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Tiagabine add-on for drug-resistant partial epilepsy

Jennifer Pulman¹, Anthony G Marson², and Jane L Hutton³

¹Department of Molecular and Clinical Pharmacology, Cochrane Epilepsy Group, Liverpool, UK

²Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

³Department of Statistics, University of Warwick, Coventry, UK

Abstract

Background—Epilepsy is a common neurological condition, affecting almost 0.5 to 1% of the population. Nearly 30% of people with epilepsy are resistant to currently available drugs. Tiagabine is one of the newer antiepileptic drugs and its effects as an adjunct (add-on) to standard drugs are assessed in this review.

Objectives—To evaluate the effects of add-on treatment with tiagabine upon seizures, adverse effects, cognition and quality of life for people with drug-resistant localisation related seizures.

Search methods—This is an updated version of the original Cochrane review published in issue 10, 2010. We searched the Cochrane Epilepsy Group's Specialised Register (December 2011), the Cochrane Central Register of Controlled Trials (CENTRAL, issue 4, 2011 of *The Cochrane Library*), and MEDLINE (1948 to November 2011). No language restrictions were imposed. We also contacted the manufacturers of tiagabine and experts in the field to seek any ongoing or unpublished studies.

Selection criteria—Randomised placebo controlled add-on trials of people of any age with localisation related seizures, in which an adequate method of concealment of randomisation was used were included. The studies could be double, single or unblinded and be of parallel or crossover design. They had to have a minimum treatment period of eight weeks. Trials using an active drug control group were also included.

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Contact address: Jennifer Pulman, Department of Molecular and Clinical Pharmacology, Cochrane Epilepsy Group, Lower Lane, Liverpool, Merseyside, L9 7LJ, UK. jennifer.pulman@liv.ac.uk.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW: Within the original protocol only trials using a placebo control group would be included within the review if meeting all other inclusion criteria. We have decided to extend this to include any other active add-on drug used as a control group to tiagabine for inclusion.

Data collection and analysis—Two review authors independently selected trials for inclusion and extracted data. Any disagreements were resolved by discussion. Outcomes investigated included 50% or greater reduction in seizure frequency; treatment withdrawal; adverse effects; effects on cognition and quality of life. The primary analyses were by intention-to-treat. Worst case and best case analyses were also calculated for seizure outcomes. Dose response was evaluated in regression models.

Main results—Four parallel group and two crossover group trials were included. The overall relative risk (RR) with 95% confidence intervals (CIs) for a 50% or greater reduction in seizure frequency (tiagabine versus placebo) was 3.16 (95% CI 1.97 to 5.07). Due to differences in response rates among trials, regression models were unable to provide reliable estimates of responses to individual doses. The RR for treatment withdrawal was 1.81 (95% CI 1.25 to 2.62). The 99% CIs for the following adverse effects: dizziness; fatigue; nervousness and tremor did not include unity, indicating that they are significantly associated with tiagabine. For cognitive and quality of life outcomes the limited data available suggested that there were no significant effects on cognition and mood and adjustment.

Authors' conclusions—Tiagabine reduces seizure frequency but is associated with some adverse effects when used as an add-on for people with drug-resistant localisation-related seizures.

Medical Subject Headings (MeSH)

*Drug Resistance; Anticonvulsants [adverse effects; *therapeutic use]; Cognition [drug effects]; Epilepsies, Partial [*drug therapy]; Fructose [analogs & derivatives; therapeutic use]; Nipicotic Acids [adverse effects; *therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans

BACKGROUND

Epilepsy is a common neurological condition, with an estimated incidence of 50 per 100,000 and a prevalence of 5 to 10 per 1000 in the developed world (Sander 1996). Between two to three cent of the population will be given a diagnosis of epilepsy some time in their lives (Hauser 1993), the majority of whom will go into remission. However, up to 30% will continue to seizures (i.e. become drug-resistant) despite treatment with quate doses of antiepileptic drugs (AEDs) (Cockerell 1995), are often treated with combinations of AEDs. There is no internationally accepted definition of drug-resistant, and for the purposes of this review people will be considered drug-resistant if they failed to respond to a minimum of two AEDs given as monotherapy. The majority of these drug-resistant individuals have partial onset seizures which are divided into three types: simple partial, complex partial and secondary generalised tonic-clonic seizures (Commission 1989).

Over the past 10 to 15 years, there has been renewed interest in development of new AEDs as standard drugs (e.g. carbamazepine, phenytoin, valproate) do not leave all patients' seizure free, they are not without adverse effects. Tiagabine, the subject of review, is one of these new drugs and exerts its antiepileptic by inhibiting pre-synaptic and glial uptake of

gamma-amino-butyric-acid (GABA) (Ostergaard 1995). In this review, we assess effects of tiagabine upon seizures, adverse effects, cognition quality of life when used as an add-on treatment for people drug-resistant localisation related seizures.

This review is part of a series of reviews investigating the AEDs. An initial tiagabine review reported its effect on seizure frequency and adverse effects (Marson 1996; Marson 1997). In this initial review, the most common adverse effects were investigated. There is however concern that AEDs may impair cognitive abilities, and in this Cochrane review we have included outcomes assessing cognitive effects. In addition, we have chosen to include quality of life outcomes in order to assess the global impact of drug upon well-being.

OBJECTIVES

To evaluate the effects of tiagabine upon seizures, adverse effects, cognition and quality of life when used as an add-on treatment for people with drug-resistant localisation-related seizures.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trials, in which an adequate method of concealment of randomisation was used (e.g. allocation of sequentially sealed packages of medication, sealed opaque envelopes, telephone randomisation).
2. Double, single or unblinded trials.
3. Placebo controlled or active drug control group.
4. Parallel group or crossover studies. For crossover studies, the first treatment period was treated as a parallel trial (i.e. only data from the first treatment period was used).
5. Minimum treatment period of eight weeks.

Types of participants—People of any age with drug-resistant localisation related seizures (i.e. experiencing simple partial, complex partial or secondary generalised tonic-clonic seizures).

Types of interventions—The active treatment group received treatment with tiagabine in addition to conventional antiepileptic drug treatment; the control group received matched placebo or a different add-on AED in addition to conventional antiepileptic drug treatment.

Types of outcome measures

50% or greater reduction in seizure frequency: The proportion of people with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period was chosen as the primary outcome. This outcome was

chosen as it is commonly reported in this type of study, and can be calculated for studies that do not report this outcome provided that baseline seizure data were recorded.

Treatment withdrawal: The proportion of people having treatment withdrawn during the course of the treatment period was used as a measure of global effectiveness. Treatment is likely to be withdrawn due to adverse effects, lack of efficacy or a combination of both, and this is an outcome to which patients make a direct contribution. In trials of short duration, it is likely that adverse effects will be the most common reason for withdrawal.

Adverse effects

- a. The proportion of people experiencing any of the following five adverse effects, considered by the reviewers to be common and important adverse effects of antiepileptic drugs:
 - i. ataxia;
 - ii. dizziness;
 - iii. fatigue;
 - iv. nausea;
 - v. somnolence.
- b. The proportion of people experiencing the commonest five adverse effects if different from (a) above.

Cognitive effects: At present, there is no consensus as to which instruments should be used to assess the effects of AEDs on cognition, and as a result the assessment of cognitive effects has been approached in a heterogeneous way (Cochrane 1998). In view of this difficulty, in the first instance we tabulated results, but made no attempt to combine results in a meta-analysis.

Quality of life: Once again, there is no consensus as to which instruments should be used to assess this (Baker 2000), and in the first instance we tabulated results, but made no attempt to combine results in a meta-analysis.

Search methods for identification of studies

Electronic databases—This review is an update of a previously published Cochrane review in 2010. We searched the following databases. There were no language restrictions.

- The Cochrane Epilepsy Group Specialised Register (15 December 2011).
- The Cochrane Central Register of Controlled Trials (CENTRAL issue 4 of 4, *The Cochrane Library* 2011) using the search strategy outlined in Appendix 1.
- MEDLINE (Ovid) (1948 to November week 3, 2011) was searched using the strategy outlined in Appendix 2.

References from published studies—We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Other sources—We contacted Sanofi-Synthelabo (makers of tiagabine), and experts in the field for information about any unpublished or ongoing studies.

Data collection and analysis

Two review authors (Jennifer Pulman and Tony Marson) independently assessed trials for inclusion. Disagreements were resolved by mutual discussion. The same two review authors extracted the following information from included trials, disagreements again resolved by mutual discussion.

Trial design

- a. Method of sequence generation and randomisation concealment.
- b. Method of blinding.
- c. Whether any people had been excluded from reported analyses.
- d. Duration of baseline period.
- e. Duration of treatment period.
- f. Dose(s) of tiagabine tested.

Participant demographic information—

- a. Total number of people allocated to each treatment group.
- b. Age/sex.
- c. Number with localisation related/generalised seizures.
- d. Seizure frequency during the baseline period.
- e. Number of background drugs.

All trials found so far have been sponsored by Sanofi-Synthelabo who confirmed the following information.

1. The method of randomisation.
2. The total number randomised to each group.
3. The number of people in each group achieving a 50% or greater reduction in seizure frequency per treatment group.
4. The number of people having treatment withdrawn post randomisation per treatment group.
5. For those excluded:
 - a. the reason for exclusion;
 - b. whether any of those excluded completed the treatment phase;

- c. whether any of those excluded had a 50% of greater reduction in seizure frequency during the treatment phase.

Outcomes—The number of people experiencing each outcome was recorded per randomised group.

Analysis

Efficacy and adverse effects: Clinical heterogeneity was assessed by comparing the distribution of important participant factors between trials (age; seizure type; duration of epilepsy; number of AEDs taken at time of randomisation), and trial factors (randomisation concealment; blinding; losses to follow-up). Statistical heterogeneity was assessed by using a chi squared test where $p < 0.05$ indicates significant heterogeneity. Provided no significant heterogeneity was present, data were synthesised using a fixed-effect model. Results are presented as relative risks (RR). For the outcomes 50% reduction in seizure frequency and treatment withdrawal, 95% confidence intervals (CIs) are quoted. For individual adverse effects 99% CIs are quoted to make allowance for multiple testing.

All analyses included all participants in the treatment groups to which they had been allocated. For the efficacy outcome (50% or greater reduction in seizure frequency) three analyses were undertaken:

1. Primary (intention-to-treat) analysis: participants lost to follow up or with inadequate seizure data were assumed non responders.
2. Worst case: participants lost to follow up or with inadequate seizure data were assumed non responders in the tiagabine group, and responders in the placebo group.
3. Best case: participants lost to follow up or with inadequate seizure data were assumed responders in the tiagabine group, and non responders in the placebo group.

Dose-regression analysis: Dose response relationships were examined using logistic regression, in the framework of generalised linear models (McCullagh 1989), using the package GLIM. For these models a binary variable was defined with value 0 if the response was less than 50% and value 1 otherwise. Models included an indicator variable for trials. In order to examine the effect of dose, the following were considered as possible explanatory variables: dose levels; dose as a continuous variable; and a logarithmic transformation of dose. Interactions between dose and trials were also considered. Odds ratios and response rates were calculated.

Cognitive and quality of life data: As stated under 'outcomes', in the first instance, data for these outcomes were tabulated but no attempt made to undertake a meta-analysis. We found that trials had not used the same outcome measure, so we did not undertake a meta-analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We found three parallel-group studies and two crossover studies comparing tiagabine with placebo for people with drug-resistant localisation related seizures (Crawford 2001; Kalviainen 1998; Richens 1995; Sachdeo 1997; Uthman 1998). All trials were initially sponsored by Novo Nordisk as part of a pre-licensing programme but the drug patent is now owned by Sanofi-Synthelabo. People were excluded from these studies if there was a history of non-epileptic attacks; any active progressive disease of the central nervous system (e.g. brain tumour); any significant illness within the previous three months; any medical or neurological disorder requiring frequent changes in medication or dosage; abnormal laboratory findings that were not attributable to their concomitant AEDs; a history of drug abuse or addiction (including alcohol); poor compliance with past medication or medical advice. Women who were pregnant or at risk of pregnancy or lactating were also excluded. Valproate monotherapy was not allowed in two studies (Sachdeo 1997; Uthman 1998). We found one further parallel study (Fritz 2005), which examined tiagabine and topiramate in patients with refractory epilepsy. This study was previously excluded from the review due to the lack of a placebo control group. It has now been included as a head-to-head trial.

The parallel trial Kalviainen 1998 had a 12 week pre-randomisation baseline period and people having eight or more localisation related seizures during this period were eligible to be randomised. The treatment period lasted 22 weeks and 154 individuals were randomised, 77 to placebo and 77 to 30mg tiagabine per day. Data on the cognitive and quality of life effects on a subset of 43 people were reported separately (Kalviainen 1996).

Another parallel trial Fritz 2005 had an 8-week screening period, a titration phase of 3 months and a 3 month maintenance phase. Twenty-one patients were randomised to tiagabine (final dose at least 20mg/day) and 20 were randomised to topiramate treatment (final dose at least 200mg/day). This study reported seizure outcome, cognitive outcome and quality of life effects.

Sachdeo 1997, a parallel trial, had an eight week pre-randomisation baseline period and people having eight or more seizures during this period were eligible to be randomised. The treatment period lasted 12 weeks and 318 individuals were randomised, 107 to placebo and 211 to 32 mg tiagabine per day. Of those randomised to tiagabine, 106 were allocated 16mg twice a day whilst 105 were allocated 8mg four times a day. No effects on cognition or quality of life were reported for this study.

The parallel trial Uthman 1998 had a 12 week pre-randomisation baseline period and people having eight or more localisation related seizures during this period were eligible to be randomised. The treatment period lasted 20 weeks and 297 individuals were randomised, 91 to placebo, 61 to 16mg, 88 to 32mg and 57 to 56mg tiagabine per day. Data on the cognitive and quality of life effects were reported separately on a subset of 162 individuals (Dodrill 1997).

The crossover trials Richens 1995 and Crawford 2001 were similar in design, using what has been called a response conditional design. People having six or more seizures in the eight weeks prior to the study were entered into a 12-week screening phase. During the screening phase all participants were given tiagabine, the dose of which was titrated up with a target dose of 52mg/day in Richens 1995 or 64mg/day in Crawford 2001. Participants with a reduction in seizure frequency of 25% or more during the screening phase were eligible to be randomised (hence response conditional). Eligible individuals were randomised into a two by two crossover trial and to a sequence of placebo-tiagabine or tiagabine-placebo. The treatment periods lasted seven weeks and the crossover periods three weeks. Richens 1995 screened 94 individuals, 46 of whom were randomised; Crawford 2001 screened 88 individuals, 44 of whom were randomised. The reports for these two studies contain insufficient information to allow the planned analyses using data from the first treatment period. For the cohort recruited in Richens 1995, the cognitive effects of tiagabine were reported separately on a subset of 22 individuals (Sveinbjornsdottir 1994). In total the studies assessing seizure outcomes and treatment withdrawal randomised 900 individuals. Studies assessing adverse effects randomised 859 patients. Data on cognitive effects were available for 251 individuals whilst data on quality of life were available for 229. Further details are provided in the table of characteristics of included studies.

Risk of bias in included studies

Randomisation: all studies randomised patients to treatment arms. Out of the six trials included, only two used computer-generated sequences to allocate their patients (Fritz 2005; Kalviainen 1998). The other studies did not provide details of how their sequence allocation was generated.

Concealment: all but Fritz 2005 used sequentially allocated sealed packages to conceal group allocation. Fritz 2005 used no methods of concealment.

Blinding: all studies report to be double-blinded except for Fritz 2005, which was an open-label study and thus no blinding techniques were used in the study. In the other four included studies, identical packaging and medication were used to maintain blinding. No specific details regarding who were blinded was detailed within the papers, i.e. patients, study personnel or outcome assessors.

Missing Data: all trials reported attrition rates and reasons for drop-out. An intention-to-treat analysis was used by all studies in order to deal with this missing data.

Outcome Reporting: most of the studies detailed outcomes within the methods of the paper and reported the data. Fritz 2005 selected a sub-set of the patients randomised and reported data for this sub-set only on baseline measures.

See Figure 1 for risk of bias graph.

Effects of interventions

See: **Summary of findings for the main comparison** Tiagabine versus placebo: 50% seizure reduction

As already outlined in the description of studies, we found four parallel group and two crossover studies. The crossover studies used a response conditional design in which participants are given tiagabine during a screening period, and those with a 25% or greater reduction in seizure frequency are eligible to be randomised. The people randomised are therefore highly selected and are biased towards a response to tiagabine. We have therefore chosen to report separately the effects on seizure frequency from the parallel and crossover trials. In addition, the reports of the crossover studies do not give detailed side effect data or data on treatment withdrawal and only the parallel studies contribute the results for these outcomes. The parallel study which examined tiagabine and topiramate was assessed separately (Fritz 2005).

Tiagabine versus placebo control

50% or greater reduction in seizure frequency: parallel trials

Overall results irrespective of dose: A chi-squared test for heterogeneity for a response to tiagabine indicated no significant heterogeneity between trials (intention-to-treat analysis: $\chi^2 = 0.81$, $df = 2$, $p = 0.67$; worst case scenario: $\chi^2 = 0.41$, $df = 2$, $p = 0.81$; best case scenario: $\chi^2 = 1.09$, $df = 2$, $p = 0.58$). The overall relative risk for a response to tiagabine is 3.16 (95% CI 1.97 to 5.07), indicating that participants are significantly more likely to respond to tiagabine than placebo. The relative risk for the worst case and best case scenario are 2.70 (95% CI 1.75 to 4.19) and 3.32 (95% CI 2.08 to 5.32), respectively (Figure 2).

Dose regression analysis

Intention-to-treat: Due to differences in response rates in individual trials, it is not possible to give valid estimates of precise responses to individual doses. Due to the different response rates among trials, the model with the best summary of the log odds includes a contrast between Kalviainen 1998, Uthman 1998 and the third (Sachdeo 1997). After adjusting for the trial effects, this model includes two contrasting dose groups, one group containing placebo and 16 mg and the other 30, 32 and 56 mg tiagabine per day. The reduction in deviance due to dose at these two levels, adjusting for trial effects is 40.6 on 1 df, $p = 0.001$. With a contrast of trials included, the residual deviance is 4.8 on 5 df.

The estimated odds ratio relative to placebo is 3.67 (95% CI 2.30 to 5.86). Odds ratio for trials two and three versus trial one is 1.65 (95% CI 1.11 to 2.44).

The actual and estimated response rates are given in Table 1. Although we are unable to give precise overall estimates for the proportion responding to individual doses, there is strong evidence of an effect for daily dose of 30 to 56mg or more. As an indication of the possible effects, we can say that, with placebo rates in the range 6 to 10%, at least an additional 13%, and possibly 20%, of people similar to those in these trials would experience a 50% or greater reduction in seizure frequency on a dose of 30mg tiagabine per day or more.

Best and worst case scenarios: The best case results are very similar to the intention-to-treat results. After adjusting for the trial effects, a contrast between placebo or 16mg and 30, 32 or 56mg gives the best summary of the log odds. The reduction in deviance due to dose,

adjusting for trial effects is 47.7 on 1 df, $p = 0.001$. With a contrast of trials included, the residual deviance is 6.7 on 5 df.

The estimated odds ratio relative to placebo is 4.03 (95% CI 1.97 to 8.25). Odds ratio for trials two and three versus trial one is 1.51 (95% CI 0.98 to 2.33). The actual and estimated response rates are given in Table 2.

The worst case results are also very similar to the intention-to-treat results. After adjusting for the trial effects, a contrast between placebo or 16mg and 30, 32 or 56mg gives the best summary of the log odds. The reduction in deviance due to dose, adjusting for trial effects is 35.4 on 1 df, $p = 0.001$. With a contrast of trials included, the residual deviance is 4.5 on 5 df.

The estimated odds ratio relative to placebo is 3.22 (95% CI 2.05 to 5.05). Odds ratio for trials two and three versus trial one is 1.70 (95% CI 1.15 to 2.50). The actual and estimated response rates are given in Table 3.

50% or greater reduction in seizure frequency: crossover trials: The reports of the crossover trials contain insufficient data from the first treatment period to allow the analyses that were planned. The reported results from the two crossover trials have therefore been summarised below.

Of the 46 people randomised in Richens 1995, eleven (24%) had a 50% reduction in seizure frequency in the tiagabine compared to the placebo phase. Of the 44 people randomised in Crawford 2001, twelve (27%) had a 50% reduction in seizure frequency in the tiagabine compared to the placebo phase. Pooling these data, weighted according to the inverse variance gives an estimate of the proportion of responders of 0.25 (95% CI 0.16 to 0.34). The proportion of responders is higher than that seen in the parallel group trials which is not surprising given that people in the crossover trials had to have an apparent response to tiagabine in order to be randomised.

Treatment withdrawal: Treatment withdrawal data were only available for the parallel trials. A chi-squared test for heterogeneity suggest no significant statistical heterogeneity ($\chi^2 = 1.75$, df = 2, $p = 0.42$). The overall relative risk for discontinuation for any reason is 1.81 (95% CI 1.25 to 2.62) indicating that people are significantly more likely to withdraw from tiagabine than placebo (Analysis 2.1).

Adverse effects: The results for the parallel and crossover trials are reported separately. For the parallel trials, in addition to the five side effects specified in the protocol for this review, headache, infection, nervousness and tremor were amongst the five most commonly reported adverse effects. A chi squared test for heterogeneity for adverse effects indicated no significant heterogeneity between trials. The 99% CIs around RR estimates for the following did not cross unity, indicating that they are significantly associated with tiagabine: dizziness 1.69 (99% CI 1.31 to 2.51); fatigue 1.38 (99% CI 0.89 to 2.14); nervousness 10.65 (99% CI 0.78 to 146.08); tremor 4.56 (99% CI 1.00 to 20.94). The 99% CI for the following adverse effects did not cross unity and were therefore not significantly associated with tiagabine:

ataxia 1.24 (99% CI 0.34 to 4.55); nausea 1.24 (99% CI 0.69 to 2.22); somnolence 1.18 (99% CI 0.76 to 1.83); headache 1.15 (99% CI 0.48 to 2.79); infection 1.00 (99% CI 0.36 to 2.76) (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9).

For the crossover trials, Crawford 2001 reported that eight people experienced side effects whilst taking tiagabine and ten people reported adverse effects whilst taking placebo. Whilst taking tiagabine, two people reported dizziness and another two incoordination. Whilst taking placebo three people reported accidental injury. All other adverse events were reported by one individual only. Richens 1995 did not report a detailed breakdown of adverse events occurring on either tiagabine or placebo.

Cognitive effects: Reviewing the cognitive effects of tiagabine is complicated by the lack of uniformity of approach in the included studies (Dodrill 1997; Kalviainen 1996; Sveinbjornsdottir 1994). In total, these studies used 24 neuropsychological tests, only two of which, the Stroop test and the Rey auditory verbal learning test were used in all 3 studies that reported cognitive effects. Three tests were used by two of the three studies and the remaining 19 tests were used in just one study. Even where the same test had been used in two or more studies, it was not already clear that the same aspects of the test had been used. The tests used in the individual studies are outlined in Table 4.

There were no statistically significant differences at the 0.01 level of confidence in any test and for only three tests there were statistically significant differences at the 0.05 level (Table 5). There is therefore insufficient evidence to conclude that tiagabine has an effect on cognition.

Quality of life measures: There are two reports addressing quality of life outcomes (Dodrill 1997; Kalviainen 1996). Both report effects on mood and adjustment but used different tests to assess them (Table 6). Neither study found a significant difference between tiagabine and placebo, hence there is insufficient evidence to conclude that tiagabine has an effect on quality of life.

Tiagabine versus topiramate—Only Fritz 2005 compared tiagabine with an active control drug (topiramate), therefore the pooling of data was not undertaken for this comparison.

50% or greater reduction in seizure frequency: Within this study, there were no significant differences between the two add-on drugs (RR 0.54, 95% CI 0.19 to 1.58). According to the authors' analysis of 37 patients, three patients (one tiagabine, two topiramate) became seizure free; eleven patients (four tiagabine, seven topiramate) reduced their seizure frequency by 50% or more (Analysis 4.1).

Treatment withdrawal: No significant differences were found between tiagabine and topiramate from withdrawal from the study (RR 1.43, 95% CI 0.74 to 2.74) (Analysis 4.2).

Cognitive effects: For this outcome authors of this study did not compare the two add-on antiepileptic drugs. Both add-on drugs were examined over separate time points, baseline - post-titration phase and post-titration - maintenance phase. Within the first evaluation, baseline - post-titration significant deteriorations were found in phonematic verbal fluency $p=0.001$, semantic verbal fluency $p=0.006$, language comprehension $p=0.002$, working memory $p<0.05$ and visual block tapping $p=0.032$ within the topiramate group. A significant deterioration for the tiagabine group was also found in verbal memory $p=0.039$.

Within the period post-titration - maintenance phase one significant improvement was found in mental flexibility in the topiramate group $p=0.045$. No changes were found for the tiagabine group for any of the cognitive outcomes.

Quality of life measures: Again, authors did not use appropriate analysis; therefore we are unable to compare the two add-on antiepileptic drugs. Within the baseline - post-titration phase, there were significantly more complaints about medication within the tiagabine group $p=0.048$. Patients taking topiramate reported significantly higher depression scores $p=0.011$, lower cognitive functioning $p=0.024$, and more medication side effects $p=0.008$.

For the post-titration - maintenance phase evaluation the tiagabine group were significantly more fatigued/had less energy $p=0.025$. No other differences from post-titration to maintenance were found.

DISCUSSION

All the trials included in this review were sponsored by Sanofi-Synthelabo as part of a drug licensing programme. Five out of the six included trials used adequate methods of concealment of randomisation, however only two of the trials were rated as low risk of bias for how the randomisation sequence was generated. All trials except one were double-blinded and used identical packaging and medication to maintain this, however little detail was reported about whether specific study personnel and outcome assessors were blinded. All studies were rated as low of bias for missing data and how this was dealt with due to the use on intention-to-treat analyses. We had no access to the protocols for any of the studies and therefore selective outcome reporting bias is unclear in each of the studies. Limitations for two of the trials include the use of a response conditional design, the aim of which was to select and randomise a group of people that are likely to respond favourably to tiagabine. In theory, this will maximise the effects observed and may have the efficiency of requiring the recruitment of fewer individuals into trials. This is not a process that mimics clinical practice and the results of these studies are difficult to translate into every day clinical practice. The length of the treatment periods was a limitation for all of the included trials, seven weeks in the crossover studies and 12 to 22 weeks in the parallel studies. Clinical practice will be better informed by trials of longer duration, especially for a chronic condition such as epilepsy.

Despite these limitations, this review does provide strong evidence that tiagabine reduces seizure frequency for people with drug-resistant localisation related seizures. Due to differences in response rates among trials, regression models were unable to give valid

estimates for the proportion of participants responding to specific doses of tiagabine. We can however say that for people similar to those recruited into the trials reviewed, compared to placebo, we might expect at least an additional 13%, and possibly 20%, of people to experience a 50% or greater reduction in seizure frequency on a dose of 30mg tiagabine per day or more.

Results for the outcome treatment withdrawal show that tiagabine is more likely to be withdrawn than placebo. In trials of relatively short duration, such as those reviewed here, this is likely to represent problems with tolerability rather than poor seizure control. Of the adverse effects investigated, dizziness, nervousness and tremor were significantly more likely to occur with tiagabine than with placebo.

Due to lack of uniformity in the approach to testing for cognitive effects and quality of life, as well as the relatively small numbers of participants tested, there is insufficient evidence to conclude whether tiagabine has an effect upon these outcomes or not.

Given that only one trial included in this review compared add-on tiagabine with another add-on antiepileptic drug, the results from this study have to be interpreted with caution. Authors of this study only compared the two drugs in two of the outcomes reported. Given the increasing number of licensed antiepileptic drugs, this is an important issue which must be addressed in trials that compare one drug with another. We should also emphasise that the results of this review do not provide information about the effects of tiagabine when used as monotherapy, and that the results only apply to localisation related seizures.

AUTHORS' CONCLUSIONS

Implications for practice

Add-on tiagabine reduces the frequency of seizures for people with drug-resistant localisation related seizures. Doses between 30 and 56mg per day are likely to reduce the frequency of seizures by 50% or more for between 13 and 20% of people. Doses higher than 56mg per day were not tested in the trials included in this review.

Implications for research

In order to further evaluate the place of tiagabine in the armamentarium of available AEDs, further studies are required addressing the following:

- The long-term effects of add-on tiagabine.
- How tiagabine compares with other add-on treatments in drug-resistant partial epilepsy.
- The role of tiagabine in childhood and generalised epilepsies.
- How tiagabine compares with standard antiepileptic drugs such as:
 - tiagabine as monotherapy in partial epilepsy;
 - tiagabine as monotherapy in generalised epilepsy;
- Economic aspects of tiagabine therapy.

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External sources

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- This review presents independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Appendix 1: CENTRAL search strategy

- #1 MeSH descriptor Epilepsy explode all trees
- #2 MeSH descriptor Seizures explode all trees
- #3 epilep* or seizure* or convulsion*
- #4 (#1 OR #2 OR #3)
- #5 (tiagabine or gabitril)
- #6 (#4 AND #5)

Appendix 2: MEDLINE search strategy

For the June 2010 and December 2011 update of this review, the following search strategy was used. It is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2009.

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Epilepsy/
12. Seizures/

13. (epilep\$ or seizure\$ or convuls\$).tw.
14. 11 or 12 or 13
15. (tiagabine or gabitril).tw.
16. 10 and 14 and 15

Earlier versions of this review employed the following search strategy. It was combined with phases 1 and 2 of the earlier Cochrane highly sensitive search strategy for MEDLINE as set out in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.4, updated March 2005) (Higgins 2005).

1. tiagabine.tw.
2. exp epilepsy/ OR epilep\$.tw.
3. exp seizures/ OR seizure\$.tw.
4. convulsion\$.tw.
5. 2 OR 3 OR 4
6. 1 AND 5

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Tiagabine versus placebo: 50% seizure reduction

Patient or population: Patients with drug-resistant partial epilepsy

Settings:

Intervention: Tiagabine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Tiagabine versus placebo				
Intention-to-treat analysis	Study population		RR 3.16 (1.97 to 5.07)	769 (3 studies)	⊕⊕⊕⊕⊕ high	
	7 per 100	22 per 100 (14 to 35)				
	Moderate					
	6 per 100	21 per 100 (13 to 33)				
Worst case scenario	Study population		RR 2.7 (1.75 to 4.19)	769 (3 studies)	⊕⊕⊕⊕⊕ high	
	8 per 100	22 per 100 (14 to 34)				
	Moderate					
	6 per 100	18 per 100 (11 to 27)				
Best case scenario	Study population		RR 3.32 (2.08 to 5.32)	769 (3 studies)	⊕⊕⊕⊕⊕ high	
	7 per 100	23 per 100 (14 to 37)				
	Moderate					
	6 per 100	22 per 100 (14 to 35)				

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Crawford 2001

Methods	Randomised, double-blind, placebo-controlled, crossover study, based upon a response-dependent design. Two treatment arms: 1 TGB, 1 PCB. Patients randomised to one of two sequences. TGB started during screening phase starting at 12mg/day QID. 7-week double-blind treatment period where patients continued on TGB or crossed over to PCB arm	
Participants	Multicentre study (5 centres: 2 in UK, 2 in The Netherlands and one in Denmark). 44 patients with drug-resistant partial epilepsy were randomised (30 male), aged 18 to 53 years. Patients already taking 1 to 3 background AEDs. Median baseline seizure frequency = 2.7/week .	
Interventions	Group 1: PCB Group 2: TGB (optimal does 64mg/day) The mean daily dose for all randomised people was 46mg during the double-blind phase	
Outcomes	1	50% responder rates
	2	Median percentage reduction in 4 weekly seizure rate
	3	Adverse events
Notes	From the 44 people randomised to the double-blind phase seven were excluded from the intent-to-treat analysis. All participants were evaluated for adverse events	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients randomly assigned in a 1:1 ratio at each centre to one of two sequences. No further details on how the sequences were generated
Allocation concealment (selection bias)	Low risk	Sequentially allocated sealed packages used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Used identical packaging and medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes

Fritz 2005

Methods	Open-label, head-to-head controlled, parallel study. Two treatment arms: 1 TGB, 1 TPM. Patients were randomised using non-random component. Duration of screening period: 8-weeks, followed by a titration phase of 3 months and maintenance period of 3 months
Participants	No information regarding study sites or countries. 41 patients with drug-resistant partial epilepsy randomised. Baseline data only reported for 30 patients who completed whole study Patients already taking 1-3 background AED's.

Interventions	Group 1: TGB at least 20mg/day Mean 32mg/day Group 2: TPM at least 200mg/day Mean 335mg/day	
Outcomes	1	50% responder rates
	2	Cognitive effects
	3	Quality of life
Notes	Non-accurate baseline data reported. 4 patients excluded from ITT analysis for seizure reduction outcome	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomisation component employed in the sequence generation process. Sequence generated by odd versus even number of week in which patient was seen
Allocation concealment (selection bias)	High risk	No concealment used.
Blinding (performance bias and detection bias) All outcomes	High risk	Study was open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	High risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes. Patient characteristics only reported for 30 patients who completed the whole study out of the 41 randomised

Kalviainen 1998

Methods	Randomised, double-blind, placebo-controlled, two treatment parallel group study. Two treatment arms: 1 PCB, 1 TGB. Patients randomised using computer-generated sequence. Treatment period: 22 weeks (6-week run in period, 12-week fixed dose period, 4-week termination period)		
Participants	Multicentre study (11 centres in Europe - 1 each in Denmark and Sweden, 2 in Finland and 7 in UK). 154 patients with drug-resistant partial epilepsy were randomised (90 male), aged 17 to 71 years. 77 were randomised to placebo and 77 to 30mg/day tiagabine. Patients already taking 1 to 3 background AEDs. Median 4 weekly baseline seizure frequency: placebo = 10.5, tiagabine = 12.2. Cognitive and quality of life effects were assessed on a subset of 43 individuals		
Interventions	Group 1: PCB Group 2: TGB 30mg/day TDS		
Outcomes	1	50% responder rates	
	2	Treatment withdrawal	
	3	Adverse effects	
	4	Cognitive effects	
	5	Quality of life	
Notes	No participants were excluded from analysis. 29 people withdrew from the study: 21 receiving tiagabine and 8 receiving placebo		
Risk of bias			

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a computer-generated allocation sequence.
Allocation concealment (selection bias)	Low risk	Used sequentially allocated sealed packages.
Blinding (performance bias and detection bias) All outcomes	Low risk	Used identical packaging and medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes

Richens 1995

Methods	Randomised, double-blind, placebo-controlled, crossover study, based upon a response-dependent design. Two treatment arms: 1 PCB, 1 TGB. Patients randomised using 1:1 ratio. Treatment period: 23 weeks (3-week run in period, 7-week assessment period, 3-week crossover period, 7-week assessment period, 3-week termination period)	
Participants	Multicentre study (5 centres in UK and Denmark). 94 patients with drug-resistant partial epilepsy were randomised (61% male), aged 19 to 71 years. 25 patients were randomised to placebo-tiagabine sequence and 21 to tiagabine-placebo. Patients already taking 1 to 3 AEDs. Median complex partial seizure rate per 4 weeks = 6. Cognitive effects were reported for a subset of 22 individuals	
Interventions	Group 1: PCB Group 2: TGB 52mg/day QID. The mean daily dose was 33.4mg (range 12 to 52 mg).	
Outcomes	1	50% responder rates
	2	Median percentage reduction in four-weekly seizure rate
	3	Adverse events
	4	Cognitive effects
Notes	From the 46 people randomised to the double-blind phase 7 failed to complete the study. Of these only 4 were excluded from the intent-to-treat analysis. All participants were evaluated for adverse events. The characteristics of the people ineligible for the double-blind phase were similar to those of people qualifying, with regards to epilepsy history, seizure frequency and concurrent treatment	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1:1 ratio employed at each centre. No further details of sequence generation
Allocation concealment (selection bias)	Low risk	Used sequentially allocated sealed packages.
Blinding (performance)	Low risk	Used identical packaging and medication.

bias and detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes

Sachdeo 1997

Methods	Randomised, double-blind, placebo-controlled, parallel group study. Three treatment arms: 1 PLC, 2 TGB. Patients randomised using ratio 1:1:1 in blocks of 6. Treatment periods = 12 weeks.	
Participants	Multicentre US study (26 centres). 318 patients with drug-resistant partial epilepsy were randomised (178 male) aged 12 to 71 years. 107 to PCB, 106 to TGB 16mg BID, 105 to TGB 8mg QID. Valproate allowed in combination with an enzyme inducing drug but not as monotherapy. Median baseline 4 weekly complex partial seizures frequency during baseline was: PCB = 8.4; TGB 16mg BID = 8.4; TGB 8mg QID = 7.9	
Interventions	Add-on placebo, TGB 16mg BID or TGB 8mg QID.	
Outcomes	1	50% responder rates
	2	Treatment withdrawal
	3	Adverse effects
Notes	From the 318 people randomised to the double-blind phase 4 were excluded from the intention-to-treat analyses. All 318 people were evaluated for adverse events. 47 people withdrew from the study: 10 receiving PLC; 16 receiving TGB16mg BID; 21 receiving TGB 8mg QID	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used ratio of 1:1:1 in blocks of 6 per study centre.
Allocation concealment (selection bias)	Low risk	Used sequentially allocated sealed packages.
Blinding (performance bias and detection bias) All outcomes	Low risk	Used identical packaging and medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes

Uthman 1998

Methods	Randomised, double-blind, placebo-controlled, parallel group study. Four treatment arms: 1 PCB, 3 TGB. Patients randomised using ratio of 3:2:3:2. Treatment period 20 weeks (4-week titration phase, 12-week fixed dose treatment period, 4-week tapering period)
Participants	Multicentre US study (21 centres). 297 patients with drug-resistant partial epilepsy were randomised (172 male) aged 12 to 77 years. patients already taking 1 to 3 AEDs, valproate allowed in combination with an enzyme inducing drug but not as monotherapy. Median 4 weekly baseline complex partial seizure frequency was: PCB = 7.4; TGB 16mg = 8.5; TGB 32mg = 9.6; TGB 56mg = 9.1. Cognitive effects were reported for a subset of 162 individuals
Interventions	Group 1: PCB Group 2: TGB 16mg/day QID Group 3: TGB 32mg/day QID Group 4: TGB 56mg/day QID
Outcomes	<ol style="list-style-type: none"> 1 50% responder rates 2 Treatment withdrawal 3 Adverse effects 4 Cognitive effects 5 Quality of life
Notes	From the 297 people randomised to the double-blind phase 5 were excluded from the intention-to-treat analyses because no double-blind assessments were done or their centres lacked participants in all treatment groups. All 297 people were evaluated for adverse events. 54 people withdrew from the study: 13 receiving PCB; 6 receiving 16mg TGB; 18 receiving 32mg TGB and 17 receiving 56mg TGB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A ratio of 3:2:3:2 was used, no further details of sequence generation reported in text
Allocation concealment (selection bias)	Low risk	Used sequentially allocated sealed packages.
Blinding (performance bias and detection bias) All outcomes	Low risk	Used identical packaging and medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported and intention-to-treat analysis employed
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in method section were reported in text, however no protocol available to compare outcomes

Abbreviations

- AED = antiepileptic drug
- BID = twice daily
- ITT = intention-to-treat analysis
- PCB = placebo
- QID = four times daily
- TGB = tiagabine

- TPB = topiramate
- TID = three times daily

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arroyo 2005	This is a non-placebo controlled study.
Bauer 1995	This is an open add-on study of tiagabine in treatment of people with resistant partial and/or secondarily generalised seizures. In this study the results reported were part of an ongoing multinational, multicentre trial. It is not randomised
Gustavson 1997	This is an open-label, single-dose study that was designed to examine the pharmacokinetics of tiagabine in children with epilepsy. It is not randomised
Uldall 1995	This is a single-blind study of safety, tolerability and preliminary efficacy of tiagabine as adjunctive treatment of children with epilepsy. It is not randomised

DATA AND ANALYSES

Comparison 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intention-to-treat analysis	3	769	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.97, 5.07]
2 Worst case scenario	3	769	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.75, 4.19]
3 Best case scenario	3	769	Risk Ratio (M-H, Fixed, 95% CI)	3.32 [2.08, 5.32]

Comparison 2 Treatment withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment withdrawal	3	769	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.25, 2.62]

Comparison 3 Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ataxia	1	297	Risk Ratio (M-H, Fixed, 99% CI)	1.24 [0.34, 4.55]
2 Dizziness	3	769	Risk Ratio (M-H, Fixed, 99% CI)	1.69 [1.13, 2.51]
3 Fatigue	3	769	Risk Ratio (M-H, Fixed, 99% CI)	1.38 [0.89, 2.14]
4 Nausea	3	769	Risk Ratio (M-H, Fixed, 99% CI)	1.24 [0.69, 2.22]
5 Somnolence	3	769	Risk Ratio (M-H, Fixed, 99% CI)	1.18 [0.76, 1.83]
6 Headache	1	154	Risk Ratio (M-H, Fixed, 99% CI)	1.15 [0.48, 2.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Infection	1	154	Risk Ratio (M-H, Fixed, 99% CI)	1.0 [0.36, 2.76]
8 Nervousness	1	318	Risk Ratio (M-H, Fixed, 99% CI)	10.65 [0.78, 146.08]
9 Tremor	1	297	Risk Ratio (M-H, Fixed, 99% CI)	4.56 [1.00, 20.94]

Comparison 4 Tiagabine versus topiramate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency (ITT)	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.19, 1.58]
2 Treatment withdrawal (ITT)	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.74, 2.74]

Analysis 1.1 Comparison 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency, Outcome 1 Intention-to-treat analysis

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency

Outcome: 1 Intention-to-treat analysis

Analysis 1.2

Comparison 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency, Outcome 2 Worst case scenario

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency

Outcome: 2 Worst case scenario

Analysis 1.3

Comparison 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency, Outcome 3 Best case scenario

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency

Outcome: 3 Best case scenario

Analysis 2.1

Comparison 2 Treatment withdrawal, Outcome 1

Treatment withdrawal

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 2 Treatment withdrawal

Outcome: 1 Treatment withdrawal

Analysis 3.1

Comparison 3 Adverse effects, Outcome 1 Ataxia

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 1 Ataxia

Analysis 3.2

Comparison 3 Adverse effects, Outcome 2 Dizziness

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 2 Dizziness

Analysis 3.3

Comparison 3 Adverse effects, Outcome 3 Fatigue

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 3 Fatigue

Analysis 3.4

Comparison 3 Adverse effects, Outcome 4 Nausea

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 4 Nausea

Analysis 3.5

Comparison 3 Adverse effects, Outcome 5 Somnolence

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 5 Somnolence

Analysis 3.6

Comparison 3 Adverse effects, Outcome 6 Headache

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 6 Headache

Analysis 3.7

Comparison 3 Adverse effects, Outcome 7 Infection

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 7 Infection

Analysis 3.8

Comparison 3 Adverse effects, Outcome 8 Nervousness

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 8 Nervousness

Analysis 3.9

Comparison 3 Adverse effects, Outcome 9 Tremor

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 3 Adverse effects

Outcome: 9 Tremor

Analysis 4.1

Comparison 4 Tiagabine versus topiramate, Outcome 1

50% or greater reduction in seizure frequency (ITT)

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 4 Tiagabine versus topiramate

Outcome: 1 50% or greater reduction in seizure frequency (ITT)

Analysis 4.2

Comparison 4 Tiagabine versus topiramate, Outcome 2

Treatment withdrawal (ITT)

Review: Tiagabine add-on for drug-resistant partial epilepsy

Comparison: 4 Tiagabine versus topiramate

Outcome: 2 Treatment withdrawal (ITT)

WHAT'S NEW

Last assessed as up-to-date: 18 January 2012.

Date	Event	Description
15 December 2011	New citation required but conclusions have not changed	Searches updated 15 December 2011; no new trials identified.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2002

Date	Event	Description
11 June 2010	New search has been performed	Searches updated 11 June 2010; no new trials identified.
21 August 2008	Amended	Converted to new review format.
15 February 2008	New search has been performed	Searches updated 15 February 2008; no new trials identified.

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- *. Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Tiagabine add-on for drug-resistant partial epilepsy

Tiagabine in combination with other antiepileptic drugs as an add-on agent can reduce seizures, but with some adverse effects.

Nearly a third of people with epilepsy become resistant to antiepileptic drugs. Older antiepileptic drugs do not prevent seizures for everyone and they have adverse effects. The new antiepileptic drugs have been developed as 'add-on' treatments to try and improve this. Tiagabine is one of these newer agents. The review of trials found that for people who have drug-resistant partial epilepsy, use of tiagabine in combination with other antiepileptic drugs can decrease seizures further. There is also an increase in adverse effects such as dizziness, fatigue, nervousness and tremor. More research is needed to determine how this drug performs in comparison with other newer antiepileptic drugs.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 2. Forest plot of comparison: 1 Tiagabine versus placebo control - 50% or greater reduction in seizure frequency, outcome: 1.1 Intention-to-treat analysis

Table 1
Proportion of 50% responders (95% CI), intention-to-treat regression analysis

Trial	Placebo, proportion	16 mg/day	30 to 32 mg/day	56 mg/day
Uthman 1998 actual	4.4	8.2	19.3	18.1
Kalviainen 1998 actual	6.5		14.3	
Uthman 1998 and Kalviainen 1998 fitted	6.3 (4.1 to 9.4)	6.3 (4.1 to 9.4)	19.7 (15.2 to 25.0)	19.7 (15.2 to 25.0)
Sachdeo 1997 actual	10.2		28.6	
Sachdeo 1997 fitted	9.8 (6.4 to 14.9)		28.7 (23.3 to 34.9)	

Table 2
Proportion of 50% responders (95%CI), best case regression analysis

Trial	Placebo	16 mg/day	30 to 32 mg/day	56 mg/day
Uthman 1998 actual	4.4	8.2	21.6	31.6
Kalviainen 1998 actual	6.5		14.3	
Uthman 1998 and Kalviainen 1998 fitted	6.2 (4.9 to 9.3)	6.2 (4.9 to 9.3)	21.5 (16.9 to 27.1)	21.5 (16.9 to 27.1)
Sachdeo 1997 actual	9.3		29.4	
Sachdeo 1997 fitted	9.2 (5.9 to 14.0)		29.5 (24.0 to 35.6)	

Table 3
Proportion of 50% responders (95%CI), worst case regression analysis

Trial	Placebo	16 mg/day	30 to 32 mg/day	56 mg/day
Uthman 1998 actual	5.5	8.2	19.3	28.1
Kalvainen 1998 actual	6.5		14.3	
Uthman 1998 and Kalvainen fitted	7.0 (4.7 to 10.2)	7.0 (4.7 to 10.2)	19.4 (15.0 to 24.7)	19.4 (15.0 to 24.7)
Sachdeo 1997 actual	12.1		28.6	
Sachdeo 1997 fitted	11.3 (7.5 to 16.6)		29.0 (23.6 to 35.1)	

Table 4
Neuropsychological tests used

Study	Test
Dodrill 1997	Stroop test
	Rey auditory verbal learning test
	Controlled oral word association test
	Lafayette grooved pegboard
	Benton visual retention test
	Symbol digit modalities test
	Wonderlic personnel test
	Digit cancellation
Fritz 2005	Edinburgh inventory
	Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)
	Kurztest zur cerebralen Insuffizienz (c.I. test)
	Trailmaking Test
	Weiner test system
	HAWIE-R (verbal memory)
	Corsi block test
	Verbal learning and memory test (VLMT)
	Diagnosticum fur cerebralschaden (DSC-R) (visual memory)
	Boston naming test
	Word fluency test (LPS)
	Token test
Kalviainen 1996	Stroop test
	Rey auditory verbal learning test
	Controlled oral word association test
	Modified finger tapping test
	Binary choice reaction
	Full-scale I.Q. (WAIS)
	Logical prose, story A from the Wechsler memory scale
	Forward digit span
	Corsi block span
	Alternating S-task
	Letter cancellation task
	The WMS visual reproduction subtest
Sveinbjornsdottir 1994	Auditory and visual reaction-times
	Stroop test
	Rey auditory verbal learning test
	Binary choice reaction
	Modified finger tapping

Study	Test
	Semantic processing
	Information processing speed
	Bimanual hand movements
	Simple reaction time
	Tapping rate
	Verbal memory

Table 5
Neuropsychological tests with statistically significant differences

Test	Study	Result (P)	Treatment favoured
Benton visual retention test, form F	Dodrill 1997	0.049	Placebo
Benton visual retention test, form G	Dodrill 1997	0.051	Placebo
Symbol digit modalities test	Dodrill 1997	0.051	Placebo

Table 6
Tests of mood and adjustment

Study	Test	Domain
Dodrill 1997	Profile of Mood States (POMS)	Tension-anxiety
		Depression-dejection
		Anger-hostility
		Vigour-activity
		Fatigue-inertia
		Confusion-bewilderment
		Total mood disturbance
	Washington Psychosocial Seizure Inventory (WPSI)	Family background
		Emotional adjustment
		Interpersonal adjustment
		Vocational adjustment
		Financial status
		Adjustment to seizures
		Medicine and medical management
		Overall functioning
		Lie
		Rare items
	Mood Rating Scale	Average score
Fritz 2005	Befindlichkeits-Skala (BFS)	Dysphoria
	Beck Depression Inventory	Depression
	Self-rating Anxiety Scale (SAS)	Anxiety
	QOLIE-31	Health-related quality of life
Sveinbjornsdottir 1994	The Mood Adjective Check List (MACL)	Depression
		Anxiety
		Fatigue
		Activity
		Aggression
	Rating Scale Adapted from Brooks and McKinlay	Individual's behaviour