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Zonisamide for essential tremor (Review)

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[Intervention Review]

Zonisamide for essential tremor

Elisa Bruno[1], Alessandra Nicoletti[1], Graziella Filippini[2], Graziella Quattrocchi[1], Carlo Colosimo[3], Mario Zappia[1]

[1]Department GF Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy. [2]Scientific Direction, Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy. [3]Department of Neurology, Terni University Hospital, Terni, Italy

Contact address: Elisa Bruno, Department GF Ingrassia, Section of Neurosciences, University of Catania, Catania, 95123, Italy. e.bruno@hotmail.it.

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ABSTRACT

Background

Essential tremor (ET) is one of the most common movement disorders. The treatment is primarily based on pharmacological agents. Although primidone and propranolol are well established treatments in clinical practice, they can be ineffective in 25% to 55% of patients, and can produce serious adverse events in a large percentage of them. For these reasons, it may be worthwhile evaluating the treatment alternatives for ET. Zonisamide has been suggested as a potentially useful agent for the treatment of ET but there is uncertainty about its efficacy and safety.

Objectives

To assess the effect on functional abilities and the safety profile of zonisamide in adults with essential tremor (ET).

Search methods

We carried out a systematic search, without language restrictions to identify all relevant trials. We searched CENTRAL, MEDLINE, Embase, NICE, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) to January 2017. We searched BIOSIS Citation Index (2000 to January 2017) for conference proceedings. We handsearched grey literature and examined the reference lists of identified studies and reviews.

Selection criteria

We included all randomised controlled trials (RCTs) of zonisamide versus placebo or any other treatment. We included studies in which the diagnosis of ET was made according to accepted and validated diagnostic criteria. We excluded studies conducted in patients presenting secondary forms of tremor or reporting only neurophysiological parameters to assess outcomes.

Data collection and analysis

Two review authors independently collected and extracted data using a data collection form. We assessed the risk of bias and the quality of evidence.We used inverse variance methods for continuous outcomes and measurement scales. We compared differences between treatment groups as mean differences. We combined results for dichotomous outcomes using Mantel-Haenszel methods and obtained risk differences to compare treatment groups. We used Review Manager 5 software for data management and analysis.

Main results

We only considered one study eligible for this review (20 participants). Assessments of risk of bias for most domains were unclear or low. Adverse events were only reported in participants from the zonisamide group, making it possible that they were aware of treatment group assignment. We are uncertain as to the effects of zonisamide on motor tasks (mean difference (MD) -0.00, 95% confidence interval (CI) -1.51 to 1.51, very low-quality evidence) and functional disabilities (MD -0.30, 95% CI -1.23 to 0.63, very low-quality evidence) when

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compared with placebo. Three participants in the zonisamide group (30%) and two participants in the placebo group (20%) discontinued the treatment and withdrew from the study for any reason (very low-quality evidence), however the increased risk of withdrawal in the zonisamide group was statistically non-significant (risk difference (RD) 0.1, 95% CI -0.28 to 0.48). Six participants in the zonisamide group (60%) and none of the participants in the placebo group (0%) developed adverse events (AEs), with a RD of 0.60 (95% CI 0.28 to 0.92; very low quality evidence). The most common AEs, experienced with zonisamide treatment, were headache, nausea, fatigue, sleepiness, and diarrhoea. Quality of life was not assessed in the study included.

Authors' conclusions

Based on currently available data, there is insufficient evidence to assess the efficacy and safety of zonisamide treatment for ET.

PLAIN LANGUAGE SUMMARY

Use of zonisamide for the treatment of essential tremor

Review question

The authors of this review tried to assess the effectiveness and safety of zonisamide in people (16 years or older) with essential tremor.

Background

Essential tremor is the most common movement disorder. Although benign, in term of its effect on life expectancy, it is typically progressive and potentially disabling. The treatment is primarily based on pharmacological agents (propranolol and primidone as first-line therapy) but these are ineffective in 25% to 55% of participants. Zonisamide has been suggested as a potentially useful agent for the treatment of essential tremor.

Study characteristics

We found one study comparing zonisamide versus placebo, involving a total of 20 randomised participants with essential tremor.

Key results

The impact of zonisamide on functional abilities, risk of treatment discontinuation, and adverse events is uncertain because the quality of evidence is very low. Adverse events were only reported in participants from the zonisamide group, making it possible that they were aware of which treatment they had been receiving. Quality of life was not assessed in the study included.

Quality of evidence

The single study we found was small and the possibility of study participants becoming aware of the treatment group means that we cannot be certain about the risk-benefit profile of this treatment.

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Summary of findings for the main comparison. Zonisamide versus placebo for essential tremor

Zonisamide versus placebo for essential tremor						
Patient or population: participants with essential tremor **Settings:** outpatients **Intervention:** zonisamide **Comparison:** 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	**Zonisamide**				
Functional abilities Change in TRS part B score (motor tasks) Change in TRS part C score (functional disability) (higher scores indicate a better outcome) Follow-up: 28 days	The mean change in the control group was **0.9 points** in TRS part B score and **0.3 points** in TRS part C score at the end of follow-up, compared to baseline.	The mean change in the intervention group was **0.0 points higher** (1.51 points lower to 1.51 points higher) in TRS part B score and **0.3 points higher** (0.63 points lower to 1.23 points higher) in TRS part C score, compared to control.	MD 0.00 (-1.51 to 1.51) MD -0.30 (-1.23 to 0.63)	20 (1 study)	⊕⊝⊝⊝ **very low**[1, 2]	
Study withdrawal for any reason Number of participants withdrawn from the study Follow-up: 28 days	Three participants in the zonisamide group (30%) and two participants in the placebo group (20%) discontinued the treatment and dropped out from the study.		**RD 0.10** (-0.28 to 0.48)	20 (1 study)	⊕⊝⊝⊝ **very low**[1, 2]	

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Adverse events Number of adverse events Follow-up: 28 days	Six participants in the zonisamide group (60%) and none of the participants in the placebo group (0%) developed adverse events.	**RD 0.60** (0.28 to 0.92)	20 (1 study)	⊕⊖⊖⊖ **very low**[1, 2]

*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).
AEs: adverse events; **CI:** confidence interval; **MD**: mean difference; **RD:** risk difference; **TRS:** Tremor Rating Scale.

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.

[1]Downgraded one level due to serious risk of bias: blinding of outcome assessors not adequately described and zonisamide participants may have become aware of treatment group assignment due to the occurrence of adverse events.
[2]Downgraded two levels due to very serious imprecision: small sample size; short duration of follow-up.

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BACKGROUND

Description of the condition

Essential tremor (ET) is one of the most common movement disorders, presenting an overall estimated prevalence ranging from 0.9% to 2.2%, even higher among people over 65 years of age (4.6%) (Louis 2010).

It is characterised by postural and kinetic tremor involving the arms, and less commonly the head, lower limbs and voice, frequently accompanied by a family history of a similar tremor (Louis 2005). However, ET is a heterogeneous disorder and there is little agreement among neurologists regarding both clinical definition and diagnostic criteria (Jankovic 2002). Although benign in term of its effect on life expectancy, it often causes embarrassment and, in a small percentage of participants, also serious disability (Koller 1986; Busenbark 1991). Moreover, symptoms are typically progressive and potentially disabling, often forcing people to change job or seek early retirement (Deuschl 2000).

Description of the intervention

The treatment is primarily based on pharmacological agents, although surgical intervention may be an option in the most disabling cases. Pharmacotherapy may be used to improve function or reduce the embarrassment associated with ET, but treatment should be tailored to patient's level of disability. Although propranolol and primidone are well established agents for the treatment of ET, additional medications may be useful in reducing tremor (Sullivan 2004). In fact, even though it has been reported that both propranolol and primidone improve tremor in about two-thirds of participantspatients (Koller 1989; Wasielewski 1998), these agents tend to lose efficacy over time (Louis 2001a). In addition, their use is limited, particularly among elderly persons (> 70 years) (Zesiewicz 2002), due to the interactions with medications commonly used in these participantspatients (e.g. digoxin, calcium channel blockers and antiarrhythmics) (Hansten 2004). Anticonvulsants have been suggested as potentially useful agents for the treatment of ET and they are usually well tolerated (Pahwa 1998; Ondo 2000; Ondo 2006; Zesiewicz 2007).

Zonisamide is a sulphonamide derivative (1,2-benzisoxazole-3-methanesulphonamide). It has a number of different properties that contribute to its antiepileptic effect, including binding to the benzodiazepine gamma-aminobutyric acid (GABA) A receptor. It also has effects on voltage-gated sodium channel, T-type calcium channels, acts on excitatory glutaminergic transmission, and inhibits dopamine turnover and carbonic anhydrase activity. In addition, it has neuroprotective properties in some experimental models, due to its effect as a free radicals scavenger. Zonisamide is rapidly absorbed orally, with a bioavailability close to 100%. The time to peak blood levels is achieved in about two to six hours. It is metabolised by the cytochrome P450 system, and eliminated via renal mechanism (Shorvon 2000).

How the intervention might work

Although the biochemical pathophysiology of ET is still not well known, cellular hypersynchronicity is suspected to play a major role (Schnitzler 2009). In vitro pharmacological studies suggest that the zonisamide effect on sodium channels and voltage-dependent T-type calcium currents results in the stabilization of neuronal hypersynchronization (Leppik 2004). Moreover, in vitro studies have demonstrated that zonisamide binds the GABA receptor in an allosteric fashion, producing beneficial effects on tremor (Murata 2001; Nakanishi 2003).

Why it is important to do this review

In 2005 the American Academy of Neurology published the Practice Parameter for essential tremor (Zesiewicz 2005), basing the recommendation on an arbitrary four-tiered level of evidence scheme, and concluding that propranolol and primidone should be used as first-line therapy. Studies considering zonisamide were examined in the review update (Zesiewicz 2011), showing insufficient evidence to support or refute the use of this treatment for ET. Another recent work based on the use of the GRADE system for grading the quality of evidence and the strength of recommendations (Zappia 2013), considered zonisamide as a second-line treatment for ET, assigning a weak recommendation, with very low-quality evidence. As primidone or propranolol administration may be limited by the occurrence of serious adverse events and loss of efficacy after long-term treatment, it may be worthwhile evaluating treatment alternatives for ET. As there is uncertainty about the efficacy of zonisamide, a Cochrane Review to evaluate whether this agent could be an effective alternative for participants with ET (requiring additional drugs), may generate clinically useful information.

OBJECTIVES

The primary objective is to assess the effect on functional abilities and the safety profile of zonisamide compared to placebo or to other treatments in adults with essential tremor (ET). The secondary objective is to examine the effect on tremor severity and on quality of life of zonisamide compared to placebo or to other treatments in adults with ET

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), both parallel group and cross-over design.

Types of participants

Adults (aged 16 years or older) with essential tremor (ET) diagnosed according to the criteria proposed by the Tremor Investigation Group (Bain 2000a), the Consensus Statement of the Movement Disorder Society on Tremor (Deuschl 1998), or previous accepted and validated clinical criteria (Rajput 1984; Snow 1989; Haerer 1992; Salemi 1994; Chouinard 1997; Louis 1998).

We excluded from our review studies considering participants with any secondary forms of tremor (e.g. thyroid disease).

Types of interventions

Zonisamide for ET compared to: (1) placebo; (2) any other pharmacological treatment.

We did not exclude trials on the basis of dose or route of administration.

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Types of outcome measures

We excluded studies that reported only neurophysiological parameters (e.g. electromyographic recordings, accelerometry, spirography, digitising tablets) to assess outcomes. These instrumental tests have important limitations since their accuracy and reproducibility are not well established, and they have only a weak correlation with participants' functional disability (Bain 1997; Bain 2000b).

Primary outcomes

1. Functional abilities component related to tremor, measured by the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) subscales B and C at the end of follow-up (Fahn 1993).
2. Study withdrawal, defined in a standard manner, and number of adverse events (AEs) associated with treatment.
3. AEs: number and type

The TRS assesses rest, postural, and action tremor. The TRS total score is derived from the following three TRS subscales.

i. Examiner-reported upper limb postural and action tremor severity (amplitude); four elements.
ii. Examiner-reported ability to perform specific motor tasks (writing, drawing, and pouring with dominant and nondominant hands); nine elements.
iii. Patient-reported functional disabilities due to tremor (eating, speaking, drinking, hygiene, dressing, writing, working, and social activities); eight elements.

Each subscale element is rated from 0 to 4 (none to severe tremor) giving a maximum score of 16, 36, and 32 for each subscale. The overall TRS score is the sum of individual elements calculated as a fraction of the subscale's maximum score and converted to a 100-point scale (0 to 100).

We considered other validated scales to assess and measure tremor severity: the Unified Tremor Rating Scale (UTRA) (Findley 1995; Jankovic 1996); the Bain scale (Bain 1998); and the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) rating scale (Louis 2001b).

In order to analyse the main causes of study withdrawal, we grouped participant's reason for discontinuation using the following categories: adverse events; other reasons (including patient choice, lost to follow-up, noncompliance, and unknown reasons).

Secondary outcomes

1. Tremor severity, measured by:
   a. the Fahn-Tolosa-Marin TRS subscale A and total score;
   b. patient self-rated severity score: Patient Global Impression (PGI);
   c. clinician-rated global score: Clinical Global Impression (CGI).
2. Quality of life, measured by:
   a. validated quality of life scale or questionnaire: SF-36, EuroQoL.

Search methods for identification of studies

We carried out a systematic search without language restrictions to identify all relevant published and unpublished RCTs.

Electronic searches

We searched the following databases for relevant trials.

1. The Cochrane Central Register of Controlled Trials (CENTRAL: 2017, Issue 1) in the Cochrane Library (searched 30 January 2017).
2. MEDLINE (January 1966 to 30 January 2017).
3. Embase (January 1988 to 30 January 2017).
4. NICE (1999 to 30 January 2017).
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 30 January 2017).
6. WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en; searched 30 January 2017).

We additionally searched BIOSIS Citation Index (2000 to 30 January 2017) for conference proceedings.

We based the search strategies for each database on the strategy developed for MEDLINE, revising it appropriately for each database to take into account the differences in controlled vocabulary and syntax rules. See Appendix 1 and Appendix 2.

Searching other resources

In addition to the electronic searches, we:

1. screened reference lists of all available review articles and primary studies;
2. handsearched the references quoted in the recent abstract books of the European Federation of Neurological Societies (2005 to 2016), American Academy of Neurology (2003 to 2016), American Neurological Association (2006 to 2016), World Federation of Neurology (2008 to 2016), and of the Movement Disorder Society (2003 to 2016);
3. contacted the corresponding authors of relevant trials; and
4. contacted drug manufacturers for information on ongoing trials.

Data collection and analysis

Two review authors (EB and GQ) independently assessed the titles and abstracts of all the studies identified by the electronic searching or handsearching. We obtained the full text of potentially relevant trials.

Selection of studies

After reading the abstracts, EB and GQ independently selected the eligible articles and independently scrutinised the full texts of the selected studies and decided which trials met the inclusion criteria considered for this review. We resolved any disagreements concerning inclusion and exclusion of trials by discussion. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

EB and GQ independently used a data collection form to extract data about:

- trial design;
- randomisation methods;
- allocation concealment;
- blinding of treatments and assessments;

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- comparability of treatment groups in terms of demographic and clinical characteristics;
- inclusion and exclusion criteria;
- duration of treatment;
- length of follow-up;
- outcome measures (use of validated scales);
- number of withdrawals and respective causes; and
- description of adverse events.

We resolved disagreements on extracted data by discussion.

Assessment of risk of bias in included studies

The review authors independently judged trial quality according to the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We considered seven specific domains relating to:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting; and
- other sources of bias.

Two review authors (EB, GQ) independently assessed the risk of bias of each included studyand resolved disagreements by discussion to reach consensus. We based the overall assessment of risk of bias on recommendations reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we assessed one or more domains as having a high risk of bias, we rated the overall score as high. If we judged all domains as having a low RoB, we considered the overall score as low. We rated all the other combinations as unclear overall risk of bias.

We took the risk of bias in included studies into account in the interpretation of primary outcome results using the GRADE approach (Atkins 2004). We also examined consistency, directness, and precision to grade the quality of evidence according to GRADE guidelines (Atkins 2004). We rated overall quality of evidence as 'high', 'moderate', 'low', or 'very low'. Through the GRADE approach, we assigned RCTs an initial high rating that may be subsequently modified by the sequential judgement of limitations, inconsistency of the results, indirectness of the evidence, imprecision of data, and presence of publication bias. The primary outcomes we considered were functional abilities, number of study withdrawals, and number of adverse events. Two review authors (EB, GQ) independently graded the body of evidence using GRADE guidance and resolved discrepancies through discussion aimed at achieving consensus. We reported and summarised the results of this assessment using GRADEpro GDT and Summary of findings for the main comparison (GRADEpro GDT 2015).

Measures of treatment effect

We analysed measurement scales to assess ET as continuous variables. We calculated and expressed the intervention effect as mean differences (MDs) and standard deviations (SDs). We used changes from baseline for all continuous variables. We expressed dichotomous outcomes (number of study withdrawals and number of adverse events) as percentages and risk differences (RDs).

Unit of analysis issues

To avoid the 'carry-over' effect that can induce alteration of the response to subsequent treatment (Sibbald 1998), we considered only data from the first treatment phase after randomisationfor cross-over studies.

Dealing with missing data

In order to estimate the effect of participants' withdrawal or loss to follow-up on primary outcomes, we extracted available information about incomplete data and about the intention-to-treat analysis performed. We only included data for participants whose results were reported. We calculated the frequency of withdrawals for each treatment group. We considered the impact of missing data during the assessment of risk of bias.

Assessment of reporting biases

We did not assess potential reporting biases due to the single trial included in the present review. We a priori planned to assess reporting bias by visual interpretation of the funnel plots and testing for funnel plot asymmetry (Egger 1997).

Data synthesis

We checked data for normality. The check involved calculating the observed mean minus the lowest possible value of the outcome scale and dividing this by the SD (Deeks 2011). A ratio less than 2 suggests skew. If the ratio is less than 1 there is strong evidence of a skewed distribution. Since this rough check may not be appropriate for change from baseline measures, we have applied this method only for the means measured at baseline and at the end of the follow-up and reported in the included study. Within the different comparisons, we calculated MDs and SDs to assess efficacy. We calculated frequencies and percentages for withdrawals and adverse events. Provided that, for each comparison, an outcome of interest was reported by, at least, two included studies, we a priori planned to combine data in a meta-analysis without restrictions based on risk of bias. We used, in the presence of between-trial homogeneity, a fixed-effect model. In case of heterogeneity, we combined datausing a random-effects model. We used inverse variance methods for continuous outcomes and measurement scales. We compared the difference between treatment groups as MD. We planned to combine results for dichotomous outcomes (withdrawals, adverse events) using Mantel-Haenszel methods and obtained RDs to compare treatment groups. We used Review Manager 5 software for data management and analysis (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting subgroup analyses based on prespecified study characteristics. We a priori planned to investigate potential positive or negative interactions between zonisamide and other anti-tremor medications on primary outcomes, performing a subgroup analysis of trials in which only the experimental anti-tremor medication was allowed (zonisamide/placebo/other treatment), and of trials including participants using other concomitant anti-tremor medications during the study period. For trials in which treatment effects were reported for more than one dose, we planned to investigate the

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effect of the different doses reported separately. We assessed heterogeneity using the I^2 statistic (Higgins 2003).

Sensitivity analysis

We a priori planned to perform a sensitivity analysis to investigate the effect of inclusion or exclusion of studies at high risk of bias, by removing single trials at high risk of bias. We planned to use best- and worst-case scenarios for taking into account missing binary data

RESULTS

Description of studies

Results of the search

The electronic databases retrieved a total of 16 references; we excluded five because they were review articles, two because they included participants with Parkinson's disease or neuropsychiatric participants, one because it was performed on animal models, and another one because it was a case report of adverse events due to zonisamide treatment. We selected and obtained the full text of seven studies aimed at evaluating zonisamide treatment for essential tremor (ET). We did not identify any additional records as a result of searching other resources. A flowchart describes the results of the search in Figure 1.

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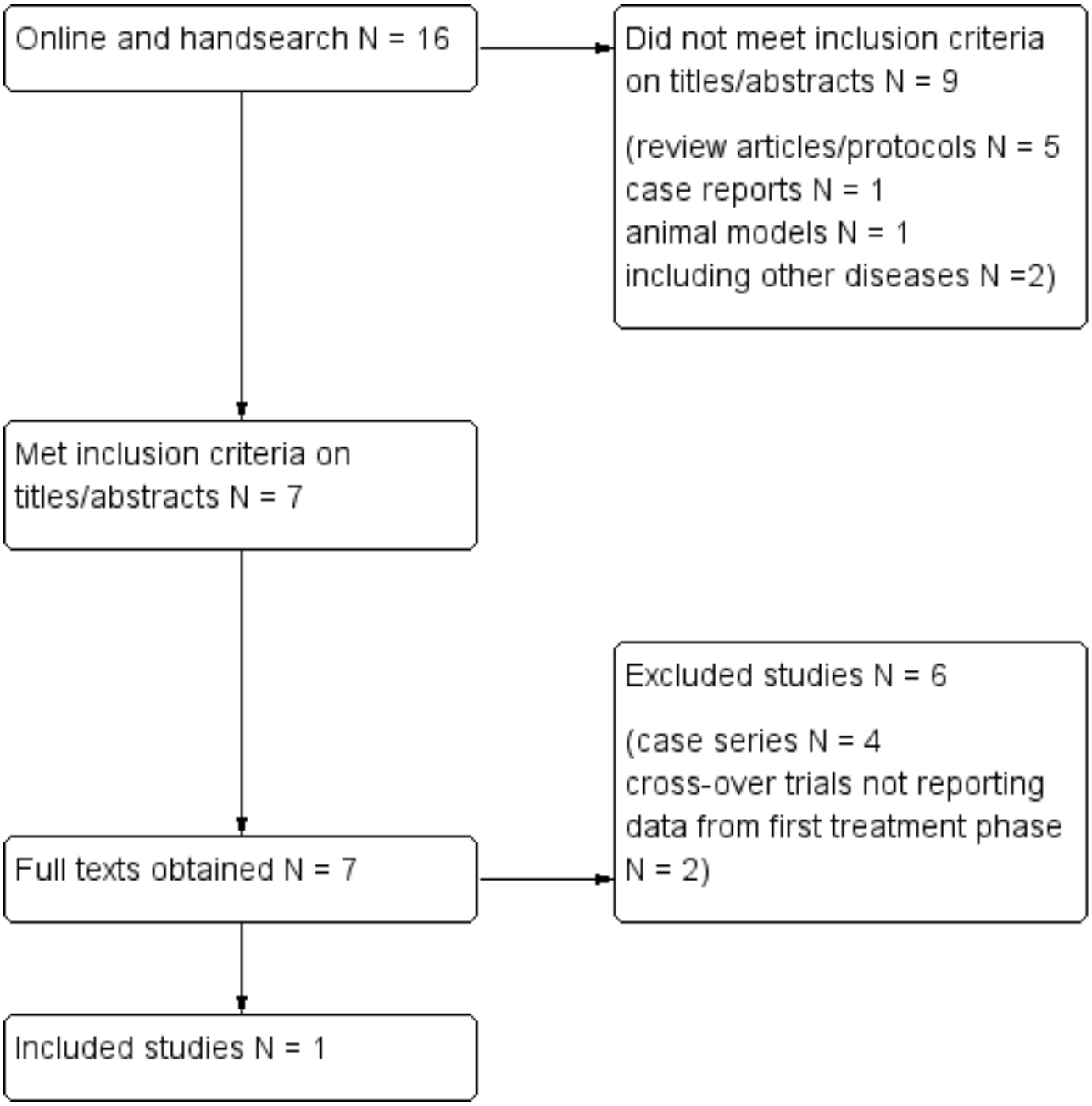
Figure 1. Flowchart of the literature search on zonisamide and essential tremor.



Included studies

We considered only one study as eligible for this review (Zesiewicz 2006).

Trail design

This study was a double-blind RCT. The study duration was 28 days.

Participants

The study included participants defined as having upper limb ET, according to criteria proposed by the Tremor Investigator Group (Bain 2000a). Moreover, the study included participants treated with a stable anti-tremor medication started at least 14 days before randomisation.The co-therapy was maintained throughout the study period. The mean age was 57.6 (standard deviation (SD) 15) years. Baseline Tremor Rating Scale (TRS) total score was 21 (SD 11.3) for the zonisamide group and 29.8 (SD 10.4) for the placebo group, with a disease duration of 7.4 (SD 3.3) years for zonisamide and 4.6 (SD 1.6) for the placebo group. Even if not statistically significant, the two arms showed differences in baseline characteristics, and participants treated with zonisamide had an 8-point lower TRS total score and 3-year longer disease duration. Participants with concomitant systemic disease (severe renal disease), other neurological diseases, psychiatric disorders, and history of alcohol or drug addiction were excluded. Moreover, participants who underwent botulinum toxin treatment for upper limb tremor, deep brain stimulation, other brain surgery, or

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zonisamide treatment 30 days prior to the study entry were excluded from the study.

Intervention

Zesiewicz 2006 included 20 ET participants randomly assigned to receive either zonisamide or placebo over a period of 28 days. Zonisamide treatment was initiated at a dosage of 100 mg/day, escalated to 200 mg/day after 14 days. The mean dose reached was 160 (SD 50) mg/day.

Outcome measures

The primary efficacy parameter used were the TRS scores. TRS total score and TRS part A, B and C scores at baseline and at the study endpoint were reported. A clinician-rated global assessment was reported (Clinical Global Impression (CGI)).

Adverse events

The number of participants experiencing adverse events and the number of those who were withdrawn/dropped out were reported in the study.

Studies awaiting classification

Two studies were listed as 'awaiting classification': Song 2008 was a randomised cross-over trial. Twelve ET participants, with isolated head tremor, received (in random order), zonisamide or propranolol for four weeks, with a two-week wash-out period between each treatment. Data from the first treatment phase after randomisation were not reported in the text, and so the study did not meet the inclusion criteria. We contacted the corresponding author of this paper in the attempt to obtain further information, but we are still waiting for a reply. Morita 2005 was an open-label, pilot cross-over study in which a group of 14 participants received zonisamide or arotinolol for two weeks in random order. Data from the first treatment phase after randomisation were not reported in the text, and so again, the study did not meet the inclusion criteria. We contacted the corresponding author of this paper in the attempt to obtain further information, but we are still waiting for a reply.

Excluded studies

We excluded four case series after reading the full texts (Bermejo 2007; Ondo 2007; Bermejo 2008; Handforth 2009).

Risk of bias in included studies

The results are reported in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

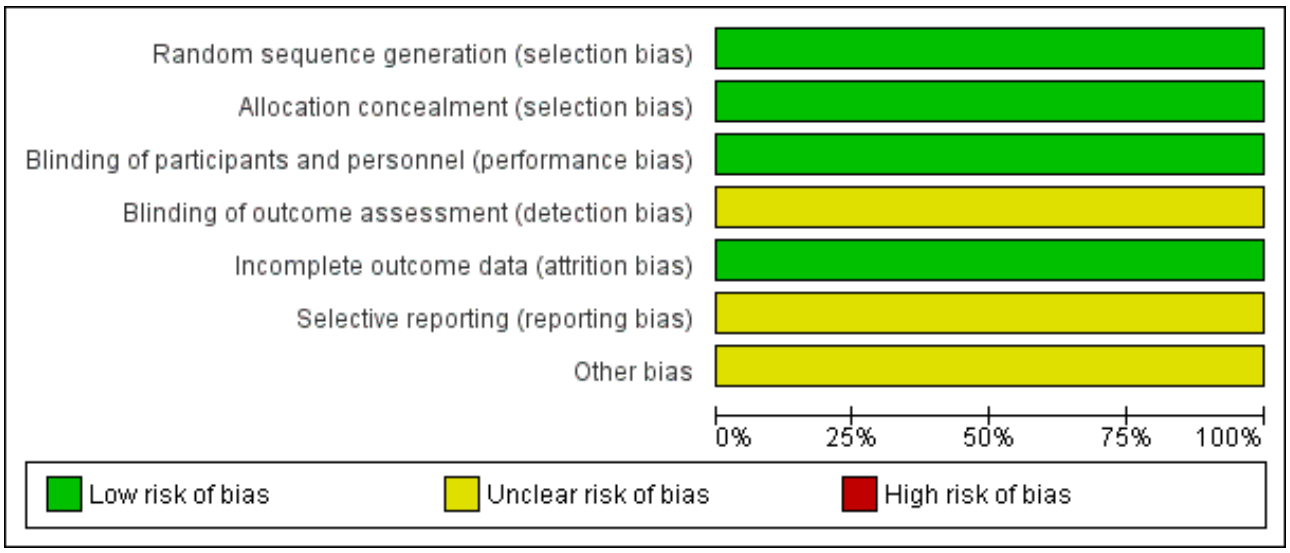

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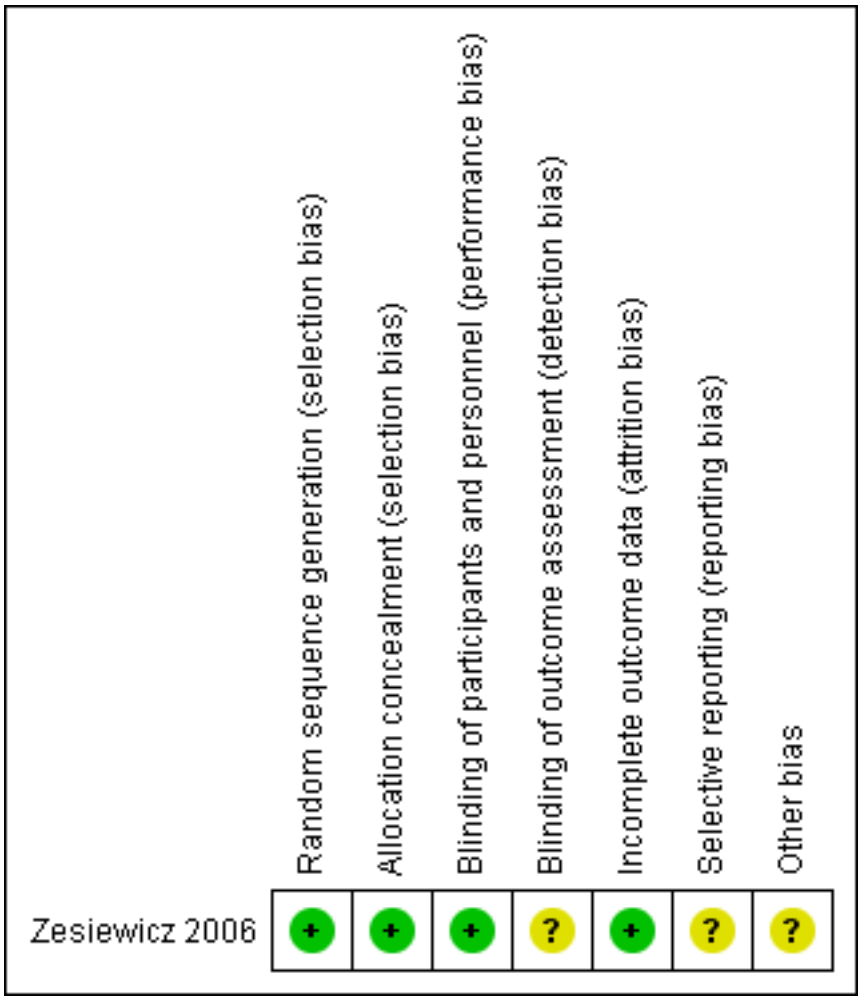
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The authors reported the use of a computer-generated randomisation schedule and the use of identical and numbered containers for drug supply. We considered the methods for sequence generation and allocation concealment at low risk of bias.

Blinding

The study was presented as double-blind. Methods for blinding personnel and participants were reported and we judged the risk of bias to be low. We have rated the study as unclear risk of detection bias as zonisamide participants may have become aware of treatment group assignment due to the occurrence of AEs in the treatment group.

Incomplete outcome data

Three of the ten randomised participants in the zonisamide group and two of the ten participants in the placebo group discontinued before study completion. Even if the number of withdrawals was balanced between the zonisamide and placebo groups, reasons for missing data were different, since more participants withdrew for adverse events in the zonisamide group.

Selective reporting

The secondary outcome (Clinical Global Impression CGI) was probably assessed in the placebo group but not reported. The missing comparison affects the interpretation of the meaning of CGI results of the treated group.

Other potential sources of bias

Other sources of bias were related to the low number of participants, to the short duration of follow-up, to the use of concomitant anti-tremor therapies during the study period, and to the method of adverse events' monitoring, probably based on spontaneous reporting. The participation and the role of potential sponsors or funders were not reported in the study. Thus, we judged the presence of 'other bias' as high.

Effects of interventions

See: **Summary of findings for the main comparison** Zonisamide versus placebo for essential tremor

See: Summary of findings for the main comparison, reporting the comparison 'zonisamide versus placebo for essential tremor' and GRADE assessment.

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The included study compared zonisamide and placebo, involving a total of 20 participants (10 zonisamide and 10 placebo). We rated the overall risk of bias as unclear. We considered the overall quality of evidence as very low.

We checked data for normality. For the zonisamide group, the result of the check was 1.9 (21.0 to 0)/11.3) for baseline Tremor Rating Scale (TRS) total score and 1.8 (15.7 to 0)/8.7) for study endpoint TRS total score, suggesting that data were probably not normally distributed, but roughly very close to a normal distribution. For the placebo group, the result of the check was 2.9 (29.8 to 0)/10.4) for baseline TRS total score and 2.6 (26.7 to 0)/10.3) for baseline TRS total score, indicating normally distributed data. We did not check data concerning TRS part A, TRS part B, and TRS part C scores for normality because they were reported as mean changes and raw data were not available.

We used a last observation carried forward (LOCF) method to analyse data for participants who prematurely withdrew from the study.

Primary outcomes

The functional abilities assessment and the number of adverse events and withdrawals were reported in the study.

Functional abilities

At the study endpoint (28 days), examiner-reported specific motor tasks function was reduced by 0.9 (standard deviation (SD) 1.4) points for zonisamide and by 0.9 (SD 2.0) for placebo; patient-reported functional disability was reduced by 0.6 (SD 1.2) for zonisamide and by 0.3 (SD 0.9) for placebo. Data analysis showed no statistically significant difference between zonisamide and placebo in terms of efficacy measured by TRS part B (mean difference (MD) 0.00, 95% confidence interval (CI) -1.51 to 1.51) (Analysis 1.1); and TRS part C (MD -0.30, 95% CI -1.23 to 0.63) (Analysis 1.2). We rated the quality of evidence as very low.

Study withdrawal

Three participants in the zonisamide group (30%) and two participants in the placebo group (20%) discontinued the treatment and withdrew from the study. A statistically non-significant increased risk of withdrawal was reported for zonisamide, with a risk difference (RD) of 0.1 (95% CI -0.28 to 0.48; very low quality evidence) (Analysis 2.1). The occurrence of adverse events represented the only reason for zonisamide discontinuation, whilst not otherwise specified "personal reasons" were related to placebo discontinuation (see Analysis 2.1).

Adverse events

Considering adverse events, the trial reported their occurrence, without specifying severity. Six participants in the zonisamide group (60%) and none of the participants in the placebo group (0%) developed adverse events, with a RD of 0.60 (95% CI 0.28 to 0.92; very low quality evidence) between the two groups (Analysis 2.2). The most common adverse events, experienced with zonisamide treatment, were headache, nausea, fatigue, sleepiness, and diarrhoea.

We did not perform a meta-analysis, since we included only one study. We did not perform a subgroup analysis to assess differences on efficacy and safety due to the interaction between combined anti-tremor treatments since there were not enough trials included.

Secondary outcomes

Tremor severity

At the study endpoint (28 days), a mean reduction from baseline of the overall TRS score of 5.3 (SD 3.9) points was reported for zonisamide, with 3.1 (SD 6.4) points for the placebo group. Examiner-reported upper limb tremor severity was reduced by 4.2 (SD 2.9) points for zonisamide and by 1.8 (SD 3.3) for placebo. Data analysis showed no statistically significant difference between zonisamide and placebo in terms of efficacy, measured with TRS total score (MD -2.20, 95% CI -6.85 to 2.45; Analysis 1.3) and TRS part A (MD -2.40, 95% CI -5.12 to 0.32; Analysis 1.4).

At the study endpoint, the Clinical Global Impression of Change (CGI-C) assessment indicated that six participants (60%) taking zonisamide considered their tremor "unchanged" compared to baseline, while two participants (20%) reported a "minimal improvement" of their tremor. Scores for participants belonging to the placebo group were not reported.

Quality of life

Quality of life was not assessed in the study included.

DISCUSSION

Summary of main results

One randomised controlled trial (RCT), comparing zonisamide with placebo for the treatment of essential tremor (ET), was included in this review. In this study, performed by Zesiewicz 2006, 20 participants were enrolled and randomised. After a follow-up of 28 days, no significant improvement in motor function or functional abilities were reported among ET participants treated with zonisamide compared to placebo. Moreover, a very high risk of adverse events was found for participants treated with zonisamide. Nevertheless, these data should be interpreted cautiously due to the scarce number of trials included, the high risk of bias, and the very low-quality of evidence provided. Moreover, the analysis presented, included data for which a normal distribution was not clearly demonstrated. This could have influenced the validity of the results obtained, further limiting the possibility to draw firm conclusions

Overall completeness and applicability of evidence

Important factors limited the validity of the results reported in the study. The two groups were not balanced at baseline, and the treated group presented with a likely milder disease than the placebo group. The sample size was very small and 30% of participants dropped out from the zonisamide group while taking the initial dose of 100 mg/day, without reaching the established maintenance dose (200 mg/day). Furthermore, the authors did not report the mean change in Tremor Rating Scale (TRS) scores of participants who prematurely withdrew from the study, applying a last observation carried forward (LOCF) analysis that, indeed, estimated the efficacy of a 'combined dosage' (100 mg and 200 mg) of zonisamide given for less than two weeks to 30% of participants. This could have led to an important alteration of the final assessment. Moreover, considering the lack of studies assessing the minimum efficacious dose of zonisamide for the treatment of

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ET, the dose chosen in this trial could have been inadequate. An additional factor that could have heavily influenced the efficacy measures is the presence of a large proportion of participants (50% in the zonisamide group, 30% in the placebo group) receiving other anti-tremor medications (propranolol, primidone, topiramate, clonazepam) during the study period. Furthermore, the analysis performed in the present review might be influenced by the presence of not normally distributed data among the treated group.

Despite being considered a recommended scale in the assessment of tremor severity (Elble 2013), the TRS scale has demonstrated limited inter-rater reliability, unless the raters have been rigorously trained (Stacy 2007). This could influence results and should especially be taken into account. Moreover, since TRS sensitivity in detecting relevant clinical changes in studies assessing ET therapies has not been evaluated, the clinical relevance of statistically significant changes in TRS scores is unclear.

Finally, two potentially relevant cross-over studies were not included in the analysis as they did not report data for the first phase of the trial (Morita 2005; Song 2008), and they are still awaiting classification. All these factors represent a limitation in the overall completeness of the assessment and hamper the ability to balance benefit and risk linked to zonisamide treatment.

Quality of the evidence

See Summary of findings for the main comparison. We judged the risk of bias to be unclear for detection bias and selective reporting. We downgraded the evidence one level for serious risk of bias, and two levels for very serious imprecision due to the small sample size and short duration of follow-up. Although participants and study personnel in the study were blinded, only participants belonging to the zonisamide group developed adverse events during the study period. This likely made treated participants aware of the treatment received. We judged the global quality of the evidence provided as very low and thus insufficient to provide adequate conclusions.

Potential biases in the review process

To identify all relevant studies minimising the risk of biases, we performed a comprehensive systematic review, searching different databases, without language restrictions. Two review authors performed data management.

Agreements and disagreements with other studies or reviews

There are two reviews of the literature analysing zonisamide treatment for ET (Zesiewicz 2011; Zappia 2013). The Practice Parameter for Essential Tremor gave to zonisamide a level U recommendation (Zesiewicz 2011), meaning uncertain efficacy, due to the inconclusive results of the studies identified. The systematic review of evidence and recommendations from the Italian Movement Disorders Association (DISMOV-SIN) assigned a weak recommendation with very low-quality of evidence (2D) for the use of zonisamide for ET participants (Zappia 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The impact of zonisamide on functional abilities, risk of treatment discontinuation, and adverse events in essential tremor (ET) is uncertain because the quality of evidence is very low. The limitations of the evidence relate to high or unclear risk of bias and the small amount of data available..

Implications for research

ET represents one of the most prevalent movement disorders. Nevertheless, its management still remains a challenge for a large percentage of participants who are often refractory to or intolerant of conventional therapies. This systematic review highlighted a paucity of well designed studies aimed at investigating the efficacy and safety of potential new drugs, such as zonisamide, as additional treatment options for ET. Randomised controlled trials (RCTs) with adequate methodology should be performed on larger samples of ET participants assessing long-term efficacy with appropriate duration of follow-up. The inclusion of participants using other concomitant anti-tremor treatment should be better controlled by stratifying this variable at randomisation and by performing adequate prespecified subgroup analysis. Moreover, considering the substantial impact of ET on participants' everyday life, adequate quality of life measures should always be considered as important outcomes to be assessed in trials.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Zesiewicz 2006

Methods	Double-blind, placebo controlled, parallel study.
Participants	20 participants; 10 randomised to zonisamide, 10 to placebo; mean age 57.6 (SD 12.8); male 50%; baseline TRS 25 (SD 10)
Interventions	Zonisamide versus placebo; 100 mg to 200 mg (titration 14 days); follow-up 28 days.
Outcomes	TRS total score and subscales (severity, motor tasks, and functional disability); CGI.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomization schedule".

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Zesiewicz 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured by the use of coded, identical containers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Zonisamide and placebo were supplied in identical containers that were marked with code numbers"; "both patients and staff were blind to randomization".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Both patients and staff were blind to randomization". We have rated the study as unclear risk of detection bias, because zonisamide participants may have become aware of treatment group assignment due to the occurrence of adverse events in the treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced number of withdrawals between the two groups; LOCF analysis unlikely to significantly affect tremor scores considering the short duration of follow-up.
Selective reporting (reporting bias)	Unclear risk	CGI-C evaluation probably assessed, but not reported for placebo group.
Other bias	Unclear risk	Participation and role of potential sponsors not reported.

CGI: Clinical Global Impression
CGI-C: Clinical Global Impression of Change
LOCF: last observation carried forward
SD: standard deviation
TRS: Tremor Rating Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bermejo 2007	Case-series.
Bermejo 2008	Case-series.
Handforth 2009	Case-series.
Ondo 2007	Case-series.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Morita 2005

Methods	Open, randomised, cross-over.
Participants	14 participants randomised to start either zonisamide or arotinolol treatment; mean age 68.4 years (SD 15.6); male 50%; baseline TRS 32.4 (SD 12.2).
Interventions	Zonisamide versus arotinolol; zonisamide 100 mg/day to 200 mg/day, arotinolol 10 mg/day to 20 mg/day; follow-up two weeks.
Outcomes	TRS total score and subscales (severity, motor tasks and functional disability).

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Morita 2005 *(Continued)*

Notes	

Song 2008

Methods	Randomised, cross-over.
Participants	12 participants with isolated head tremor, randomised to either zonisamide or propranolol for four weeks and switched to the other drug after a two-week wash-out period; mean age 72.3 (SD 3.65); female 100%; baseline TRS part A 3.75 (SD 1.54).
Interventions	Zonisamide versus propranol; zonisamide 100 mg/day to 200 mg/day, propranolol 40 mg/day to 160 mg/day; follow-up four weeks.
Outcomes	TRS part A.
Notes	

SD: standard deviation
TRS: Tremor Rating Scale

DATA AND ANALYSES

Comparison 1. Comparison for efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in TRS part B score between baseline and end of follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Change in TRS part C score between baseline and end of follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in TRS total score between baseline and end of follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Change in TRS part A score between baseline and end of follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Comparison for efficacy, Outcome 1 Change in TRS part B score between baseline and end of follow-up.

Study or subgroup	Zonisamide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Zesiewicz 2006	10	-0.9 (1.4)	10	-0.9 (2)		0[-1.51,1.51]

Zonisamide Placebo

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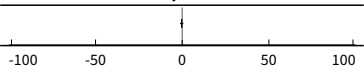
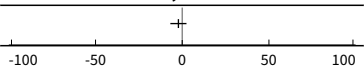
Analysis 1.2. Comparison 1 Comparison for efficacy, Outcome 2 Change in TRS part C score between baseline and end of follow-up.

Study or subgroup	Zonisamide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Zesiewicz 2006	10	-0.6 (1.2)	10	-0.3 (0.9)		-0.3[-1.23,0.63]



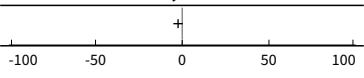
Analysis 1.3. Comparison 1 Comparison for efficacy, Outcome 3 Change in TRS total score between baseline and end of follow-up.

Study or subgroup	Zonisamide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Zesiewicz 2006	10	-5.3 (3.9)	10	-3.1 (6.4)		-2.2[-6.85,2.45]



Analysis 1.4. Comparison 1 Comparison for efficacy, Outcome 4 Change in TRS part A score between baseline and end of follow-up.

Study or subgroup	Zonisamide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Zesiewicz 2006	10	-4.2 (2.9)	10	-1.8 (3.3)		-2.4[-5.12,0.32]



Comparison 2. Comparison for safety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Study withdrawals	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.1 Number of study withdrawals	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adverse events	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Other reasons	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

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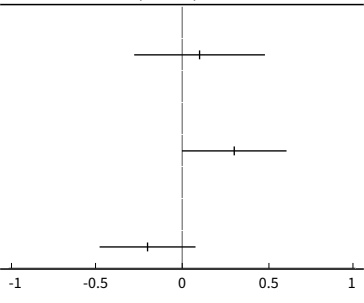
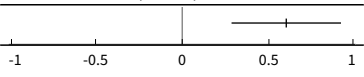
Analysis 2.1. Comparison 2 Comparison for safety, Outcome 1 Study withdrawals.

Study or subgroup	Experimental n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
2.1.1 Number of study withdrawals				
Zesiewicz 2006	3/10	2/10		0.1[-0.28,0.48]
2.1.2 Adverse events				
Zesiewicz 2006	3/10	0/10		0.3[-0,0.6]
2.1.3 Other reasons				
Zesiewicz 2006	0/10	2/10		-0.2[-0.48,0.08]



Analysis 2.2. Comparison 2 Comparison for safety, Outcome 2 Adverse events.

Study or subgroup	Zonisamide n/N	Placebo n/N	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Zesiewicz 2006	6/10	0/10		0.6[0.28,0.92]



APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE search strategy

1 exp Essential Tremor/ (1183)

2 (essential adj3 tremor*).ab,ti. (2473)

3 (familia* adj3 tremor*).ab,ti. (132)

4 1 or 2 or 3 (2654)

5 Zonisamide.mp. (1006)

6 Zonegran.mp. (15)

7 5 or 6

8 randomized controlled trial.pt. (367656)

9 controlled clinical trial.pt. (87895)

10 randomized.ab. (287683)

11 placebo.ab. (151722)

12 drug therapy.fs. (1677138)

13 randomly.ab. (208754)

14 trial.ab. (298006)

15 groups.ab. (1332158)

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16 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (3287589)

17 exp animals/ not humans.sh. (3903063)

18 16 not 17 (2818660)

19 4 and 7 and 18 (12)

Appendix 2. CENTRAL search strategy

1. MeSH descriptor: [Essential Tremor] explode all trees (62)

2. essential tremor*:ti,ab,kw (Word variations have been searched) (202)

3. familia* tremor*:ti,ab,kw (Word variations have been searched) (7)

4. #1 OR #2 OR #3 (208)

5. "zonisamide":ti,ab,kw (Word variations have been searched) (122)

6. "Zonegran":ti,ab,kw (Word variations have been searched) (5)

7. #5 OR #6 (123)

8. #4 AND #7 (4)

WHAT'S NEW

Date	Event	Description
14 August 2017	Amended	amended according to copy edit comments

HISTORY

Protocol first published: Issue 3, 2012
Review first published: Issue 8, 2017

Date	Event	Description
16 May 2017	Amended	amended according to CEU screening report
30 January 2017	Amended	amended version
19 October 2015	Amended	amended
18 October 2014	Amended	Amended according to the reviewer comments
3 March 2014	Amended	all the sections have been largely revised
7 July 2013	Amended	Review updated and completed
4 August 2011	Amended	revised version

CONTRIBUTIONS OF AUTHORS

EB: protocol and review editing, literature searching, study selection, quality assessment, data extraction.
AN: protocol and review editing.

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GQ: literature searching, quality assessment, data extraction.
CC: protocol editing, quality assessment, study selection.
GF: protocol editing, editing and revising the review.
MZ: protocol editing, revising review.

DECLARATIONS OF INTEREST

EB: none.
AN: none.
GQ: none.
CC: none.
GF: none.
MZ: none.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In an attempt to provide a standardised and reliable assessment of the quality of the evidence of the study outcomes, we decided to use the GRADE evidence profile, a systematic and explicit system for grading the evidence into four quality categories. We reported the results obtained through this approach in a 'Summary of findings' table.

Changes to the outcome measures

We prioritised the functional abilities component related to tremor as a primary outcome, and changed 'tremor severity' from a primary to a secondary outcome. We judged the assessment of changes in functional abilities to be a more relevant and clinically significant indicator of treatment efficacy for participants and decision makers as compared to the overall tremor severity score.

Data collection and analysis > measures of treatment effect

The protocol reported plans to analyse dichotomous outcomes using odds ratio. We modified this plan during the review and preferred the use of percentage and risk difference as it appeared that the calculation of the absolute effect was more informative to the scope of the review.

Methods > data synthesis

Analyses based on means are appropriate for data that are at least approximately normally distributed, and for data from very large trials. As the trial included in the current review has a small sample size, we considered the addition of a method to check for skewed data as appropriate and implemented it in the review.

Methods for future updates

We did not perform two pre-planned analyses due to insufficient data. We will eventually implement them, if possible, in future updates of the review.

Methods for analysing continuous data: the scales used to assess tremor in the majority of the studies are continuous. We will transform ordinal scales with enough categories to continuous scales by assigning a score to each grade so that we can express the intervention effect as a difference in means or as a standardised mean difference (SMD). In the case of an ordinal scale with few categories, we will combine data from adjacent categories into two categories, and use methods for binary data as odds ratios (ORs) or risk differences (RDs) to evaluate the intervention effect.

Sensitivity analysis: we will undertake sensitivity analyses to assess the robustness of results to fixed-effect versus random-effects assumptions, and the inclusion or exclusion of studies at high risk of bias (i.e. inadequate allocation concealment and lack of blinded outcome assessor). We will use best- and worst-case scenarios for taking into account missing data.

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INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Essential Tremor [*drug therapy]; Isoxazoles [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Zonisamide

MeSH check words

Humans

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