

# Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial



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## Summary

**Background** The relative risks and benefits of starting or withholding antiepileptic drug treatment in patients with few or infrequent seizures are unclear. We sought to compare policies of immediate versus deferred treatment in such patients and to assess the effects of these policies on short-term recurrence and long-term outcomes.

**Methods** We undertook an unmasked, multicentre, randomised study of immediate and deferred antiepileptic drug treatment in 1847 patients with single seizures and early epilepsy. Outcomes comprised time to first, second, and fifth seizures; time to 2-year remission; no seizures between years 1 and 3 and between years 3 and 5 after randomisation; and quality of life. Analysis was by intention to treat.

**Findings** 404 patients invited to join the trial did not consent to randomisation; 722 were subsequently assigned immediate treatment with antiepileptic drugs and 721 were assigned deferred treatment. Immediate treatment increased time to first seizure (hazard ratio 1.4 [95% CI 1.2 to 1.7]), second seizure (1.3 [1.1 to 1.6]), and first tonic-clonic seizure (1.5 [1.2 to 1.8]). It also reduced the time to achieve 2-year remission of seizures ( $p=0.023$ ). At 5-years follow-up, 76% of patients in the immediate treatment group and 77% of those in the deferred treatment group were seizure free between 3 and 5 years after randomisation (difference  $-0.2\%$  [95% CI  $-5.8\%$  to  $5.5\%$ ]). The two policies did not differ with respect to quality of life outcomes or serious complications.

**Interpretation** Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years, but does not affect long-term remission in individuals with single or infrequent seizures.

## Introduction

When to begin treatment with antiepileptic drugs in patients with few or infrequent seizures is a difficult decision. For every individual, a risk–benefit assessment is necessary in which the benefits of treatment, in terms of short-term seizure recurrence and long-term outcomes of epilepsy, are weighed against adverse effects and costs of treatment. Seizure recurrence after a first, typically tonic-clonic, seizure has been investigated in observational studies; reported recurrence rates over 2 or 3 years have varied between 23% and 71%.<sup>1</sup> In a systematic review, Berg and Shinnar<sup>1</sup> noted that, on average, 50% of people do not experience a recurrence after a first seizure and that previous brain disease or insults and an abnormal electroencephalogram can affect recurrence rates. The risk of future seizures increases with the number of previous seizures; consequently, uncertainty about the need to start treatment diminishes with increasing numbers of seizures.<sup>2</sup>

Much more difficult to quantify is the effect of early antiepileptic drug treatment on the natural history of epilepsy. Most patients enter remission shortly after diagnosis and start of treatment with antiepileptic drugs; however, 20–30% never achieve long-term remission.<sup>3</sup> Some researchers have suggested that epilepsy could be a self-facilitating process in which seizures beget seizures.<sup>4</sup> Work done in animals lends support to this hypothesis,<sup>5</sup> but few studies have been done in man.<sup>6</sup> A

few randomised controlled trials have been undertaken to compare a policy of immediate versus deferred treatment with antiepileptic drugs after a single tonic-clonic seizure.<sup>7–12</sup> Most trials have assessed short-term outcomes, with the exception of a study that looked at achievement of 2-year remission of seizures.<sup>13</sup> These reports that assessed short-term outcomes provide only an imprecise estimate of the effect of treatment on risk of further seizures after a first seizure and minimum evidence of any effect on time to 2-year remission.

We undertook a pragmatic, multicentre, unmasked randomised controlled trial to compare policies of immediate versus deferred treatment with antiepileptic drugs in patients who, along with their clinicians, were uncertain about starting treatment. We assessed the effects of these policies on short-term recurrence and long-term outcome, including quality of life.

## Methods

### Patients

Patients were eligible for inclusion if they were aged at least 1 month, had an adequately documented history of one or more clinically definite, spontaneous, unprovoked epileptic seizures (excluding febrile convulsions or acute symptomatic seizures), and if both the clinician and the patient were in equipoise—ie, uncertain whether to proceed with treatment. Patients were excluded if they had already been treated with antiepileptic drugs (other

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than a short-acting drug to treat serial seizures or status, or previous prophylactic treatment for acute symptomatic seizures), or had progressive disease.

The study was approved by the northwest multicentre research ethics committee in the UK and by the ethics committees for participating non-UK centres.

### Procedures

After providing written informed consent, patients were allocated treatment by an independent randomisation centre. For every patient enrolled the recruiting physician contacted the randomisation centre by telephone or fax, provided basic identification and stratification details, and was informed to which policy the patient had been allocated. Treatment was assigned by the minimisation method to balance across two factors: centre or region, and number of seizures at randomisation (single seizures versus two or more seizures).

For patients randomly assigned immediate treatment, the clinician selected the optimum antiepileptic drug for the individual patient and started treatment as soon as possible. Patients randomly assigned to the deferred treatment group received no drugs until the clinician and patient agreed that treatment was necessary. Choice of antiepileptic drug, dose, and duration of treatment was dependent on the clinician's usual practice.

Demographic and baseline clinical information were obtained for all patients randomised and for those who were eligible but who did not give consent for randomisation. An electroencephalogram was requested for all randomised patients and CT or MRI was undertaken if clinically indicated. Follow-up occurred at 3 months, 6 months, 1 year, and successively at yearly intervals from randomisation, and at other times if clinically indicated. At every visit, data were obtained for

occurrence of and type of seizure and antiepileptic drug treatment and side-effects; date and cause of any death were also obtained from individual centres.

Primary seizure outcomes were: time from randomisation to first seizure of any type; time from randomisation to first tonic-clonic seizure; time from randomisation to second and fifth seizures of any type; time from randomisation to 2-year remission of seizures; and the proportion of patients who were seizure free for 2 years between 1 and 3 years after randomisation and between 3 and 5 years after randomisation. Secondary clinical outcomes consisted of adverse events in each group. Patients who did not have a significant learning disability received a quality of life (QOL) questionnaire; for resource reasons this was confined to UK patients. Questionnaires were mailed to all eligible adults (>16 years) and to parents of eligible children (5–15 years) as early as possible after randomisation, and subsequently at 2 and 4 years after the initial mailing. For adults, the QOL measures assessed three broad domains—physical, psychological, and social—by various validated measures of these aspects of function.<sup>14–19</sup>

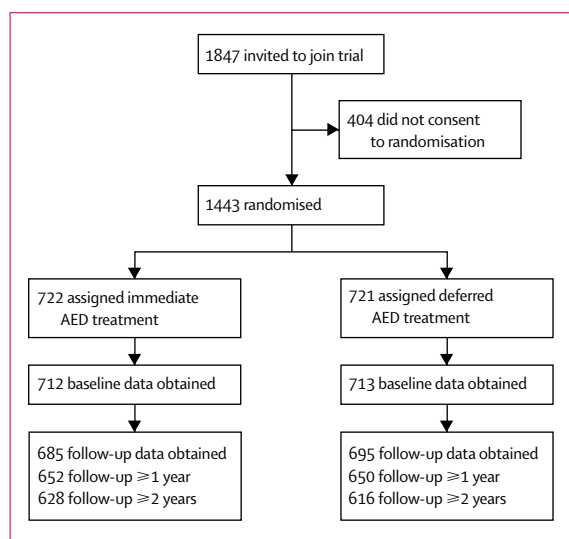
### Statistical analysis

We fixed the overall type I error at 5% (two-sided), and to allow for multiple primary endpoints with a Bonferroni correction we set a test-specific error of 1%; the type II error was fixed at 10%. We opted for a target of 1500 patients, and in total we recruited 1443. Our initial intention was to recruit 3000 patients to enable model testing and validation with a split-half approach. Unfortunately, recruitment was slower than expected, and although we recruited sufficient patients for the primary analyses, the power for generation and validation of the predictive models was diminished. The trial was powered to detect an increase from 50% to 60% or higher in the proportion of patients seizure-free at 2 years, and a reduction from 20% to 10% or lower in the proportion of patients who never attain a 2-year remission of seizures.

To analyse the time to each outcome event, we used the log-rank test or Cox's proportional hazards model when adjusting for number of seizures at entry—ie, single versus multiple. Results are reported as absolute differences in proportions or hazard ratios with 95% CIs. For binary outcomes, such as proportion of patients treated with antiepileptic drugs or those reporting adverse effects, differences between groups are reported with 95% CIs estimated by Newcombe's method.<sup>20</sup> All analyses were by intention to treat.

### Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.



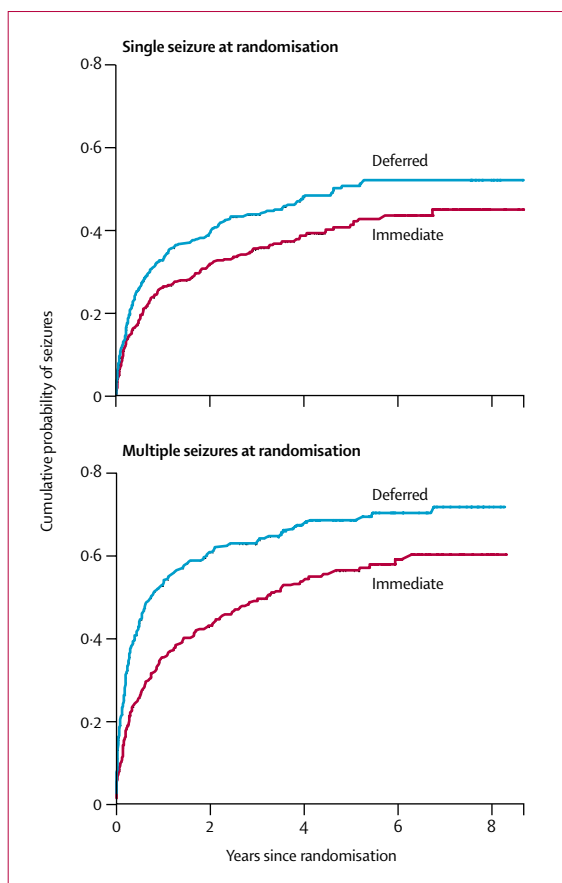
**Figure 1: Trial profile**

Three patients (one in the immediate treatment group and two in the deferred treatment group) had follow-up data but no baseline data.

	Immediate treatment (n=722)	Deferred treatment (n=721)	Not randomised (n=404)
<b>Sex</b>			
Male	403 (56%)	423 (58%)	225 (56%)
Female	319 (44%)	298 (41%)	179 (44%)
<b>Centre</b>			
UK	363 (50%)	354 (49%)	328 (81%)
Non-UK	359 (50%)	367 (51%)	76 (19%)
<b>Age, years</b>			
<5	23 (3%)	29 (4%)	17 (4%)
5-9	47 (7%)	60 (8%)	19 (5%)
10-19	210 (29%)	178 (25%)	113 (28%)
20-29	175 (24%)	153 (21%)	110 (27%)
30-39	76 (11%)	96 (13%)	73 (18%)
40-49	73 (10%)	76 (11%)	31 (8%)
50-59	49 (7%)	56 (8%)	16 (4%)
60-69	40 (6%)	32 (4%)	17 (4%)
≥70	29 (4%)	41 (6%)	7 (2%)
Median (IQR)	23 (17-42)	26 (16-46)	23 (16-34)
<b>Clinical and family history</b>			
Developmental delay/learning disability (NK: 20, 24, 5)	34 (5%)	23 (3%)	9 (2%)
Neurological deficit (NK: 23, 17, 11)	52 (7%)	40 (6%)	12 (3%)
Previous neurological insult (NK: 10, 9, 0)	99 (14%)	90 (12%)	48 (12%)
Previous febrile seizures (NK: 10, 8, 1, 0)	53 (7%)	52 (7%)	31 (8%)
Previous acute symptomatic seizures (NK: 10, 9, 2)	14 (2%)	19 (3%)	11 (3%)
First-degree family history of seizures (NK: 9, 8, 2)	76 (11%)	86 (12%)	41 (10%)
<b>EEG abnormalities (NK: 59, 53, 0)</b>			
Non-specific abnormality only	83 (11%)	88 (12%)	-
Generalised	131 (18%)	105 (15%)	-
Focal	184 (25%)	200 (28%)	-
Imaging abnormal (NK: 184, 172, 0)	71 (10%)	69 (10%)	-
<b>Seizure types before randomisation (NK: 10, 8, 0)</b>			
Simple partial	15 (2%)	20 (3%)	6 (1%)
Complex partial	36 (5%)	32 (4%)	25 (6%)
Secondary generalised TC	239 (33%)	215 (30%)	121 (30%)
Myoclonus only	6 (<1%)	5 (<1%)	1 (<1%)
Absence only	3 (<1%)	3 (<1%)	-
TC seizures	375 (52%)	406 (56%)	227 (56%)
Combinations of generalised seizures	21 (3%)	19 (3%)	11 (3%)
Other seizures	17 (2%)	13 (2%)	13 (3%)
<b>Timing of seizures (NK: 10, 9, 0)</b>			
During sleep only	140 (19%)	125 (17%)	67 (17%)
On awakening only	189 (26%)	204 (28%)	131 (32%)
<b>Number of seizures before randomisation (NK: 10, 8, 2)</b>			
1	404 (56%)	408 (57%)	239 (59%)
2	183 (25%)	165 (23%)	73 (18%)
3	50 (7%)	58 (8%)	34 (8%)
4	28 (4%)	18 (2%)	9 (2%)
5-9	30 (4%)	36 (5%)	20 (5%)
≥10	17 (2%)	28 (4%)	27 (7%)
<b>Time between first &amp; last seizures before randomisation (NK: 13, 10, 0)</b>			
Single seizure or <24 h	462 (64%)	455 (63%)	246 (61%)
1-30 days	40 (6%)	43 (6%)	20 (5%)
1-3 months	33 (5%)	31 (4%)	20 (5%)
4-12 months	66 (9%)	74 (10%)	42 (10%)
1-5 years	68 (9%)	70 (10%)	37 (9%)
>5 years	39 (5%)	38 (5%)	38 (9%)

NK=not known; EEG=electroencephalogram; TC=tonic-clonic.

**Table 1: Demographic and clinical features of randomised and non-randomised patients**



**Figure 2:** Cumulative proportion of patients with first seizure after randomisation, by treatment group and stratified by number of seizures reported at randomisation

## Results

Of 1847 individuals invited to join the trial between Jan 1, 1993, and Dec 31, 2000, 404 (22%) did not consent to randomisation, and 1443 patients were randomly assigned to a treatment group (figure 1). Final follow-up was attempted between Dec 31, 2001, and June 30, 2002. 717 (50%) patients were recruited in the UK and 726 (50%) from other countries (webappendix). 54 deaths were reported during follow-up, 31 in the immediate and 23 in the deferred treatment group; six were sudden unexplained deaths (four in the immediate group, two in the deferred group).

Table 1 shows demographic and clinical features of randomised and non-randomised individuals. 30% of patients were randomised within a week of their last seizure, 55% within a month, and 81% within 3 months. There were no important clinical differences between groups.

For those randomised to immediate treatment, carbamazepine was chosen for 328 (46%), valproate for 325 (46%), phenytoin for 25 (3%), and lamotrigine for 19 (3%) patients; no other drug was chosen for more than nine patients. For those treated with carbamazepine, the

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for webfigure 1 and webfigure 2

median initial daily target dose for participants younger than 16 years was 11.1 mg per kg bodyweight (IQR 9.1–16.7) and for participants aged 16 years and older it was 400 mg (300–600). For those treated with valproate, the median initial daily target dose for participants younger than 16 years was 18.5 mg/kg (15.3–22.2), and for participants 16 years and older it was 900 mg (500–1000). In the deferred treatment group, 332 patients started treatment during the course of the trial: 134 (40%) with carbamazepine, 142 (43%) with valproate, 20 (6%) with phenytoin, and 17 (5%) with lamotrigine; no other drug was chosen in more than three patients. During follow-up, the difference between the proportion of individuals receiving treatment with

antiepileptic drugs in the two groups becomes smaller with time. At 5 years after randomisation, 60% of those allocated immediate treatment were still receiving treatment, compared with 41% in the deferred treatment group who had started treatment (webfigure 1).

693 (48%) of those randomised had a seizure during follow-up; 43% (311/722) of the immediate treatment group, and 53% (382/721) of the deferred treatment group. For time to first seizure, the difference between the two treatment groups was highly significant (stratified logrank test,  $\chi^2=21.4$ ,  $p<0.0001$ ; hazard ratio stratified for single and multiple seizures before randomisation was 1.4 [95% CI 1.2–1.7]. Estimates for the proportion of patients with a seizure recurrence at a range of time points are shown in table 2. At the 2-year follow-up, 32% of patients with a single seizure had had a recurrence with immediate treatment versus 39% of those with deferred treatment. Kaplan-Meier plots for time to first seizure are shown in figure 2.

Results were closely similar for time to first tonic clonic seizure (552 events, stratified logrank test,  $\chi^2=21.0$ ,  $p<0.0001$ ; hazard ratio 1.5 [95% CI 1.2–1.8]). Time to second seizure also differed significantly between groups (482 events,  $\chi^2=9.2$ ,  $p=0.0025$ ; 1.3 [1.1–1.6]), but there was no difference with respect to time to fifth seizure (262 events,  $\chi^2=1.4$ ,  $p=0.23$ ; 1.2 [0.9–1.5]).

The actuarial estimate for achieving a 2-year remission by 8 years is very high, at over 95% (table 2, webfigure 2). There was a substantial difference between treatment policies at 2 years, with 64% in the immediate treatment group and 52% in the deferred group achieving immediate remission ( $\chi^2=18.7$ ,  $p<0.0001$ ; stratified logrank test,  $\chi^2=5.2$ ,  $p=0.023$ ). This difference diminished with time as the curves converge by 6 years for the single seizure group and by 8 years for the multiple seizure group. Estimates for the proportion of patients achieving a 2-year remission at a range of time points are given in table 2. At 2 years, for patients with a single seizure, 69% entered a 2-year remission with immediate treatment versus 61% with deferred treatment.

The final seizure outcome was the proportion of patients who were seizure free between 1 and 3 years and between 3 and 5 years after randomisation. 1302 (90%) and 1061 (74%) patients reached 1-year follow-up and 3-year follow-up, respectively. At 3 years, 74% of the immediate treatment group and 71% of the deferred treatment group were seizure free between 1 and 3 years after randomisation (difference between groups 3.4% [95% CI –1.6% to 8.5%]). At 5 years, 76% of the immediate treatment and 77% of the deferred treatment group were seizure free between 3 and 5 years after randomisation (–0.2% [–5.8% to 5.5%]).

Table 3 provides information on adverse events. Patients in the immediate treatment group were more likely to report at least one adverse event (difference 8.6% [95% CI 3.6%–13.6%]) than those in the deferred treatment group. Most events were those potentially associated with

	Immediate treatment (n=722)	Deferred treatment (n=721)	Difference (95% CI)
<b>Time to first seizure</b>			
6 months	22%	33%	12% (7.4 to 16.5)
Single seizure before randomisation	18%	26%	
Multiple seizure before randomisation	26%	44%	
2 years	37%	48%	11% (6.2 to 16.7)
Single seizure before randomisation	32%	39%	
Multiple seizure before randomisation	43%	61%	
5 years	48%	58%	10% (4.5 to 16.0)
Single seizure before randomisation	42%	51%	
Multiple seizure before randomisation	57%	69%	
8 years	52%	61%	9% (2.6 to 15.3)
Single seizure before randomisation	46%	52%	
Multiple seizure before randomisation	60%	72%	
<b>Time to first-tonic-clonic seizure</b>			
6 months	15%	25%	10% (6.0 to 14.4)
Single seizure before randomisation	15%	22%	
Multiple seizure before randomisation	15%	30%	
2 years	27%	38%	11% (6.3 to 16.8)
Single seizure before randomisation	26%	32%	
Multiple seizure before randomisation	28%	46%	
5 years	37%	48%	12% (5.9 to 17.3)
Single seizure before randomisation	35%	44%	
Multiple seizure before randomisation	39%	55%	
8 years	41%	50%	9% (2.8 to 15.5)
Single seizure before randomisation	38%	45%	
Multiple seizure before randomisation	45%	57%	
<b>Time to second seizure</b>			
6 month	14%	19%	5% (1.1 to 8.9)
2 years	24%	32%	8% (3.6 to 13.3)
5 years	34%	40%	6% (0.9 to 12.0)
8 years	38%	44%	5% (–1.4 to 12.0)
<b>Time to fifth seizure</b>			
6 month	6%	7%	1% (–1.3 to 3.8)
2 years	12%	15%	3% (–1.1 to 6.2)
5 years	19%	22%	3% (–1.6 to 7.6)
8 years	26%	25%	–1% (–9.3 to 7.8)
<b>2-year remission</b>			
2 years	64%	52%	12% (6.3 to 17.4)
Single seizure before randomisation	69%	61%	
Multiple seizure before randomisation	57%	39%	
5 years	92%	90%	2% (–1.2 to 6.1)
Single seizure before randomisation	92%	92%	
Multiple seizure before randomisation	91%	87%	
8 years	95%	96%	1% (–2.5 to 3.9)
Single seizure before randomisation	95%	96%	
Multiple seizure before randomisation	94%	95%	

**Table 2: Actuarial cumulative percentages achieving each outcome at selected intervals from randomisation with differences (95% CI)**

antiepileptic drug treatment. Events such as injury and scalds that would most commonly be associated with seizure recurrence occurred in 50 individuals, but more frequently in the immediate than in the deferred treatment group. 11 patients had 14 episodes of status epilepticus, five of whom had a single seizure and six of whom had multiple seizures before randomisation. Nine patients in the immediate treatment group had 12 episodes, of which nine were while taking antiepileptic drugs, two while not taking treatment, and one where treatment was uncertain. In the deferred treatment group, two patients had one episode each, one while taking treatment the other while not taking treatment. The details of the adverse events reported at all follow-up sessions are summarised in the webtable.

Of the 584 UK adult patients, 527 were eligible to receive a QOL questionnaire, of whom 441 returned one at baseline (218 in the immediate treatment group and 223 in the deferred treatment group; a response of 84%). At 2-years' follow-up, the response was 77% (162 immediate, 169 deferred; 63% of all those originally eligible). Here, we report an analysis including the 132 immediate and 139 deferred treatment patients (51% of those originally eligible) who returned their baseline questionnaire within 100 days of randomisation. In this analysis we examine the change between baseline and 2-year follow-up for anxiety, depression, and mastery (an individual's perceived sense of control over their life) using analysis of covariance (ANCOVA), and including seizure frequency as a dependent variable. Anxiety, depression, and mastery are measured on a 0 to 21 point scale, with a score of zero representing no anxiety, no depression, and high mastery. Results are also presented for employment status. Immediate treatment accounted for a 0.00 change in the score for anxiety (95% CI -0.82 to 0.83), a 0.28 decrease in the change score for depression (-0.99 to 0.43), and a 0.18 decrease in the change score for mastery (-1.02 to 0.66).

	Immediate treatment (n=722)	Deferred treatment (n=721)	Total
No follow-up	37	26	63
None reported	415 (61%)	481 (69%)	896 (65%)
At least one reported	270 (39%)	214 (31%)	484 (35%)
Depression, anxiety	40	31	71
Dizziness, unsteadiness	37	32	69
Gastrointestinal symptoms	41	24	65
Tiredness, drowsiness	41	23	64
Headache	37	13	50
Injury, scalds	28	22	50
Rash, acne	31	14	45
Surgery	21	21	42
Chest pain, myocardial infarction	21	21	42
Impaired memory, concentration	19	15	34
Weight gain, increased appetite	14	19	33
Behaviour problem	20	12	32
Tremor	17	6	23

**Table 3: Patients reporting adverse events at any follow-up**

At baseline, 13 patients in the immediate treatment group and 12 patients in the deferred treatment group reported giving up work because of their attacks. By the 2-year follow-up, four of the 13 in the immediate treatment group and three of the 12 randomised to deferred treatment reported being back in paid work. Overall, at 2 years' follow-up, 61 of 131 (47%) in the group randomised to immediate treatment and 62 of 135 (46%) in the group randomised to deferred treatment reported being in paid work. Of those not in paid work or full-time education at 2 years, nine of 60 (15%) in the group randomised to immediate treatment and 13 of 60 (22%) in the deferred treatment group gave their seizures as the reason for giving up working ( $\chi^2=0.89$ ,  $p=0.35$ ).

At baseline, 66 of 104 patients (63%) randomised to immediate treatment and 82 of 123 patients (67%) randomised to deferred treatment expressed themselves as being happy with the treatment policy to which they were assigned. However, patients randomised to immediate treatment were more likely to express a preference for the alternative treatment policy than were those randomised to deferred treatment (23/104 [22%] vs 6/123 [5%]), and those randomised to deferred treatment were more likely than those treated immediately to express uncertainty about their treatment preference (35/123 [28%] vs 15/104 [14%];  $\chi^2=18.23$ ,  $p=0.0001$ ).

## Discussion

Immediate treatment increased time to first and second seizures and first tonic-clonic seizures and reduced the time to achieve 2-year remission of seizures. However, by 5 years there was little difference between seizure outcomes.

As with the MRC Study of Antiepileptic Drug Withdrawal,<sup>21</sup> we used a randomised, unmasked, pragmatic trial design to assess the effects of antiepileptic drug treatment on the most important long-term outcomes of epilepsy—remission or freedom from seizure—and on quality of life outcomes. We have sought to quantify precisely benefits in terms of seizure control, to improve the quality of information available to support clinicians and patients in making decisions about treatment options. We also aimed to identify the possible benefits of commonly used antiepileptic drugs in modification of the natural history of epilepsy. Does early suppression of seizures play a part in the prevention of chronic drug-refractory epilepsy?<sup>22</sup>

Although we were able to recruit just under half the patients in our original target (1443 [48%] of 3000), our study retained the 90% power built into its design. We did not use a placebo or mask treatments since use of a single presentation for all antiepileptic drugs was not possible and the costs for production of placebos would have been prohibitive. Furthermore, allocation of placebo after randomisation to the deferred treatment group would need identification of the antiepileptic drug likely to be prescribed after future seizure recurrence.

See [Lancet Online](#) for webtable



Use of placebos would also need restriction of trial treatments to two drugs at most, which would substantially reduce the capacity to recruit patients and generalisability would be diminished. Additionally, the outcomes could not be rated without knowledge of treatment assignment since they depended on patients' self-reports of seizure recurrence. Our results do not suggest that lack of masking introduced bias into the analyses since first seizure recurrence did not differ between groups when restricted to the more serious and more obvious tonic-clonic seizures.

Our results can be broadly compared with those from observational studies, and show that after a first seizure there is a 50% risk of further seizures by 5 years without treatment. For those with more than one seizure, there is a raised risk (about 70% by 5 years) without treatment.<sup>12</sup> The reduction in risk of seizure recurrence at 2 years associated with immediate treatment in our trial is comparable with that seen in previous trials.<sup>7,12</sup> Our results for the differences in proportions (table 2) suggest a need to treat 14 patients after their first seizure to prevent one additional patient having a seizure recurrence within 2 years. Patients with multiple seizures have a higher risk of seizure recurrence and receive greater benefit from immediate treatment (number needed to treat to prevent a seizure recurrence within 2 years is five).

Although immediate treatment was associated with a reduction in short-term seizure recurrence, there was no measurable effect on long-term outcomes. Immediate treatment increased the chance of 2-year remission at 2 years, but this effect was lost by 4 years after a first seizure and by 6 years after multiple seizures. This finding is in keeping with the Italian first-seizure study.<sup>13</sup> Finally, the proportion of patients in each group who were seizure free between 3 and 5 years after randomisation was almost identical (76% vs 77%) and the study was powered to exclude deferred treatment being any more than 6% less effective for this outcome. Indeed, immediate treatment resulted in 17% more patients receiving antiepileptic drugs 5 years into the study (webfigure 1) to achieve the same outcome as a policy of deferred treatment.

We have provided reliable evidence that early intervention with the standard antiepileptic drugs carbamazepine and valproate have no effect on the long-term prognosis of epilepsy, and in this clinical scenario do not interfere with the process of long-term epileptogenesis. In this respect our evidence accords with that from many small and diverse randomised controlled trials of antiepileptic drugs after cerebral insults that have recently been reviewed systematically by Tempkin.<sup>22</sup>

The short-term gains we identified in seizure control from immediate treatment are at some cost to patients. More patients in this group than in the deferred treatment group reported adverse events that were

probably treatment related, although these side-effects were rarely severe or life-threatening. Furthermore, there is little evidence that a policy of immediate treatment brings any short-term benefits in quality of life. The finding that a substantial proportion of patients randomised to immediate treatment would have preferred treatment to be deferred suggests that they themselves are aware of the potential for adverse drug effects. This finding could also indicate that antiepileptic drugs are stigmatising.<sup>23</sup>

In conclusion, we have shown that a policy of immediate treatment with antiepileptic drugs, mainly with carbamazepine or valproate, reduces the occurrence of seizures in the next 1–2 years, but does not modify rates of long-term remission after a first or after several seizures. At 2 years, the benefits of improved seizure control with immediate treatment seem to be balanced by the unwanted effects of drug treatment and there is no improvement in measures of quality of life. To provide estimates of the risk of seizure recurrence for individual patients, data from our study will be used to generate prognostic models that will further inform clinical decision-making.

#### Contributors

D Chadwick, A Jacoby, and A Johnson participated in the trial design, data analysis, and interpretation of results. D Chadwick and A Marson obtained the data. L Kim, A Marson, and C Gamble did data analyses and interpreted the results. All authors participated in the writing of the manuscript.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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