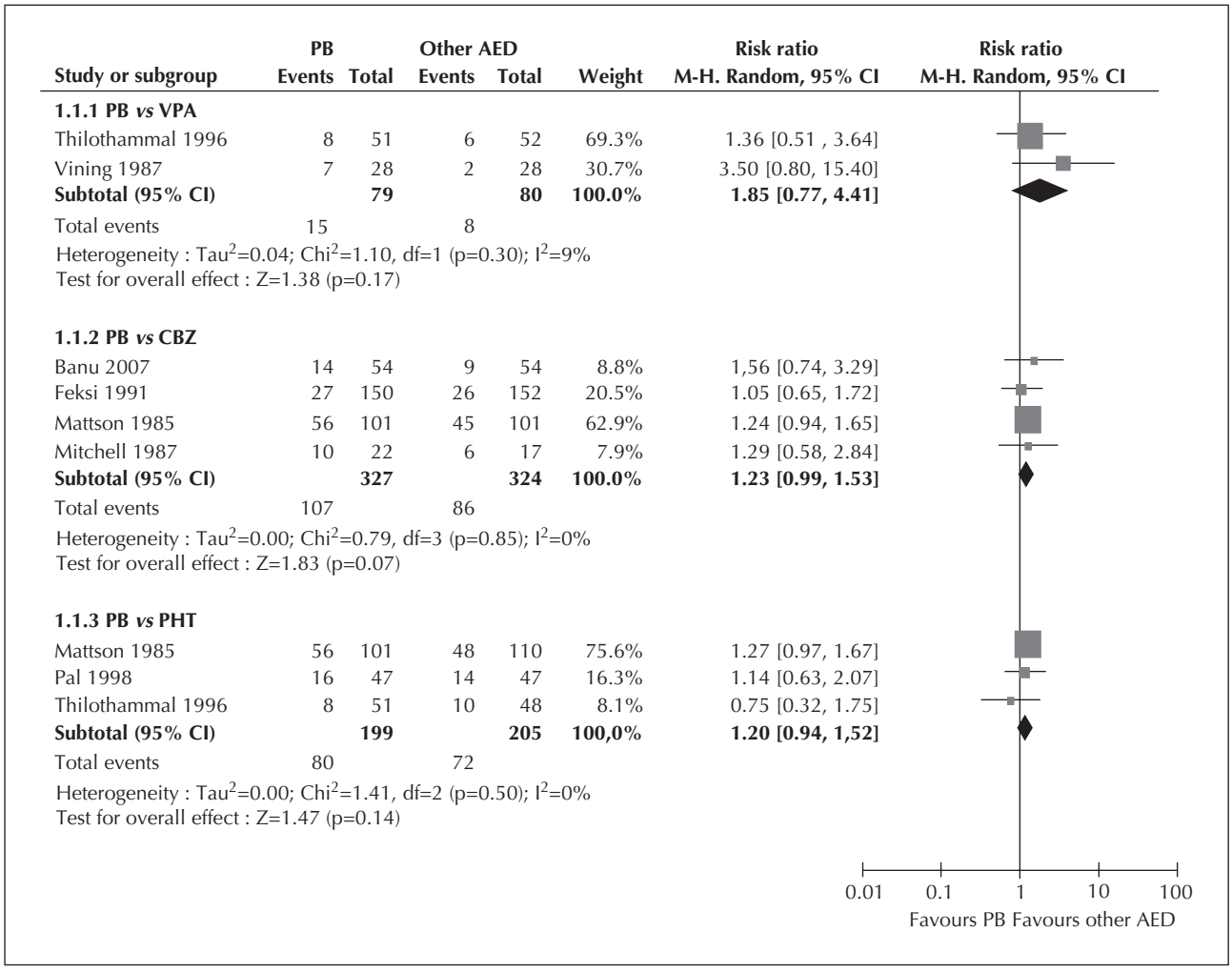

Figure 1. Total withdrawal; PB *vs* VPA, CBZ, PHT.

ADR-related withdrawal (figure 2)

Phenobarbital *vs* valproic acid. ADR-related withdrawal data was available for 234 individuals in three trials. The common estimated risk ratio was 7.64 (95% CI: 3.17-18.42), favouring valproic acid (p<0.00001).

Phenobarbital *vs* carbamazepine. ADR-related withdrawal information was available for 832 individuals in six trials. The common estimated risk ratio was 1.50 (95% CI: 0.72-3.10), favouring carbamazepine (p=0.28). However, there was evidence of quantitative heterogeneity between trials (chi^2=15.72, p=0.008).

Phenobarbital *vs* phenytoin. ADR-related withdrawal information was available for 490 individuals in four trials. Phenobarbital was more likely to be withdrawn because of ADR than phenytoin with an estimated common risk ratio of 2.75 (95% CI: 0.94-8.09). However, there was evidence of quantitative heterogeneity between trials (chi^2=15.68, p=0.001).

Conclusion. Phenobarbital appeared to be associated with a higher rate of ADR-related withdrawal compared to valproic acid, carbamazepine or phenytoin, however, significant heterogeneity existed between original trials.

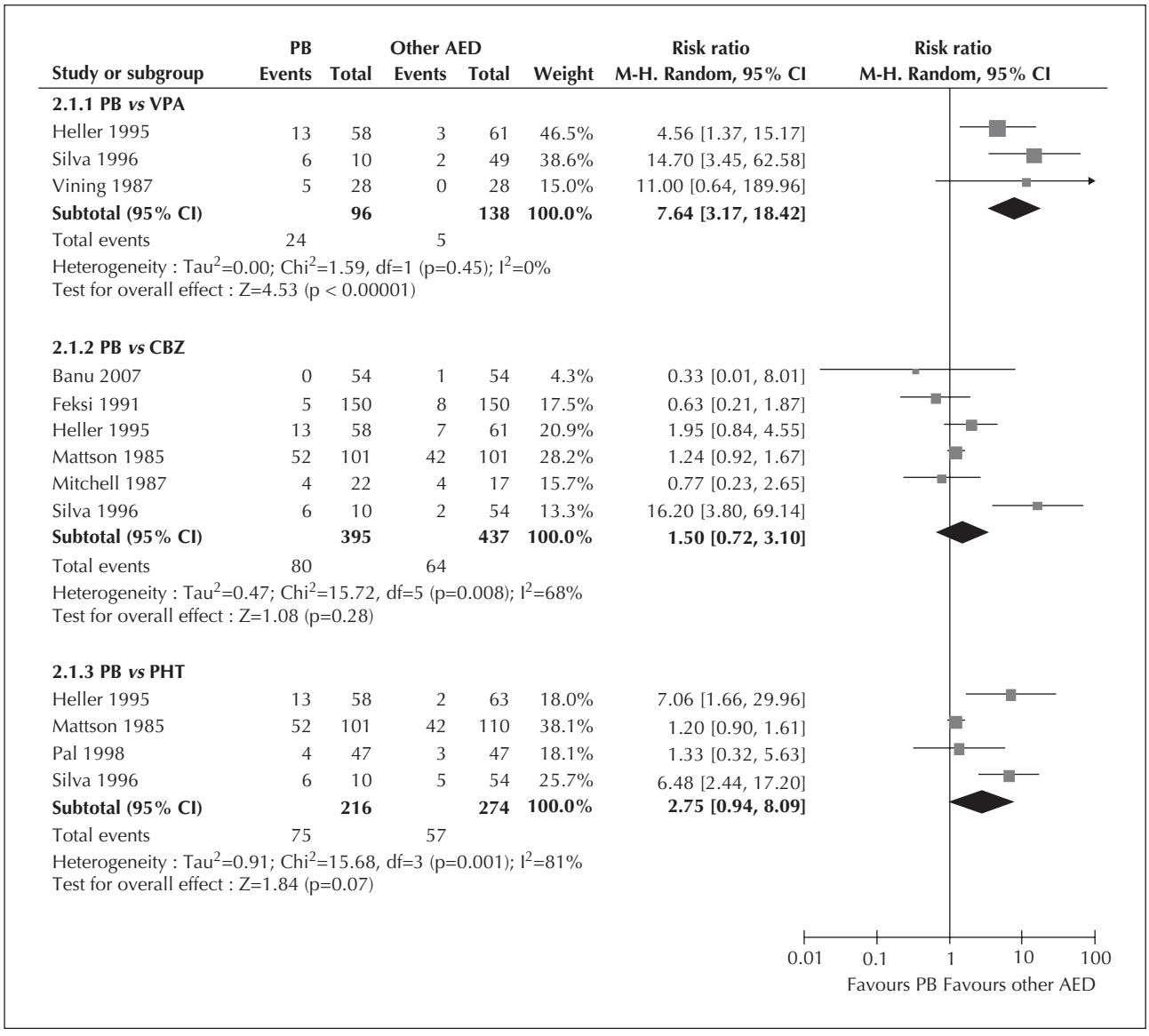

Figure 2. ADR-related withdrawal; PB *vs* VPA, CBZ, PHT.

Nervous system AEs (figure 3)

Phenobarbital *vs* valproic acid. Data of nervous system AEs were available for 333 individuals in four trials. However, the data from one trial was not considered (Thilothammal *et al*., 1996) because nervous system AEs occurred in neither the phenobarbital group nor the valproic acid group. The common estimated risk ratio was 1.41 (95% CI: 0.28-8.53). However, there was evidence of quantitative heterogeneity between trials (chi^2=6.65, p=0.04).

Phenobarbital *vs* carbamazepine. Three independent studies including 385 individuals compared nervous system AEs between phenobarbital and carbamazepine treatment groups. The common estimated risk ratio was 1.28 (95% CI: 0.46-3.60), favouring carbamazepine without statistical significance (p=0.64). There was evidence of moderate heterogeneity between studies for this outcome (chi^2=4.07, p=0.13, I^2=51%).

Phenobarbital *vs* phenytoin. Four independent trials including 472 patients compared nervous system AEs between phenobarbital and phenytoin treatment groups. However, moderate heterogeneity was shown between trials (chi^2=7.51, p=0.06). The common estimated risk ratio was 0.54 (95% CI: 0.11-2.65), favouring phenobarbital without statistical significance (p=0.45).

Conclusion. There was no evidence that phenobarbital was more likely to induce nervous system AEs, compared to valproic acid, carbamazepine or phenytoin.

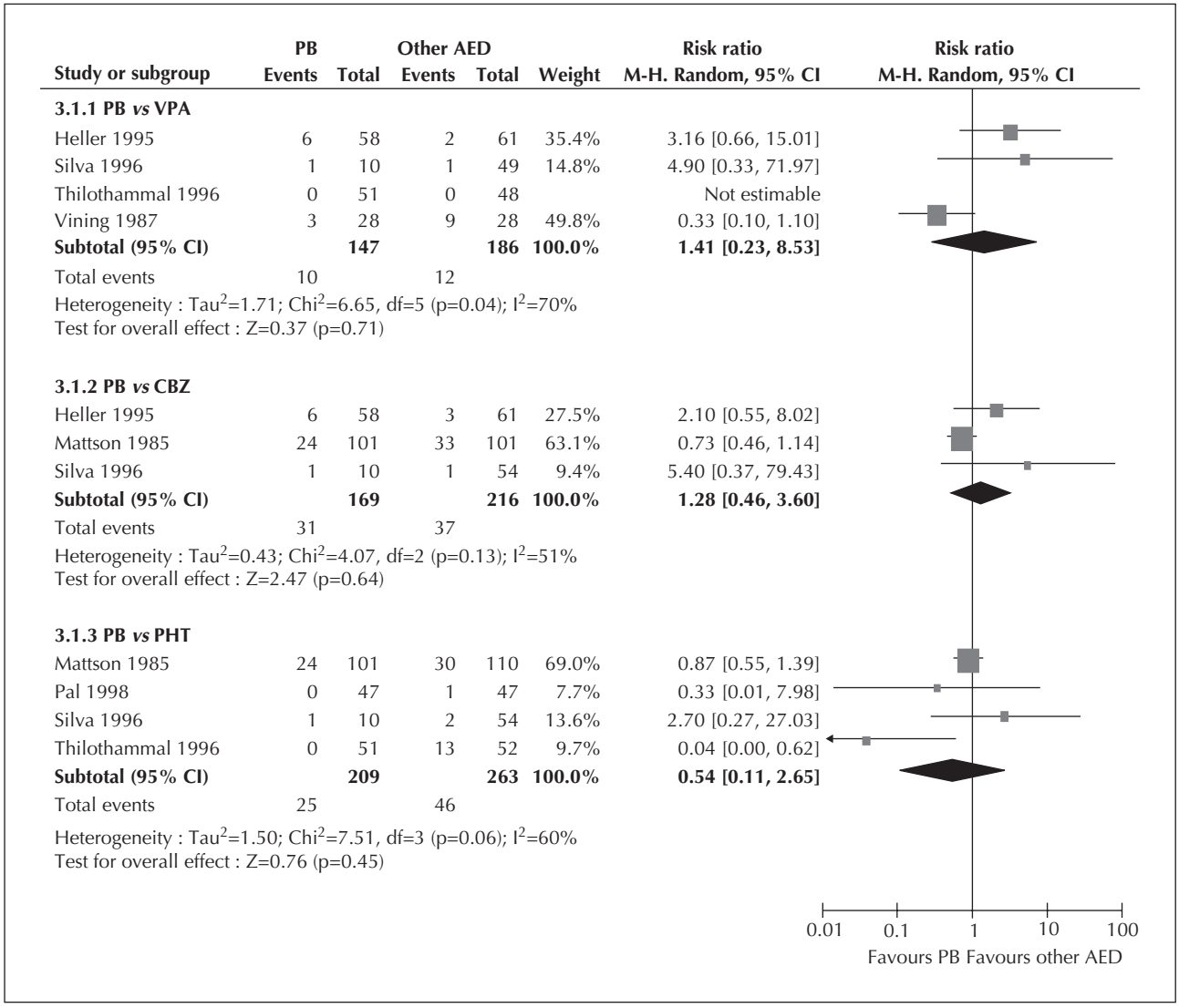

Figure 3. Nervous system AEs; PB *vs* VPA, CBZ, PHT.

Major congenital malformation (figure 4)

Phenobarbital *vs* valproic acid. Malformation information was available for 683 offspring in six trials. In one trial, no malformation was reported (Burja *et al*., 2006). The common estimated risk ratio was 0.58 (95% CI: 0.32-1.06), favouring phenobarbital but without statistical significance (p=0.08).

Phenobarbital *vs* carbamazepine. Major congenital malformation data was available from 10 studies, accounting for 1148 offspring. The common estimated

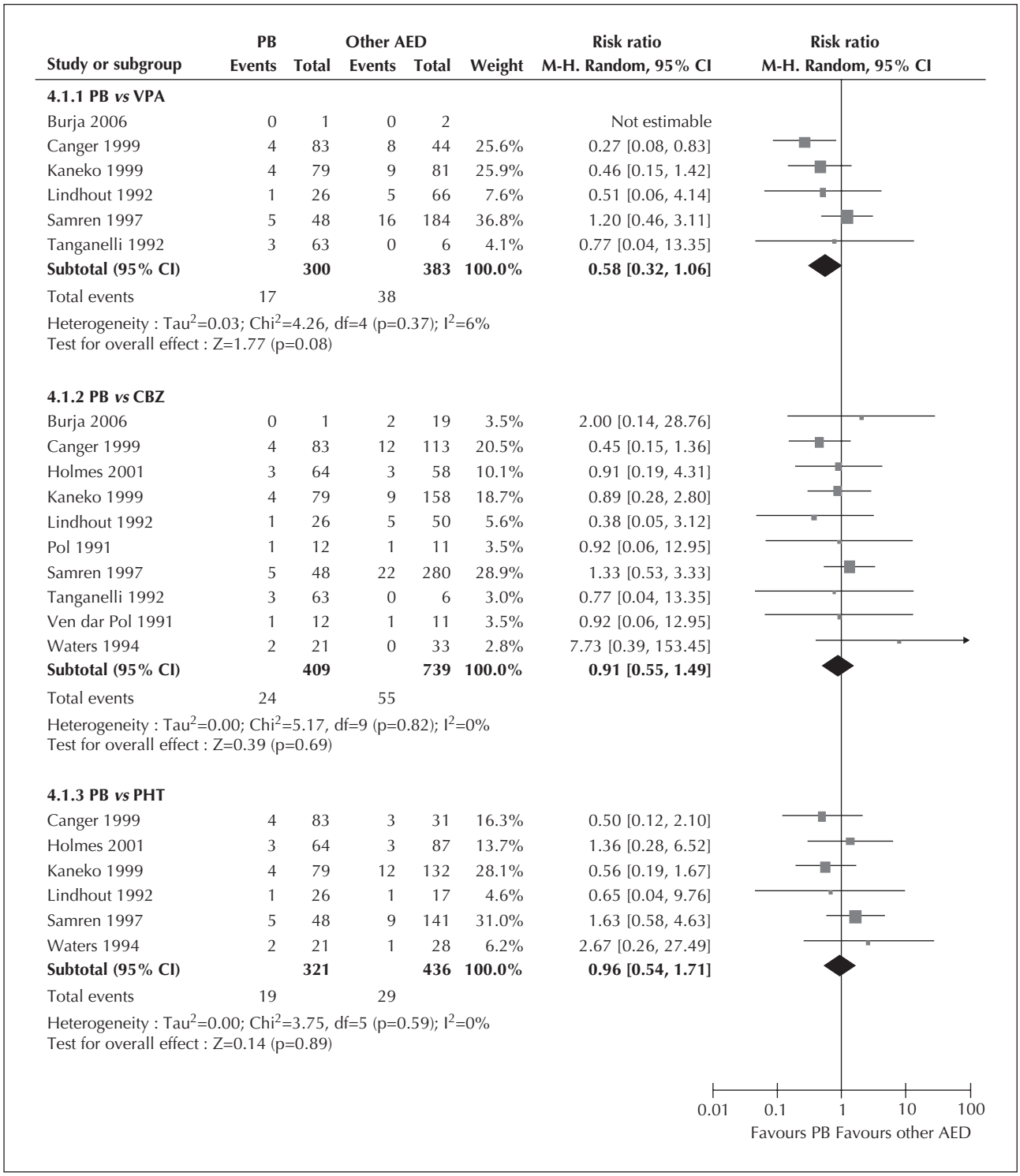

Figure 4. Major congenital malformation; PB *vs* VPA, CBZ, PHT.

risk ratio was 0.91 (95% CI: 0.55-1.49), favouring phenobarbital but without statistical significance (p=0.69).

Phenobarbital *vs* phenytoin. Six independent studies including 757 offspring compared major congenital malformation between phenobarbital and phenytoin treatment groups. The common estimated risk ratio was 0.96 (95% CI: 0.54-1.71), favouring phenobarbital, but without statistical significance (p=0.89).

Conclusion. Phenobarbital would appear to be a better choice of drug compared to valproic acid, in terms of second generation teratogenicity. No difference was reported between phenobarbital and carbamazepine or phenytoin treatments *(table 4)*.

Table 4. Major congenital malformation reported in included prospective cohort studies.

Organs and systems	Congenital malformations
Nervous system	Meningomvelocele Spina bifida Hydrocephalus Vertebral anomalies Anencelphaly
Eye, ear, face and neck	Facial malformation Cleft lip and/or palate
Circulatory system	Patent ductus arteriosus Ventricular septal defect(VSD) Heart malformation Hypoplasia of the nitral valve Multiple ventricular septal defects Single ventricle Large cavernous hemangioma on leg Interatrial defect Fallot's tetralogy
Respiratory system	Lung cyst
Digestive system	Oesophageal atresia Pyloric stenosis
Urinary system	Urogenital malformation Penile htpospadias Hydronephrosis
Genital organs	-
Musculoskeletal system	Dysplasia of hips Hip dislocation Gastroschisis Inguinal hernia Diaphragmatic hernia Umbilical hernias Omphalocele Deformity of the foot Club foot Multiple terminal transverse limb defects Arthrogryposis Skeletal malformation
Other	heterotaxia Smith-Lemli-Opitz syndrome
Chromosomal abnormalities	Down syndrome

Cognitive dysfunction and behavioural disturbance

According to our search strategy, six clinical trials were included and are described below in chronological order.

1) Mitchell and Chavez (1987) compared the cognitive and behavioural function of 33 children with partial onset seizures randomised to either phenobarbital or carbamazepine. Cognitive tests included the Weschler Intelligence Scale for Children-Revised (WISC-R) and the Raven's Colored Progressive Matrics for children over the age of six, and the McCarthy Scale of Children's Abilities for children aged three to six years. A behaviour questionnaire was conducted by a psychologist. There were no significant differences between phenobarbital and carbamazepine with regards to the effect on cognitive or behavioural function, either at six-month or 12-month follow-up ($p<0.05$).

2) Vining *et al*. (1987) used a randomised, double-blind, cross-over design with 28 subjects over six months to investigate the cognitive side effects of phenobarbital and valproic acid. Twenty one children completed the study. The WISC-R and another 11 neuropsychological function tests were used for cognitive function assessment, while behavioural patterns were assessed by the Burk's Behavior Rating Scales. For most measures, there were no differences between the two drugs. Statistically significant differences ($p<0.01$) were seen for four items, all of which favoured valproic acid. There was a tendency towards better cognitive function in children who received valproic acid.

3) Meador *et al*. (1990) investigated the cognitive effect of phenobarbital, phenytoin and carbamazepine in a randomised double-blind, triple cross-over trial with 21 patients over three months. Separate analyses of covariance using % anticonvulsant blood levels (% ABLs) and seizure frequency were performed for each of eight cognitive tests. The only significant

effect was for the Digit Symbol test in which performance with phenobarbital was worse when covaried for % ABLs ($F[2,27]=3.89$; $p \leq 0.03$) or seizure frequency ($F[2,27]=3.93$; $p \leq 0.03$).

4) Chen *et al*. (1996) investigated cognitive side effects of AEDs in children using the WISC-R. Of 76 included subjects, 25 were allocated to phenobarbital, 26 to carbamazepine and 25 to valproic acid. There were no significant differences in any neuropsychological tests among the three groups at any stage. Although children in the phenobarbital group showed a slight and sustained decrease in intelligence quotient (IQ) values after six and 12 months of treatment, these values were not statistically significant.

5) Pal *et al*. (1998) undertook a randomised comparison of phenobarbital and phenytoin to assess the behavioural effect of the two AEDs. Ninety-four children were randomly allocated to treatment with phenobarbital (n=47) or phenytoin (n=47). Behavioural side effects were assessed by the Conners Parent Rating Scale for children aged six and older, and by the preschool Behaviour Screening Questionnaire (BSQ) for those aged two to five years, after 12 months of treatment or treatment withdrawal. The odds ratio for behavioural problems (phenobarbital *vs*. phenytoin) was 0.51 (95% CI: 0.16-1.59). There was no excess in parental reports of side effects for phenobarbital.

6) Banu *et al*. (2007) conducted a randomised controlled single centre trial to compare the behavioural side effects associated with phenobarbital and carbamazepine. Side effects were compared in 85 children. The Bayley Scale was used for those aged above two years and the Richman behavioural assessment questionnaire for those aged two to three years. Behaviour function was assessed after 12 months of treatment or at drug withdrawal. The children had increased behavioural problems, which were deemed unacceptable in four (one in the phenobarbital group and three in the carbamazepine group). The authors concluded that there was no excess in behavioural side effects with phenobarbital in children with epilepsy.

Sensitivity analysis

To examine whether the results were sensitive to study design, we excluded two cross-over trials (Vining *et al*., 1987; Meador *et al*., 1990) and one randomised parallel trial (de Silva *et al*., 1996) in which no further participants were assigned phenobarbital following the ascertainment that six of the first ten participants experienced unacceptable side effects. No difference was identified apart from a decline in heterogeneity between phenobarbital and carbamazepine in ADR-related withdrawal when the study of de Silva *et al*. (1996) was excluded ($Chi^2=3.81$, $I^2=0\%$).

Discussion

Difficulties in describing AEs between studies

There were many factors that made it difficult to draw comparisons between AED adverse effects among studies. In particular, the lack of standardised descriptions of adverse events and the fact that objective quantifiable measures and severity of most complaints were not considered in reports. Furthermore, the variation in methods for data collecting also made the comparison of AED adverse effects inaccurate.

Strength of the evidence

The duration of follow-up varied between trials, ranging from 12 months (Vining *et al*., 1987, Feksi *et al*., 1991) to 91 months (Heller *et al*., 1995), which might cause detection bias. However, since AED adverse events usually occur in the first months (Wang *et al*., 2006; Nimaga *et al*., 2002), the difference in follow-up duration had limited influence on the results of this review. For the meta-analysis, we included trials performed on both children and adults. Age may therefore have been a cause of heterogeneity. However, when we performed a subgroup analysis according to age of study participants, heterogeneity still existed in most comparisons, although the number of trials became limited especially in the adult group. Thus, we did not present the results from subgroup analysis.

Reports on malformation rates were based on four prospective observational studies. Women enrolled in these studies were a diverse group. Three studies (Lindhout *et al*., 1992; Tanganelli and Regesta, 1992; Kaneko *et al*., 1999) included pregnant women with epilepsy who received AED treatment, while one study (Holmes *et al*., 2001) enrolled women who had taken AEDs no matter they were epileptic or not. However, clinical indications for using AEDs include not only epilepsy but also disorders such as migraine and pain syndromes (Lateef and Nelson, 2007). Thus, epilepsy may become a confounding factor in this review. In addition, most studies failed to account for potential confounders such as socioeconomic status and type and severity of the underlying condition, which themselves may cause adverse foetal outcomes.

Comparison with previous reviews

Some previous reviews have investigated the safety of phenobarbital, but most have focused on only specific side effects. The review of Taylor *et al*. (2003) suggests that phenobarbital was significantly more likely to be withdrawn than phenytoin, with an estimated common risk ratio of 1.62 (95% CI: 1.22-2.14).

However, there was evidence of quantitative heterogeneity between the trials (chi^2=9.34, p=0.009). The study of Tudur Smith *et al*. (2003) indicated that phenobarbital is less tolerated than carbamazepine (hazard ratio 1.63, 95% CI: 1.23-2.15). Naghme *et al*. (2004) reviewed the adverse effects of phenobarbital on maternal and foetal outcomes in pregnant women with epilepsy. No difference of cognitive function was found between children with uterus exposure to phenobarbital and the general population. However, a larger proportion of poor achievers among the phenobarbital-exposed group was found when compared with the carbamazepine-exposed group. Safety of phenobarbital has also been investigated in observational studies, especially in some developing countries. In an open label trial in rural areas of Mali (Nimaga *et al*., 2002), an excellent compliance was achieved among 80% patients treated with phenobarbital. Minor side effects were frequently observed at the beginning of treatment but they did not continue. In a hospital clinic in Nigeria (Sykes, 2002), 344 children with epilepsy were treated with phenobarbital, of whom only two discontinued because of intolerable side effects. In a prospective study conducted in rural China (Wang *et al*., 2006), medication was well tolerated and reported adverse events were mild. No obvious cognitive or behavioural impact was found. Other neurotoxic effects also became less severe as time went on. Overall, previous studies have reported similar findings to this review, that is, no evidence suggesting that phenobarbital is associated with a higher risk of adverse events.

Implications for practice

Although phenobarbital appears to be more commonly associated with a higher withdrawal rate, no statistically significant difference was found for most domains of adverse events between phenobarbital and the other three AEDs. Studies to date suggest there is no difference in major malformation rate between phenobarbital and the other three AEDs. Hence, we come to the conclusion that phenobarbital should not be cited as an AED with a high risk of side effects, based on current studies. However, it is important for clinicians to evaluate the benefits and risks of phenobarbital administration to child-bearing women before making a final recommendation.

Implications for research

One explanation for the higher withdrawal rate in the phenobarbital group is that clinicians were biased towards withdrawing phenobarbital in unblinded studies. Blinding, therefore, should be performed in future pragmatic studies. Furthermore, cognitive effects of AEDs have been studied under a variety of scales for the assessment of cognitive impairment. The lack of criteria for scale selection makes it difficult to compare or combine data from different trials. A criterion for the selection of scales in assessing cognitive function in epileptic patients is in need.

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Appendix 1. Characteristics of included randomised controlled trials.

Study-ID	Country	Study		No of centres	Sample size	Age of patients (year)	Daily dose/ Serum level	How AEs were recorded	Follow-up		Analysis			Power calculation	Funding
		Type	Blinding						Duration (years)	No. patients	Statistical method	Intention to treat	Exact p values		
Mattson *et al.*, 1985	USA	RCT	Unblinded	10	622	A 18-70	NS	Self report	1-6	198/622	Chi-square test	U	Y	Y	None
Mitchell and Chavez, 1987	USA	RCT	NS	1	39	C 2-12	PB:15-24 μg/mL CBZ: 4-7 μg/mL	Cognitive tests; Behaviour questionnaire	1	23/39	Chi-square analysis t tests ; Mann-Whitney U tests	U	Y	Y	NS
Vining *et al.*, 1987	USA	Cross-over study	Double-blinded	1	28	C 6-14.5	PB: 3.4±0.9 mg/kg/d VPA: 27±10.6 mg/kg/d	Examination performed by physician	1	21/28	Paired t test	N	Y	N	1
Meador *et al.*, 1990	Georgia	Cross-over study	Double-blinded	1	21	A 19-62 (mean 39)	PB: 15-40 μg/mL CBZ: 6-12 μg/mL PHT: 10-20 μg/mL	Cognitive tests	0.75	15/21	NS	N	N	N	2
Feksi *et al.*, 1991	Kenya	RCT	Unblinded	1	302	C and A 6-65 (mean 21)	PB: 30-60 mg/d CBZ: 400-600 mg/d	Structured interview	1	249/302	Chi-square test	N	Y	N	Ciba-Geigy
Heller *et al.*, 1995	UK	RCT	Unblinded	2	243	A Mean 29	PB: 20-40 μg/mL VPA: 50-100 μg/mL CBZ: 4-11 μg/mL PHT: 10-20 μg/mL	NS	0.08-7.58	196/243	NS	Y	Y	Y	None
Thilothammal *et al.*, 1996	India	RCT	Double-blinded	1	151	C 4-12	PB:3-5 mg/kg/d VPA: 15-50 mg/kg/d PHT: 5-8 mg/kg/d	Examination performed by physician	1.83-3	127/151	Fischer's exact test; Chi square test	U	Y	N	3

Appendix 1. (*Continued*)

Study-ID	Country	Study		No of centres	Sample size	Age of patients (year)	Daily dose/ Serum level	How AEs were recorded	Follow-up		Analysis			Power calculation	Funding
		Type	Blinding						Duration (years)	No. patients	Statistical method	Intention to treat	Exact p values		
de Silva *et al.*, 1996	UK	RCT	Unblinded	4	167	C 3-16	PB: 20-40 μg/mL VPA: 50-100 μg/mL CBZ: 4-11 μg/mL PHT: 10-20 μg/mL	NS	0.25-7.33	15/167	NS	Y	Y	Y	None
Chen *et al.*, 1996	Taiwan	RCT	Single-blinded	NS	76	C 7-15	PB: 15-40 μg/mL VPA: 50-100 μg/mL CBZ: 5-12 μg/mL	Cognitive tests	NS	73/76	ANOVA	N	Y	N	4
Pal *et al.*, 1998	Bengal, India	RCT	Unblinded	1	94	C 2-18	PB: 1.5-3.0 mg/kg/d PHT: 2.5-5.0 mg/kg/d	Self report; Behaviour questionnaire	1	62/94	NS	Y	Y	Y	5
Banu *et al.*, 2007	Bangladesh	RCT	Double-blinded	1	108	C 2-15	PB: 3-4 mg/kg/d CBZ: 16-20 mg/kg/d	Behavioural tests	1	17/108	Independent sample t tests; Mann-Whitney Paired sample t tests	Y	N	Y	6

RCT: randomised controlled trial; CBZ: carbamazepine; PHT: phenytoin; VPA: valproic acid; Y: yes; N: no; U: unclear; NS: not stated; CNS: central nervous system; A: adult; C: children.

[1] National Institute of Neurological Communication Disorders and Stroke.
[2] Ciba-Geigy Corporation; CIA grant from the NIH/NIA.
[3] International Clinical Epidemiology Network; Boots Pharmaceuticals; Reckitt and Colman of India; Rhone-Poulenc India.
[4] National Science Council of the Republic of China.
[5] Wellcome Trust Research Training Fellowship; International League Against Epilepsy.
[6] Department for International Development (DFID) administered through the British Council.

Appendix 2. Outcome of quality assessment of included experimental studies.

Study ID	Country	Study		No of centres	Population setting A: clinical/hospital-based B: community-based	Sample size	Daily dose /Serum level	How MCMs were recorded	Time of assessment	Funding
		Type	Blinding							
van der Pol *et al.*, 1991	Netherlands	Prospective cohort study	Single-blinded	1	A	25	NS	NS	6-13 years	1
Lindhout *et al.*, 1992	Netherlands	Prospective cohort study	NS	2	A	159	CBZ: 4.0-6.4 μg/mL VPA: 38-63 μg/mL PB: 13.8-17.8 μg/mL PHT: 3.3-6.1 μg/mL	NS	NS	2
Tanganelli and Regesta, 1992	Italy	Prospective cohort study	NS	1	A	78	NS	NS	NS	None
Waters *et al.*, 1994	USA	Prospective cohort study	NS	1	A	82	NS	Examination by a physician and /or nurse	At delivery	3
Samrén *et al.*, 1997	Netherlands	Prospective cohort study	NS	5	A and B	653	NS	Examination by paediatric neurologist, paediatrician or gynaecologist	At delivery; 0.25-5.5 years	4

Appendix 2. (*Continued*)

Study ID	Country	Study		No of centres	Population setting A: clinical/hospital-based B: community-based	Sample size	Daily dose /Serum level	How MCMs were recorded	Time of assessment	Funding
		Type	Blinding							
Canger *et al.*, 1999	Italy	Prospective cohort study	NS	1	A	271	NS	Examination by a paediatrician	At delivery; Day 5	None
Kaneko *et al.*, 1999	Japan, Italy, Canada	Prospective cohort study	NS	6	A	450	PB: 50 mg/d VPA: 100 mg/d CBZ: 100 mg/d PHT: 50 mg/d	[a]	At delivery; First 5 days 1 month	5
Holmes *et al.*, 2001	USA	Prospective cohort study	Single-blinded	5	A	209	NS	Examination by a study physician	First 5 days	None
Burja *et al.*, 2006	Slovenia	Prospective cohort study	NS	1	A	22	NS	Examination by midwives, neonatal nurses, doctors	5 years	None

NS: not stated.
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[3] Educational grant from Ciba-Geigy.
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[5] A grant for Scientific Research from the Japanese Ministry of Education; A grant from the Japan Epilepsy Research Foundation.
[a] A standardised checklist based on the report of the Japanese Association of Obstetricians for Maternal Welfare, performed by a team of obstetricians and neurologists.