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Meta-analysis of European placebo controlled studies of vigabatrin in drug resistant epilepsy

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1 A meta-analysis has been performed on nine placebo controlled trials of vigabatrin (GVG) administered as add-on therapy to patients suffering from drug resistant epilepsy.
2 There were two pilot placebo-controlled dose ranging studies, six double-blind crossover studies and a multicentre response controlled study.
3 There were a total of 398 patients entered and 390 have been evaluated for safety and 337 for efficacy.
4 In spite of the difficulties in the clinical evaluation of new antiepileptic drugs, a reduction in seizure frequency was reported following the addition of vigabatrin to the concomitant medication in all studies. This was statistically significant in the larger of the two pilot studies, the multicentre study and three of the six double-blind studies.
5 There was a statistically significant reduction in seizures of in all six double-blind studies when the 98 patients suffering from complex partial seizures with or without generalisation were considered. Seventy two percent of these patients showed a greater than 25% reduction in seizure frequency.
6 Vigabatrin was well tolerated. The frequency of adverse events was similar to that reported elsewhere.

Keywords vigabatrin placebo-controlled studies efficacy safety

Introduction

The difficulties of the clinical evaluation of the efficacy of a new antiepileptic drug has been a subject for debate for many years. There are many reasons for the debate. Although epilepsy is a chronic condition, it varies with time. Secondly, the most commonly chosen end point for the evaluation of efficacy—seizure frequency —may vary considerably in the same patient during any given period of observation. The usual method of recording seizures, a seizure diary, is usually completed by the patient, whose memory may be disturbed by the condition. In fact many patients with partial seizures may have a total amnesia for the seizure. In addition, the seizure itself may vary in severity and type. There is the complication of 'pseudoseizures'. All these facts make it difficult to measure objectively the response to a new anti-epileptic drug and emphasise the importance of including some form of blinding, such as a placebo period (Feinstein, 1980; Dollery, 1979), into the design of the study. In spite of all these problems well controlled studies with placebo control remain the best method of evaluating new anti-epileptic compounds.

The usual initial group of patients chosen to evaluate a new antiepileptic drug are patients with 'drug resistant epilepsy'. Such patients range from children with Lennox-Gastaut or West Syndrome, to adults with severe intractable

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partial seizures (Juul-Jensen, 1986; Reynolds *et al.*, 1983). One difficulty is to ensure that the patient population is sufficiently large and sufficiently homogenous to test effectively the new drug (Porter & White, 1986).

The purpose of this review is to examine all the placebo controlled trials of vigabatrin (GVG) completed in Europe, and to determine the influence of study design on the outcome.

Methods

The studies considered are those including a placebo control in the evalution of vigabatrin as add-on therapy in the management of drug resistant epilepsy. They fall into three categories. Firstly, two single-blind sequential dose titration pilot studies used in the early evaluation of efficacy of vigabatrin. The next group of studies which has been considered as a single entity are six double-blind short term cross-over studies. Each of these has been published as an individual report elsewhere. Finally for consideration is a large scale multicentre single-blind study which included 'response mediated' dose titration.

1. Pilot studies

The first two studies were both multiple-period sequential studies. Both started with a pre-vigabatrin baseline: in one case this was a placebo period, followed by two or three dose periods with incremental dose rises of vigabatrin and both were followed by a placebo wash-out period (Table 1). Both pilot studies evaluated the optimally effective dose of vigabatrin. The observation period for each dose was 2 or 4 weeks.

2. Double-blind cross-over studies

On the basis of the information obtained from these early pilot studies a series of placebo-controlled cross-over studies was set up. This study design has the advantage that each patient acts as his own control, therefore overcoming much of the individual patient variation seen in epilepsy. Table 2 sets out the individual study details of these six double-blind studies, with the individual design characteristics and patient populations.

The objective of these studies was to provide a definitive evaluation of the efficacy and tolerability of vigabatrin as add-on therapy over a period of 7 to 12 weeks. In the majority of the studies the dose for all patients, irrespective of bodyweight, was 3 g of vigabatrin daily (1.5 g twice daily). In two of the studies, however, the dose was adjusted according to bodyweight. In one study (Tartara *et al.*, 1986) patients of under 65 kg were stratified to a dose of 2 g day^{-1} or less and in another (Tassinari *et al.*, 1987), the maximum weight for 2 g day^{-1} was 60 kg.

3. Single-blind multicentre study

The purpose of this study was the evaluation of dose-response relationship in the range 1–4 g day^{-1} and to assist in the identification of patients who could be considered as 'vigabatrin responders' for entry into the long term safety and efficacy studies.

The multicentre protocol commenced with a 3 month baseline in order to obtain a definitive pre-vigabatrin seizure frequency. All patients then received add-on vigabatrin in place of the placebo at a dose of 2 g day^{-1} (1 g twice daily) for 2 months. The dose was then adjusted according to both response and tolerance within the range of 1–4 g day^{-1} on a 2 monthly basis until the most appropriate dose for the particular patient was found, or the patient was withdrawn from the study. The study was carried out in 22 centres by 28 investigators. Two hundred and twenty patients entered the study, 218 could be evaluated for safety, and 181 for efficacy between baseline and 2 g day^{-1}.

Table 1 Single-blind placebo controlled studies. Vigabatrin as add-on therapy in resistant epilepsy. Investigator, centre, design and patient numbers

Principal investigator	*Centre*	*Duration design and vigabatrin dosages*	*Number of patients*
Dam (Gram *et al.*, 1983)	Copenhagen, Denmark	20 weeks Placebo, 1 g, 2 g, 3 g day^{-1} followed by placebo	15
Hanke (Schechter *et al.*, 1984)	Amsterdam, Holland	6 weeks 1 g, 2 g day^{-1} vigabatrin followed by placebo	10

Results

1. Patients

The patient characteristics in the different studies are set out in Table 3.

2. Evaluation of efficacy

Efficacy has been based on the reduction in seizure frequency. This was recorded by each patient in his seizure diary. The diary was reviewed by the investigator at each visit and the frequency of seizures transcribed into the case record. The median seizure frequency has been used for the comparison in the multicentre and longer pilot studies, and mean seizure frequency in the double-blind studies.

Comparison of efficacy between studies

In one of the two pilot studies (Schechter *et al.*, 1984) the comparative dosing periods were too short to allow the proper calculation of a seizure frequency. However, every patient in this study showed some improvement in his seizures during the active period when it was compared with baseline. This change was more significant during the second active period when the dose was 2 g day^{-1}. In the Danish single-blind study (Gram *et al.*, 1983) the reduction in median seizure frequency was of statistical significance for all three active periods when compared with baseline.

One of the disadvantages with the design of the cross-over study is that if there is any delay in onset in effect of a compound, or any carry-

Table 2 Double-blind studies—individual study centre and protocol details

Principal investigator	*Centre*	*Design and dosage of vigabatrin*	*Number patients evaluated for:* *entry*	*efficacy*	*safety*
Dam (Gram *et al.*, 1985)	Copenhagen, Denmark	12 weeks, 1.5 g twice daily	21	18	21
Loiseau (Loiseau *et al.*, 1986)	Bordeaux, France	9 weeks, 1.5 g twice daily	25	19	23
Perucca (Tartara *et al.*, 1986)	Pavia, Italy	7 weeks, 0.75–1.5g twice daily*	28	25	28
Remy (Remy *et al.*, 1986)	Tain L'Hermitage France	12 weeks, 1.5 g twice daily	23	17	19
Richens** (Rimmer & Richens, 1984)	Cardiff, U.K.	9 weeks, 1.5 g twice daily	25	22	25
Tassinari (Tassinari *et al.*, 1987)	Bologna, Italy	12 weeks, 1–1.5 g twice daily*	31	30	31
Total			153	131	147

(*vigabatrin dose stratified according to body weight)
(**Merrell Dow Research Institute data includes one additional patient to that published)

Table 3 Comparison of patient characteristics in European placebo-controlled studies

Number entered (evaluated)	*Pilot studies 25 (25)*	*Double-blind studies 153 (147)*	*Multicentre studies 220 (218)*
Age range (mean)	6–69 years (42.5)	10–63 years (32.1)	8–63 years (29.0)
Males (M) Females (F)	11M 14F	75M 72F	121M 97F
% with partial seizures	72%	73.5%	85%
Mean number of antiepileptic drugs	2.44/patient	2.13/patient	2.29/patient

over effect after a compound has been withdrawn, this may partially nullify the efficacy of the test compound. In an attempt to minimise this effect in one study (Gram *et al.*, 1985), the analysis of efficacy was performed on only the last 8 weeks of each study period of 12 weeks. This point was evaluated by comparing the percentage change in the frequency of seizures seen during the active and the placebo phases when the analysis was performed on the whole 12 week period and comparing this with the last 8 week period. As can be seen from Figure 1, the results differed only to a minor degree for the two periods with only one patient (17) being an exception. This would suggest that there is minimal delay in the onset of effect of vigabatrin and that its effect is shortlived after withdrawal.

In the multicentre studies 85% of the patients were suffering from epilepsy of partial origin and these patients showed a far better response to the addition of 2 g day^{-1} of vigabatrin to their antiepileptic medication than did the patients suffering from generalised types of epilepsy (Table 4).

Evaluation of efficacy by dose

In spite of the short comparative dosing periods in one of the pilot studies (Schechter *et al.*, 1984), a dose of 1 g day^{-1} given over 2 weeks had some effect in reducing seizure frequency and this was more marked during the 2 g dose period. In the other single blind study (Gram *et al.*, 1983) the reduction in the median seizure frequency was similar for both the 1 and 2 g day^{-1} dose periods, although at 2 g day^{-1} the reduction was of greater statistical significance. The median seizure frequency, in this study, showed a still further reduction when the dose was increased to 3 g day^{-1}. The range of seizure frequency in the individual patients did, however, show an increase from 0–22 seizures at 2 g day^{-1} to 0–44 seizures at 3 g day^{-1}, suggesting that not all patients were improved by increase of dose. Both these pilot studies indicate a dose-linked efficacy. However, an increase in dosage may not be reflected by a further reduction in seizure frequency. This was the starting point for the design of the multicentre study, where all patients initially were given 2 g day^{-1}

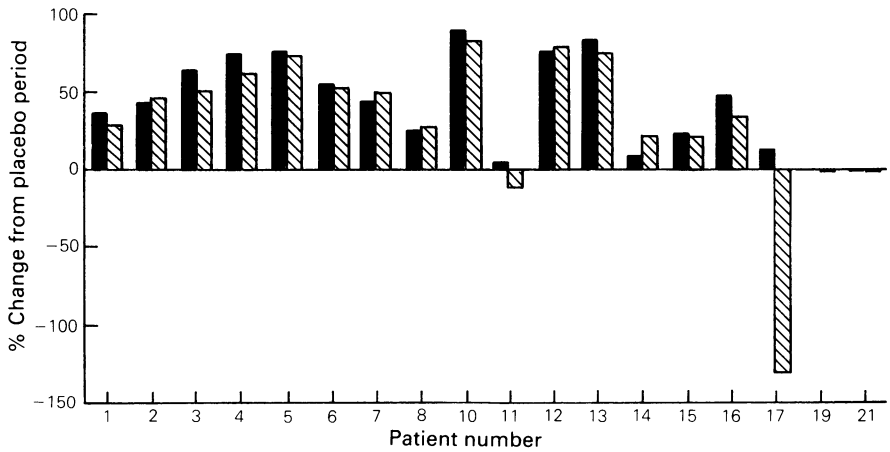

Figure 1 Danish double-blind cross-over study comparison between 8 (▨) and 12 (■) week seizure.

Table 4 Percentage decrease in median seizure frequency by main seizure type following 2 g day^{-1} vigabatrin. European single-blind multicentre study

Main seizure type	*Number of patients*	*Percentage of patients reporting reduction of:* 75 to 100	50 to 74	25 to 49	25 to −25	Worse
Partial	168	18.4	22.6	25.6	26.8	6.5
General	22	4.5	9.1	31.8	45.5	9.1
Unclassified	1	—	—	100.0	—	—

of vigabatrin and then later according to their response to the addition of this drug to anti-epileptic medication had the dose increased or decreased., This study showed that in only about 25% of patients who had their dose increased beyond 2 g day^{-1} had a still better seizure control. This point is illustrated in Figure 2 where the percentage change in seizure frequency from baseline is presented for eight typical vigabatrin responders from one of the participating centres.

This point can be further examined by a comparison of the results obtained in the double-blind cross-over and in the single blind multicentre study. Two of the six double-blind studies (Tartara *et al.*, 1986; Tassinari *et al.*, 1987) included a dose stratification by weight and those who received 2 g day^{-1} have shown a very similar efficacy to the overall population of the six studies (Figure 3). Since four of the six studies used 3 g for all patients irrespective of weight, it would be reasonable to expect a better response in the total group if there was a dose linked effect for all patients. Another comparison is the response seen at 2 g day^{-1} in the single-blind multicentre study. This almost exactly mimics that seen in the six double-blind studies. Of the 117 patients in the European multicentre studies who were given an increase in daily vigabatrin dose from 2 g to 3 g day^{-1}, only 31 (26.4%) patients showed an additional reduction of 25% or greater in their seizure frequency. These findings support the concept that there is an optimally effective dosage for an individual patient. It also suggests that a reasonable starting dose for adults would be 2 g day^{-1} and that this dose would then need to be titrated on an individual patient-by-patient basis.

Evaluation of tolerability

The pilot studies were too small in patient numbers, and one (Schechter *et al.*, 1984) covered too short a period to evaluate accurately the incidence of adverse events. The double cross-over studies, however, give an ideal opportunity to measure any increase in adverse events due to vigabatrin. The blind placebo control period in these studies can act as a measure of the 'background noise' of adverse events caused either by the other medications currently prescribed or by those given in the past to possibly near toxic levels in an attempt to control the resistant epilepsy. Another possible cause of adverse events may be the epilepsy itself.

Table 5 sets out a comparison of the incidence of adverse events reported during both the active and placebo periods of the double-blind studies. The difference between these incidences could be related to the addition of vigabatrin. This can be compared with the incidence of adverse events reported in the single-blind multicentre study that were, in the opinion of the investigator, probably or definitely attributable to vigabatrin. Although there are minor differences between these incidences the similarities are rather marked, in that the frequency of the individual events are of very similar magnitude.

Discussion

This review suggests that the efficacy of vigabatrin as an add-on therapy in drug resistant epilepsy is almost identical in all the European

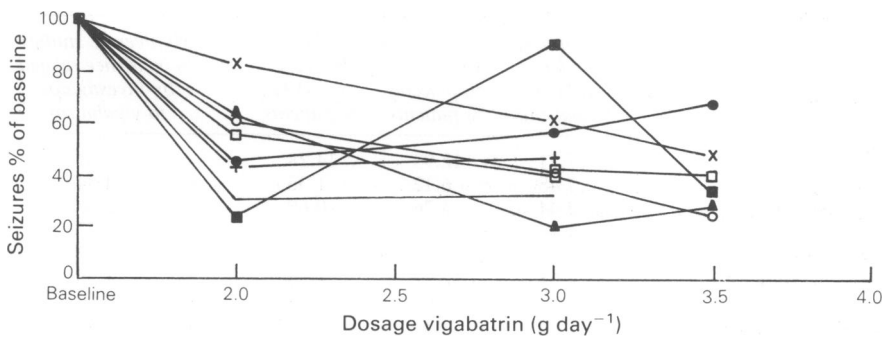

Figure 2 Multicentre study results from a single centre seizure reduction by vigabatrin dose. The results of eight typical responders to vigabatrin are shown.

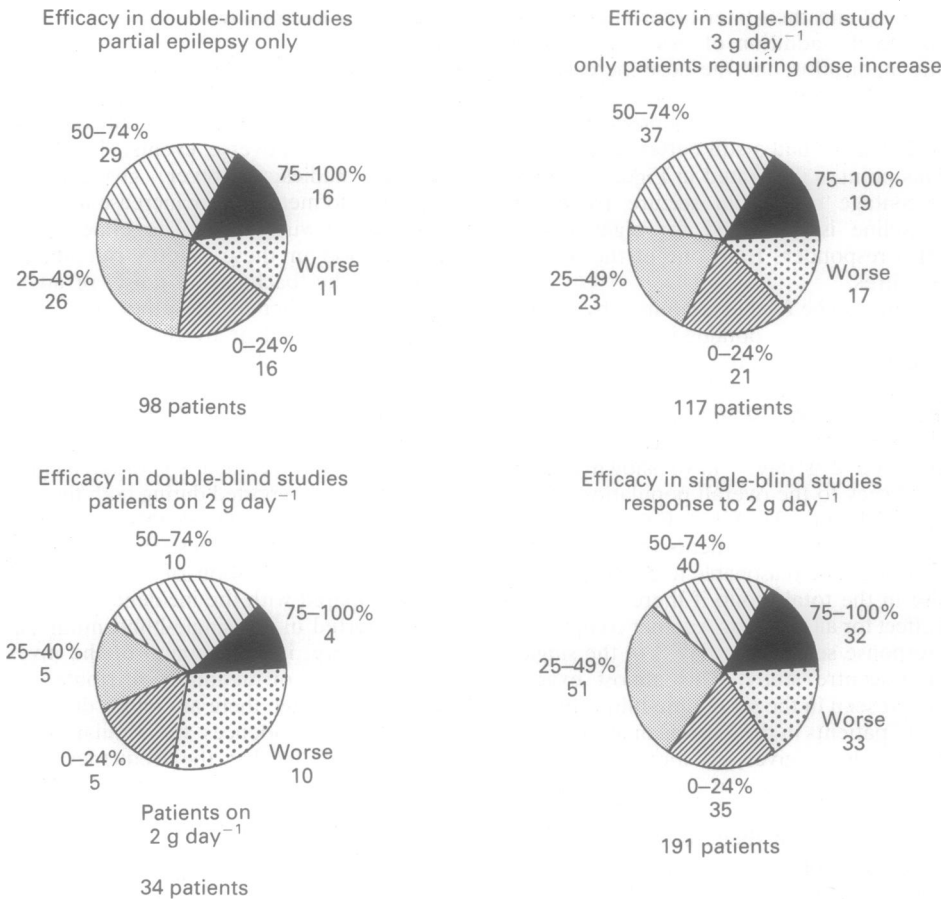

Figure 3 Comparison of response rate to vigabatrin as add-on therapy by daily dose and between single and double-blind studies.

Table 5 Comparison of frequency of reports of adverse events between the double-blind and the multicentre studies. Ten most frequently reported in double-blind studies

	Double-blind cross-over studies			*Multicentre studies*
Adverse event	*Incidence on GVG % patients*	*Incidence on placebo % patients*	*Increase on GVG % patients*	*% incidence related by investigator to vigabatrin*
1. Somnolence	27.21	12.93	14.28	21.81
2. Fatigue	7.48	6.12	1.36	4.54
3. Irritability	5.44	4.76	0.68	1.36
4. Dizziness	5.44	1.36	4.08	2.72
5. Headache	4.08	4.08	0	2.27
6. Depression	4.08	2.72	1.36	1.36
7. Confusion	3.40	0.68	2.72	0.90
8. Poor concentration	2.72	1.36	1.36	0.45
9. Abdominal pain	2.72	0.68	2.04	2.27
10. Anorexia	2.72	0.68	2.04	< 0.50

placebo controlled sudies. It is clear that vigabatrin is more effective in partial epilepsy than in seizures of generalised origin. It is also clear that vigabatrin is effective at doses of 2 g day^{-1}, although some patients may require higher doses before optimum control is reached.

The tolerability of vigabatrin in these short term studies was good. Although it is always difficult to evaluate the incidence of adverse events for any new antiepileptic drug when it is administered as an add-on therapy, due to the background noise the other drugs create, no new, unusual or disquieting adverse events were reported. Tolerability reported in these studies is in accord with that seen in the US single-blind placebo controlled study (Browne *et al.*, 1987).

It is also clear that the design of the study has very little effect on the outcome, provided that the difference between the active preparation and the control preparation is sufficiently marked.

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