

WHAT IS ALREADY KNOWN ON THIS TOPIC

Accumulating 30 minutes of moderate intensity physical activity on most days of the week substantially reduces the risk of many chronic diseases

Walking is a popular, familiar, convenient, and free form of exercise by which many sedentary people could gain the health benefits of moderate intensity physical activity

Walking may be influenced by environmental and societal conditions as well as by interventions targeted at individuals

WHAT THIS STUDY ADDS

Interventions tailored to people's needs, targeted at the most sedentary or at those most motivated to change, and delivered either at the level of the individual or household or through groups can increase walking by up to 30-60 minutes a week on average, at least in the short term

Unanswered questions and future research

Few studies in this review found unequivocal improvements in health, risk factors for disease, or even overall levels of physical activity attributable to an increase in walking. Most studies did not look for (or were inadequately powered to detect) such benefits or possible adverse effects. Future intervention studies should therefore include the capacity to investigate whether increases in walking are sufficiently frequent, intense, or sustained to produce measurable improvements in anthropometric, physiological, biochemical, or clinical outcomes, or alternatively whether increases in walking might be counterbalanced or outweighed by decreases in other forms of physical activity or an increase in injuries.

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Competing interests: NC sells pedometers in his capacity as a health promotion consultant. NM is an author of three of the primary studies included in the systematic review but played no part in the appraisal of those studies for the review.

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Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial

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ABSTRACT

Objective To compare the behavioural side effects associated with two commonly used antiepilepsy drugs—phenobarbital and carbamazepine—in children in Bangladesh.

Design Prospective randomised controlled single centre trial.

Setting Specialist children's hospital in Dhaka, Bangladesh.

Participants 108 children aged 2-15 with generalised tonic-clonic (n=51) or partial and secondarily generalised seizures (n=57).

Main outcome measures Seizure control and behavioural side effects.

Results 91 children were followed up for 12 months.

Six required a change of antiepilepsy drug. Side effects were compared in 85 children. In the last quarter of the 12 month follow-up 71 children were seizure free after one year's treatment. Thirty two in the phenobarbital group and 39 in the carbamazepine group had no seizures for 74 and 102 days after randomisation, respectively. Ten children had increased behavioural problems, which were unacceptable in four (one in the phenobarbital group and three in the carbamazepine group). Independent *t* tests, however, showed no difference between the two trial drugs.

Conclusion There was no excess in behavioural side effects with phenobarbital in children with epilepsy in a country with limited resources.

Trial registration NCT00381537.

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INTRODUCTION

The World Health Organization recommends phenobarbital as the first drug of choice for most seizures and epilepsies in developing countries, mainly because of cost, and carbamazepine for all seizures except typical absences.¹² Nevertheless a treatment gap of 90% is usual. Several studies have shown that 30-50% of children treated with phenobarbital experience behavioural side effects,³⁻⁶ and one study showed a persistent reduction in IQ.⁷ Others have found no such effect.⁸⁻¹⁰ There is a need for robust evidence about the use of phenobarbital,^{11,12} particularly in areas with limited resources.

We compared the behavioural side effect of phenobarbital and carbamazepine in the national children's hospital, Bangladesh.

METHODS

We carried out a double blind randomised controlled trial at a children's hospital.¹³ Children were recruited from April to October 2001 and followed up for 12 months.

Table 1 Characteristics of children with epilepsy and their families according to allocation to antiepilepsy drug (54 children in each group). Figures are numbers of children unless stated otherwise

	Phenobarbital	Carbamazepine	Total
Classification of seizures:			
Generalised	29	22	51
Partial	25	32	57
Aetiological classification:			
Without other impairments	40	31	71
Symptomatic*	14	23	37
Duration of seizures before start of regular drug treatment (years):			
1	27	23	50
>1-2	16	13	29
>2-3	5	8	13
>3-5	2	4	6
>5	4	6	10
Median (IQR) (months)	13 (3-27)	16 (4.5-30)	15 (3-30.24)
No of seizures in previous year:			
<10	18	21	39
10-20	15	15	30
>20	21	18	39
Previous treatment with antiepilepsy drug:			
No	42	40	82
Yes	12	14	26
Motor impairment:			
Absent	45	45	90
Present	9	9	18
Cognitive impairment:			
Absent	37	37	74
Present	17	17	34
Pre-existing behavioural problems:			
Absent	43	43	86
Present	11	11	22
Baseline mean behavioural scores (95% CI):			
BSID	100.00 (72.99 to 127.11)	109.33 (84.20 to 134.46)	—
Richman	31.17 (20.00 to 31.44)	31.58 (21.64 to 40.52)	—
CPRS-R:S	61.33 (55.05 to 73.10)	57.39 (51.57 to 63.21)	—

IQR=interquartile range; BSID=Bayley scale of infant development; CPRS-R:S=Conners' rating scales-revised. * Includes cryptogenic.

We hypothesised a 25% excess of behavioural side effects with phenobarbital compared with carbamazepine. With a predicted rate of 15% in carbamazepine and a 25% difference between the two groups, for 80% power at 5% significance (two tailed) we calculated that we would need 46 children in each group. Allowing for a 20% drop out rate, we planned to enrol 54 children into each group.

Children were aged 2-15 years with two or more generalised tonic-clonic, partial or secondary generalised seizures during the previous year. Exclusions were absence, myoclonic or severe malignant epilepsy, major motor and cognitive impairments, or current treatment with antiepilepsy drugs.

We obtained a history, and all children underwent electroencephalography. Psychological assessments used were the Bayley scale of infant development (BSID),¹⁴ the independent behaviour assessment scale (IBAS),¹⁵ and Wechsler intelligence scales for children-revised (WISC-R).^{16,17} Cognitive level was designated "normal" or "impaired," with a cut-off IQ of 70.

We assessed behaviour using age appropriate behavioural screening questionnaires; the Bayley scale¹⁴ for those aged 2 years, the Richman behavioural assessment questionnaire for those aged 2 years 1 month-4 years 11 months,¹⁸ and Conners' rating scale (revised) for children aged 5-15.¹⁹ We reassessed behaviour after 12 months of treatment or at drug withdrawal using the same assessment scale. The Conners' short questionnaire for parents (CPRS-R:S) was translated from English into Bangla, and tested for reliability and concurrent validity measure (see bmj.com).

Participants were randomly assigned to treatment with phenobarbital or carbamazepine. The treating physician was aware of the allocation but the psychologist, therapist, and researcher were blind. The researcher was unblinded at data analysis.

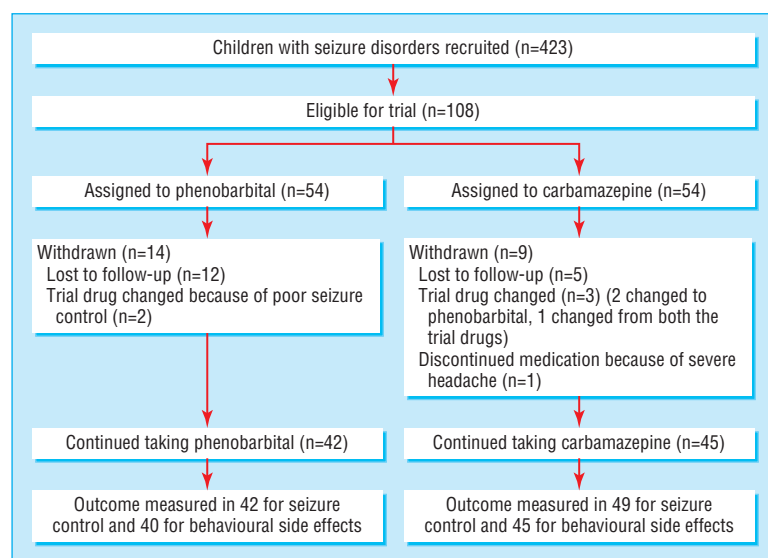
We reviewed patients at two weeks, one month, three months, and six months interval after randomisation, depending on therapeutic response and travel. Compliance was measured by verbal reply, counting tablets, and blood concentrations of antiepilepsy drugs taken on a single occasion without notice.

Outcome measures

Our main outcome measure was behavioural side effects after one year's treatment, assessed by comparing the results of the two behavioural assessments. Seizure outcome was measured as "seizure remission," defined as no seizures during the last quarter of 12 month follow-up. Drug efficacy was assessed by date of treatment allocation, time to first seizure after randomisation, time to withdrawal from treatment because of adverse effects, and date of last follow-up.

Analysis

We carried out intention to treat analysis for seizure outcome. We measured differences in behavioural side effects and compared the difference between behavioural assessment scores before and after treatment within and between the trial groups. We compared drug efficacy using time to first seizure after



Flow of children through the trial

randomisation as the primary data. Actuarial techniques were applied to the intervals from randomisation to first seizure, date of last follow-up when no seizures were recorded, or time to drug withdrawal. We used multiple logistic regression analysis to assess

Table 2 Outcome at one year in children with epilepsy according to allocation to antiepilepsy drug. Figures are numbers of children

	Phenobarbital	Carbamazepine	Total
Compliance with visits:			
Regular	29	35	64
Positive recalled*	13	14	27
Negative recalled†	12	5	17
Drug compliance:			
Continued assigned drug	40	45	85
Changed drug	2	4	6
Behavioural outcome:			
No change	28	31	59
Improved	8	8	16
Deteriorated	4	6	10
Behavioural problems:			
Mild	3	3	6
Unacceptable	1	3	4
No with behavioural problems/total in group:			
Female	3/9	4/28	7/37
Male	1/31	2/17	3/48
Age at first presentation (years)*:			
2	1/6	0/4	1/10
>2-5	0/18	5/19	5/37
>5	3/16	1/22	4/38
Seizures at 1 year (in all children):			
None in the 3 months before end of follow-up	32	39	71
None in the 6 months before end of follow-up	19	27	46
None since started treatment	3	4	7

*Missed several follow-ups but could be traced.

†Missed several follow-ups and could not be traced.

significant relations between behavioural side effects and individual variables such as age, sex, minor motor impairment, cognitive impairment, and pre-existing behavioural problems.

RESULTS

The figure shows the flow of children through the trial. See bmj.com for characteristics of children at randomisation; most came from poor and middle income families in rural areas. Travel was by walking or boat, and clinic visits often involved great effort and sometimes hardship. More girls were allocated to carbamazepine, and mean and median age at randomisation and at onset of seizures was higher in the carbamazepine group. Table 1 shows the baseline details about epilepsy and behaviour.

Behavioural side effects and seizure outcome

In 59 children there was no change in behaviour, and in 16 behaviour improved at one year (table 2). There was a significant improvement in behaviour after regular treatment with antiepilepsy drugs in both groups of 2-5 year olds (table 3). There were no significant differences between the mean, median, and range of behavioural outcome scores or between the two groups by independent *t* test (see bmj.com). Logistic regression analysis showed no association between the outcome behaviour and age, sex, motor disability, cognitive developmental delay, antiepilepsy drugs, or pre-existing behavioural problems.

One child in the carbamazepine group withdrew after four months because of severe headaches and aggressive outbursts. Another child in the carbamazepine group experienced occasional severe headaches. At the initiation of treatment three in the phenobarbital group and one in the carbamazepine group experienced disturbed sleep. In the phenobarbital group one child reported irritability and four had gastrointestinal disturbances.

Seizures became worse (increased and evolving to myoclonic seizures) in three in the carbamazepine group (two were shifted to phenobarbital and one to a third antiepilepsy drug as there was no improvement of seizure control after the shift to the other trial drug). Two in the phenobarbital group had poor seizure control with full dose and then shifted to the carbamazepine with good results. Three children taking phenobarbital and four taking carbamazepine discontinued the drug for more than seven days for various reasons—for example, returning home, running out of drugs, and starting homoeopathic treatment. Of these, four children had convulsive status epilepticus while not taking the drug (two in each group).

Actuarial analysis estimated the mean time without seizures was 102 days for phenobarbital and 74 days for carbamazepine. The cumulative seizure curves for children in both groups showed no difference in efficacy.

DISCUSSION

We found no significant difference in behavioural side effects with phenobarbital and carbamazepine using

Table 3 Mean differences (95% confidence interval)* in the behavioural test scores before and after treatment within the trial group

	Phenobarbital	Carbamazepine
BSID (2 years†)	-2.83 (-7.16 to 1.49), P=0.153 (n=6)	2.67 (-6.26 to 8.76), P=0.633 (n=4)
Richman (>2-5 years†)	5.44 (1.09 to 9.80), P=0.017 (n=18)	5.00 (0.65 to 7.15), P=0.021 (n=19)
CPRS-R:S (>5-15 years†)	4.40 (-4.36 to 13.16), P=0.348 (n=16)	4.30 (-6.4 to 5.92), P=0.109 (n=22)

BSID=Bayley scale of infant development; CPRS-R:S=Conners' rating scales-revised.

*Paired *t* test for behavioural score before and after treatment within trial group.

†Age group on presentation.

objective masked assessments and parental reporting in children with epilepsy without severe additional impairment. Ten children showed deterioration of behavioural state, of whom four received phenobarbital and six carbamazepine. Intolerable behavioural problems were more common with carbamazepine, and sleep disturbance and gastrointestinal problems were more common with phenobarbital. Headache and worsening of seizures were more common with carbamazepine, but the differences between the groups with respect to side effects were not significant. Behaviour improved in 16 children (eight in each group).

Comparison with other studies

Our population characteristics are similar to those in studies from two other resource poor countries, Kenya and India, where, like our study, no severe behavioural side effects with phenobarbital were found.^{8,9} Also a trial in the United States in children with partial seizures found no difference in behavioural or cognitive effects between the two drugs.¹⁰ Another North American trial of phenobarbital versus valproate found only marginal difference in hyperactivity between the two drugs.⁴

The phenobarbital arm of a study in the United Kingdom was stopped when six of the first 10 children were reported to have unacceptable behavioural side effects.³ The study, however, did not use a standardised behavioural assessment tool. This suggests that behavioural side effects are reported less often in countries with limited resources than in more affluent countries.

Age at randomisation, characteristics of seizures, and associated prognostic features differed in our study population compared with study populations in developed countries. Proportions of seizure types, however, were comparable with those in the UK and Indian studies. The treatment was effective, despite the high rate of seizures at entry and length of history; 78% had total remission and 11% more had 80% remission after one year. Rate of seizure remission in other studies varied from 67% to 73%.^{8,20,21}

WHAT IS ALREADY KNOWN ON THIS TOPIC

Phenobarbital is a highly effective antiepilepsy drug recommended by WHO for use in countries with limited resources

Several studies in developed countries have shown a high rate of behavioural side effects with phenobarbital

WHAT THIS STUDY ADDS

Phenobarbital was not associated with a high rate of behavioural side effects in children in Bangladesh

Conclusions

From this study in Bangladesh, phenobarbital is not associated with excess behavioural side effects when compared with carbamazepine and is therefore an effective and suitable drug to use for children with epilepsy in this setting.

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