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Zonisamide add-on therapy for focal epilepsy (Review)

Brigo F, Lattanzi S, Igwe SC, Behzadifar M, Bragazzi NL

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1	9
Figure 2.	11
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	16
CHARACTERISTICS OF STUDIES	18
DATA AND ANALYSES	30
Analysis 1.1. Comparison 1 Zonisamide versus placebo, Outcome 1 50% responder rate - whole treatment period	31
Analysis 1.2. Comparison 1 Zonisamide versus placebo, Outcome 2 50% responder rate - best-case scenario	32
Analysis 1.3. Comparison 1 Zonisamide versus placebo, Outcome 3 50% responder rate - worst-case scenario	32
Analysis 1.4. Comparison 1 Zonisamide versus placebo, Outcome 4 50% responder rate - dose-effect for Brodie 2005	33
Analysis 1.5. Comparison 1 Zonisamide versus placebo, Outcome 5 50% responder rate - dose effect for Faught 2001	33
Analysis 1.6. Comparison 1 Zonisamide versus placebo, Outcome 6 Withdrawal rates.	33
Analysis 1.7. Comparison 1 Zonisamide versus placebo, Outcome 7 Adverse effects.	34
APPENDICES	36
WHAT'S NEW	37
HISTORY	38
CONTRIBUTIONS OF AUTHORS	38
DECLARATIONS OF INTEREST	38
SOURCES OF SUPPORT	38
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	38
INDEX TERMS	39



[Intervention Review]

Zonisamide add-on therapy for focal epilepsy

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ABSTRACT

Background

The majority of people with epilepsy have a good prognosis, and their seizures can be well controlled with the use of a single antiepileptic agent, but up to 30% develop refractory epilepsy, especially those with focal seizures. In this review, we summarised the evidence from randomised controlled trials (RCT) of zonisamide, used as an add-on treatment for focal epilepsy uncontrolled by one or more concomitant antiepileptic drug. This is an updated version of the Cochrane review previously published in 2013.

Objectives

To evaluate the efficacy and tolerability of zonisamide, when used as an add-on treatment for people with focal epilepsy uncontrolled by one or more concomitant antiepileptic drugs.

Search methods

For this update, on 4 September 2017, we searched the Cochrane Epilepsy Group Specialised Register, Cochrane Register of Studies Online, MEDLINE Ovid, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform ICTRP. We searched SCOPUS on 13 February 2013, but this is no longer necessary, because RCTs and quasi-RCTs in Embase are now included in CENTRAL. In addition, we contacted Eisai Limited (makers and licensees of zonisamide) and experts in the field to seek any ongoing or unpublished studies.

Selection criteria

Randomised controlled trials, in which add-on zonisamide was compared with placebo or another antiepileptic drug in people with focal epilepsy, uncontrolled by one or more concomitant antiepileptic drugs.

Data collection and analysis

Two review authors independently selected trials for inclusion, extracted data, assessed for risk of bias using the Cochrane 'Risk of bias' tool, and assessed the quality of the evidence, using the GRADE approach. The primary outcome was at least a 50% reduction in total seizure frequency; the secondary outcomes were (1) tolerability; and (2) adverse effects. We used an intention-to-treat approach for our primary analyses. We estimated summary risk ratios (RRs) for each outcome. We displayed a summary of the estimates of effects and quality of the evidence for each outcome in a 'Summary of findings' table.

Main results

We included eight studies (1636 participants). The overall RR with 95% confidence interval (CI) for at least a 50% reduction in seizure frequency compared to placebo for 300 mg to 500 mg/day of zonisamide was 1.90 (95% CI 1.63 to 2.22; 7 trials, 1371 participants; moderate-

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quality evidence). The RR for 50% reduction in seizure frequency compared to placebo for any dose of zonisamide (100 mg to 500 mg/ day) was 1.86 (95% CI 1.60 to 2.17; 7 trials, 1429 participants; moderate-quality evidence). The number needed to treat for an additional beneficial outcome was six (95% CI 4.1 to 6.8) for this outcome. Two trials provided evidence of a dose-response relationship for this outcome. The RR for treatment withdrawal for 300 mg to 500 mg/day of zonisamide compared to placebo was 1.59 (95% CI 1.18 to 2.13; 6 trials, 1099 participants; moderate-quality evidence), and for 100 mg to 500 mg/day was 1.44 (95% CI 1.08 to 1.93; 6 trials, 1156 participants; moderate-quality evidence). The number needed to treat for an additional harmful outcome was 15 (95% CI 9.3 to 36.7). The CIs of the following adverse effects indicated that they were significantly associated with zonisamide: ataxia RR 3.85 (99% CI 1.36 to 10.93; 4 trials, 734 participants; low-quality evidence); somnolence RR 1.52 (99% CI 1.00 to 2.31; 8 trials, 1636 participants; moderate-quality evidence); agitation RR 2.35 (99% CI 1.05 to 5.27; 4 trials, 598 participants; low-quality evidence); and anorexia RR 2.74 (99% CI 1.64 to 4.60; 6 trials, 1181 participants; low-quality evidence).

Across the eight studies, we rated risk of bias domains at low or unclear risk of bias apart from two studies which we rated at high risk of attrition bias. Five of the eight studies were sponsored by the drug companies that produced zonisamide.

Authors' conclusions

When used as an add-on treatment in people with focal epilepsy uncontrolled by one or more concomitant antiepileptic drugs, moderatequality evidence found that zonisamide was more successful than placebo at reducing the frequency of seizures by at least 50%. We were unable to identify minimum effective and maximum tolerated doses. The included trials evaluated a maximum stable-dose phase of 18 weeks, so results cannot be used to confirm longer periods of efficacy in seizure control. The results cannot be extrapolated to monotherapy or to people with other seizure types or epilepsy syndromes.

PLAIN LANGUAGE SUMMARY

Zonisamide add-on for focal epilepsy that does not respond to other medication

Background

Around 70% of patients with epilepsy can become seizure-free with antiepileptic drug treatment. The remaining 30% of people with epilepsy may not respond to antiepileptic drugs, and may still experience seizures. Older drugs do not prevent seizures for everyone, and they have adverse effects. New drugs have been developed to try to treat people who do not respond to the older drugs, and to try to limit the adverse effects. These newer drugs may be taken along with the patient's existing medication, as an 'add-on' treatment.

Key results

Searches of six databases found eight randomised controlled trials (1636 participants), which compared the addition of the antiepileptic drug zonisamide to one or more antiepileptic drugs to a placebo, for a period of 12 weeks, in people with uncontrolled focal epilepsy.

Taking all the evidence of the trials into account, we found that seizure frequency was significantly reduced for people with focal epilepsy if zonisamide was added to their usual treatment. Participants treated with 300 mg to 500 mg/day of zonisamide were twice as likely as people given placebo tablets in addition to their usual treatment, to experience at least a 50% reduction in the frequency of their seizures. However, adding zonisamide to their usual treatment was associated with an increase in adverse effects, such as problems with co-ordination (ataxia), drowsiness (somnolence), agitation, and anorexia.

Quality of the evidence

We assessed that the risk of bias within the individual trials was low, or we did not have enough information to decide. Five of the eight studies were sponsored by the drug companies that produce zonisamide. We rated the quality of the evidence for the main outcomes as moderate. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. More research is needed that concentrates on examining the response of different doses of zonisamide.

The evidence is current to September 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Zonisamide compared to placebo for focal epilepsy

Zonisamide compared to placebo for focal epilepsy

Patient or population: patients with focal epilepsy Setting: hospital outpatients

Intervention: add-on zonisamide

Comparison: placebo

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Outcomes	Anticipated absolute effects [*] (95% CI)		Relative effect	№ of partici-	Certainty of	Comments
	Risk with placebo	Risk with Zonisamide		(studies)	(GRADE)	
50% responder rate	Study populatio	n	RR 1.86	1429 (7 RCTs)	ΦΦΦΘ Μορερατε 1	Relative effect for 300 mg to 500 mg/day
period - Any dose	248 per 1.000	461 per 1.000 (396 to 537)	(1.60 to 2.17)	(TRCTS)	MODERATE 1	2.22; moderate-quality evidence)
Withdrawal rates -	Study populatio	n	RR 1.44	1156 (6 RCTs)	⊕⊕⊕⊝ MODERATE ¹	RR for treatment withdrawal for 300 mg to 500 mg/day of zonisamide compared to placebo was 1.59 (95% CI 1.18 to 2.13; mod- erate-quality evidence)
Any dose	110 per 1.000	159 per 1.000 (119 to 213)	— (1.08 to 1.93)			
Adverse effects -	Study population		RR 3.85	734 (4 PCTc)		Note that for adverse events, we used a 99%
Ataxia	17 per 1.000	67 per 1.000 (24 to 189)	(1.50 to 10.55)	(4 1013)	100 12	CI.
Adverse effects -	Study population		RR 1.40	1429 (7 RCTs)		Note that for adverse events, we used a 99%
Dizziness	75 per 1.000	105 per 1.000 (68 to 164)	(0.90 to 2.18)	(7 KC13)	MODERATE	CI.
Adverse effects -	Study populatio	n	RR 1.41	1045 (C.D.C.T.c.)		Note that for adverse events, we used a 99%
Taugue	54 per 1.000	76 per 1.000 (43 to 137)	(0.19 to 2.55)	(0 ((013)	MODERATE	CI.
Adverse effects -	Study populatio	n	RR 1.10	805 (5 BCTs)		Note that for adverse events, we used a 99%
Nausea	66 per 1.000	73 per 1.000	(0.50 to 2.10)		MODERATE	01.

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			(38 to 139)				
:	Adverse effects -	Study population	ı	RR 1.52	1636 (8 BCTs)		Note that for adverse events, we used a 99%
:	Sommonchee	72 per 1.000	109 per 1.000 (72 to 166)	(1.00 to 2.51)	(01(013)	MODERATE	UI.

*The **assumed control risk** (ACR) was calculated using median control group risk across the studies that provided data for that outcome.. The **corresponding intervention risk** in the zonisamide group (and its 95% CI) was based on the assumed risk in the comparison group (ACR) and the **relative effect** of the intervention (and its 95% CI) and is calculated according to following formula: corresponding intervention risk, per 100 = 100 * ACR * RR.

Cl: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Downgraded once for methodological uncertainties in included studies (unclear risk of bias).

Some studies were at high risk of attrition bias; they did not provide reasons for differences in the number of patients in ITT and in per protocol set (PPS). However, the conclusions were unchanged following best-case (RR 2.22, 95% CI 1.92 to 2.57) and worst-case (RR 1.44, 95% CI 1.26 to 1.64) scenario analysis.

²Downgraded once for imprecision

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BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews, 'Zonisamide for drug-resistant partial epilepsy' (Carmichael 2013).

Standard antiepileptic drugs (AEDs; e.g. carbamazepine, phenytoin, valproate) cause a number of side effects, and do not control all patients' seizures. Therefore, over the past 15 to 20 years, there has been renewed interest in the development of new AEDs. Several new AEDs are now licensed for use in a variety of countries as an 'add-on' treatment: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide, eslicarbazepine acetate, perampanel, and brivaracetam.

In this review, we investigated the efficacy and tolerability of addon zonisamide in people with focal epilepsy, uncontrolled by one or more concomitant antiepileptic drugs. We included people with focal epilepsy (defined as having focal onset seizures, i.e. simple focal, complex focal, secondary generalised tonic-clonic seizures, or a combination), which had failed to respond to monotherapy with a standard AED.

Description of the condition

Epilepsy is a common neurological condition, with an estimated incidence of 50 per 100,000 and prevalence of 5 to 10 per 1000 in the developed world (Sander 1996). Between two and three per cent of the population will be given a diagnosis of epilepsy at some time in their lives, the majority of whom will go into remission. However, up to 30% will fail to respond to monotherapy, often requiring treatment with combinations of AEDs (Cockerell 1995; Hauser 1993). These individuals will often experience significant adverse psychological and quality of life outcomes, due to continued and unpredictable seizures, side effects of drugs, and reduced educational and employment prospects.

Description of the intervention

In the majority of cases, epilepsy is treated with AEDs. These AEDs have varying mechanisms of action, and certain AEDs are more effective at treating specific seizure types. For example, carbamazepine is more effective for focal seizures (Marson 2000), and valproate is more effective for generalised onset seizures (Marson 2007). Conventional first-line drugs include carbamazepine, lamotrigine, and sodium valproate, which have a broad therapeutic effect, but are associated with a number of adverse effects. In cases where monotherapy fails to induce seizure remission, AED 'add-on therapy' may be used in an attempt to improve seizure control. Zonisamide is one such add-on therapy. Zonisamide is a synthetic 1,2-benzisoxazole-3methanesulfonamide with anticonvulsant properties (Sackellares 2004). Zonisamide has a long half-life (63 to 69 hours), and the typical maintenance dose in adults over the age of 18 is 300 mg to 500 mg/day, possibly split into two doses per day (Baulac 2007; BNF 2013).

How the intervention might work

Proposed neuropharmacological mechanisms of action for zonisamide include the blockade of voltage-sensitive sodium channels, voltage-dependent T-type calcium channels, and potassium-evoked glutamate response, reduced glutamatemediated synaptic excitation, and increased synaptic concentration of gamma-aminobutyric acid (GABA; Leppik 2004; Ueda 2003). It has been proposed that zonisamide might help patients who are resistant to other AEDs, because it blocks both voltage-sensitive sodium and T-type calcium channels (Leppik 2004). Although zonisamide does not induce liver enzymes, it is metabolised by cytochrome P450. Therefore, concomitant AEDs, which are liver enzyme-inducing, will enhance zonisamide metabolism, so the zonisamide dosage strategy may need to be adjusted to compensate for the effect of other AEDs (Leppik 2004). By scavenging hydroxyl and nitric oxide free radicals, zonisamide may also be neuroprotective (Mori 1998).

Why it is important to do this review

While the majority of people with epilepsy do respond to AEDs, a treatment solution needs to be found for the 30% who do not. This review update is aimed to inform clinical practitioners of the efficacy and tolerability of zonisamide, when used as add-on therapy to treat patients with focal epilepsy who were experiencing seizures, despite the use of one or more concomitant antiepileptic drugs.

OBJECTIVES

To evaluate the efficacy and tolerability of zonisamide, when used as an add-on treatment for people with focal epilepsy, uncontrolled by one or more concomitant antiepileptic drug.

METHODS

Criteria for considering studies for this review

Types of studies

- 1. Randomised controlled trials (RCT), in which an adequate method of concealment of randomisation was used (e.g. allocation of sequentially numbered, sealed packages of medication, sealed opaque envelopes, telephone randomisation).
- 2. Double-blind trials, in which both participant and clinician treating or assessing the outcome, were blinded to treatment allocation.
- 3. Placebo-controlled or head-to-head drug trials where zonisamide was compared directly to another add-on AED.
- 4. Parallel-group or cross-over studies.
- 5. Minimum treatment period of eight weeks. This period was selected as it represents the minimum time over which changes in seizure frequency can be determined, given the propensity of seizures to occur in clusters.
- 6. Studies using a response conditional design would have been excluded, however none were found. In this type of study, participants are given active treatment during a prerandomisation baseline period, and only those having a predefined response to treatment are allocated to treatment groups. We decided to exclude this type of trial as they are really evaluating the effect of drug withdrawal in a highly selected population of individuals. In addition, there is no drug-free baseline from which a reduction in seizure frequency can be calculated.

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Types of participants

Participants of any age with focal epilepsy (i.e. experiencing simple focal, complex focal, or secondary generalised tonic-clonic seizures), uncontrolled by one or more concomitant antiepileptic drug.

Types of interventions

- 1. The active treatment group received treatment with zonisamide in addition to conventional AED treatment.
- 2. The control group received matched placebo in addition to conventional AED treatment.

Types of outcome measures

Primary outcomes

1. Efficacy

Proportion of participants with a 50% or greater reduction in seizure frequency in the treatment period compared to the prerandomisation baseline period. We chose this outcome 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.

Secondary outcomes

2. Tolerability

The proportion of participants who withdrew from treatment during the course of the treatment period was used as a measure of global tolerability. 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 participants can make a direct contribution. In trials of short duration, it is likely that adverse effects will be the most common reason for withdrawal.

3. Adverse effects

- The proportion of participants experiencing any of the following five adverse effects, which were found, through research, to be common and important adverse effects of AEDs:
 - ataxia;
 - dizziness;
 - * fatigue;
 - nausea;
 - * somnolence.
- The proportion of participants experiencing the five most common adverse effects, if different from those listed above.

Search methods for identification of studies

Electronic searches

We ran searches for the original review in December 1999. We ran subsequent searches in December 2001, March 2003, August 2005, July 2007, June 2010, February 2011, August 2012, February 2013, January 2016, and September 2017. For the latest update, we searched the following databases, with no language restrictions.

- Cochrane Epilepsy Group Specialised Register (searched 4 September 2017), using the search strategy outlined in Appendix 1
- 2. The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO; searched 4

September 2017), using the search strategy outlined in Appendix 2.

- 3. MEDLINE Ovid (1946 to 4 September 2017), using the search strategy outlined in Appendix 3.
- 4. ClinicalTrials.gov (searched 4 September 2017), using the search strategy outlined in Appendix 4.
- 5. WHO International Clinical Trials Registry Platform ICTRP (searched 4 September 2017), using the search strategy outlined in Appendix 5.

We also searched SCOPUS on 13 February 2013, using the search strategy outlined in Appendix 6, but this is no longer necessary, because RCTs and quasi-RCTs in Embase are now included in CENTRAL.

Searching other resources

We contacted Eisai Limited (makers and licensees of zonisamide) and experts in the field, to seek any ongoing or unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (Francesco Brigo and Simona Lattanzi) independently assessed trials for inclusion. They resolved any disagreement through discussion.

The same two review authors extracted the following information from included trials; they resolved disagreements by consulting a third author (Nicola Luigi Bragazzi).

Data extraction and management

We extracted the following information for each trial, using a data extraction sheet.

Methodological and trial design

- 1. Method of randomisation and allocation concealment
- 2. Method of blinding
- 3. Whether any participants had been excluded from reported analyses
- 4. Duration of baseline period
- 5. Duration of treatment period
- 6. Dose(s) of zonisamide tested

Participant and demographic information

- 1. Total number of participants allocated to each treatment group
- 2. Age, sex
- 3. Number with focal, generalised epilepsy
- 4. Seizure types
- 5. Seizure frequency during the baseline period
- 6. Number of background drugs

Four of the five studies found for Carmichael 2013 had been sponsored by Eisai (no source of funding was used to assist in the conduct of the Lu 2011 trial). They supplied copies of internal trial reports, which we used to confirm 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 postrandomisation 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% or greater reduction in seizure frequency during the treatment phase.

Outcomes

We recorded the number of participants experiencing each outcome (see Types of outcome measures) per randomised group.

Assessment of risk of bias in included studies

Two review authors (Francesco Brigo and Simona Lattanzi) independently assessed risk of bias for each of the eight included trials using the Cochrane 'Risk of bias' tool, found in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third party resolved disagreements in the assessment of the level of bias. We extracted data from the eight included studies relating to sequence generation, concealment of allocation, methods of blinding, incomplete outcome data, selective reporting, and other types of bias. We made a judgement of the level of bias involved for each of these categories for all included studies.

Measures of treatment effect

We presented the outcomes 50% or greater reduction in seizure frequency, treatment withdrawal, and adverse effects as risk ratios (RR).

Unit of analysis issues

There were no special issues to consider with the design of the included studies. All included studies used a parallel design, six with a stable-dose phase of 12 weeks (Brodie 2005; Faught 2001; Guerrini 2013; Sackellares 2004; Schmidt 1993; Wu 2010), one with a stable-phase of 13 weeks (Zhang 2011), and one with a stable-dose phase of 18 weeks (Lu 2011).

Dealing with missing data

We conducted intention-to-treat, best-case, and worst-case analyses to account for any missing data.

Assessment of heterogeneity

We assessed clinical heterogeneity by evaluating similarities of the participants and interventions, as well as the outcomes measured in the included studies and assessed methodological heterogeneity by evaluating variability in study design and risk of bias. Statistical heterogeneity was evaluated by visually inspecting forest plots. Furthermore, we assessed statistical heterogeneity using the Chi² test and I² statistic, according to section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% indicating considerable heterogeneity. Our intention was to use a fixed-effect model if we did not find statistically significant heterogeneity between the included studies. If statistical heterogeneity had been present, we would have used a random-effects model.

Assessment of reporting biases

We contacted authors of all included studies and requested trial protocols in order to identify any discrepancies between protocol and trial methodology.

Data synthesis

We used a fixed-effect meta-analysis to synthesise the collected data. Planned comparisons and outcomes included:

- 1. 50% or greater reduction in seizure frequency in the intervention group versus the control group;
- 2. treatment withdrawal rates in the intervention group versus the control group;
- 3. adverse effects in the intervention group versus the control group.

The preferred estimator was the Mantel-Haenszel risk ratio (RR). We used 95% confidence intervals (CIs) for 50% or greater reduction in seizure frequency and treatment withdrawal outcomes. We used a 99% CI for the adverse effects outcomes. All analyses included all participants in the groups to which they had been allocated.

For the 50% or greater reduction in seizure frequency and for the tolerability outcomes, we computed the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), according to methods reported in (Schünemann 2011).

For the 50% or greater reduction in seizure frequency outcome, we conducted three analyses:

(1) Primary analysis (intention-to-treat)

Participants not completing follow-up, or with inadequate seizure data, were assumed to be non-responders.

(2) Worst-case analysis

Participants not completing follow-up, or with inadequate seizure data, were assumed to be non-responders in the zonisamide group and responders in the control group. The worst-case scenario assumes missing participants in the control group had good outcomes and those in the experimental group had bad outcomes (Higgins 2008).

(3) Best-case analysis

Participants not completing follow-up, or with inadequate seizure data, were assumed to be responders in the zonisamide group and non-responders in the control group. The best-case scenario assumes missing participants in the experimental group had good outcomes and those in the control group had bad outcomes (Higgins 2008).

Dose-regression analysis

We had planned to examine dose-response relationships using logistic regression, in the framework of generalised linear models (McCullagh 1989). The structure of the data in the trials did not

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allow this approach. Hence, we simply provided the results for each dose compared to control.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analysis for adverse effects data and produced risk ratios for each different adverse effect. We also conducted subgroup analysis for mg/day dose of zonisamide.

If we had found trial methodologies to be sufficiently distinct, we would have conducted sensitivity analyses to identify which factor(s) were influential in the degree of heterogeneity.

Summary of Findings and Quality of the Evidence (GRADE)

We used the GRADE approach, as outlined in the GRADE Handbook, to assess the quality of evidence for the primary and secondary outcomes (Schünemann 2013). More specifically, we included data on the following outcomes: 50% responder rate (whole treatment period); withdrawal rates (any dose); ataxia; dizziness; fatigue; nausea; and somnolence.

We presented this information in a 'Summary of findings' table (see Summary of findings for the main comparison).

RESULTS

Description of studies

Results of the search

Our searches identified 438 records from the Cochrane Epilepsy Group Specialised Register, CENTRAL, MEDLINE, SCOPUS, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform ICTRP. We removed 139 duplicate records and screened the remaining 299 records for suitability. We excluded 287 records after initial screening, and assessed the full text of the remaining 12 records in order to ascertain eligibility, based on the extent to which the records met the inclusion criteria. Eight records was deemed ineligible and was excluded from this review (see Figure 1). A full report for a further study was unobtainable, so it was identified as awaiting classification (Anderson 1988). Two unpublished studies were found; however, a full report of them was not available, so both were identified as awaiting classification (NCT00327717; NCT01546688).



Figure 1. Study flow diagram



Included studies

The eight included studies (1636 participants) were parallel-group trials with a stable-dose phase of 12 or 18 weeks (although Faught 2001 added a cross-over phase for all participants in the final five weeks, only the parallel group data were included in analysis). Two studies allowed some dose titration according to seizure response and tolerability (Sackellares 2004; Schmidt 1993). In both studies, the median daily dose for participants completing the study was 400 mg. A third study titrated to 400 mg/day, but participants randomised to zonisamide followed different rates of titration during the first five weeks of the study, which allowed some comparison to placebo, 100 mg/day, and 200 mg/day during this period of the study (Faught 2001). In the fourth study, participants

were randomised to placebo, 100 mg, 300 mg, or 500 mg of zonisamide in a 2:1:1:2 ratio, allowing further investigation of dose-response relationships (Brodie 2005). In the fifth study, two different titration strategies were used; in the first, a 100 mg/day zonisamide dose was given for the first two weeks after baseline, 200 mg/day for the third week, and 300 mg/day from week four onwards (Lu 2011). The initial dose in the second strategy was 100 mg/day of zonisamide, increasing weekly by increments of 100 mg/ day until a target of 400 mg/day was reached in week four, and continued for the duration of the trial. In the sixth study, zonisamide was titrated in weekly increments of 1 mg/kg/day over eight weeks to a target dose of 8 mg/kg/day (max 500 mg/day), and continued unchanged over the 12-week maintenance period (Guerrini 2013).

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In the seventh study, zonisamide was titrated as follows: first two weeks 100 mg/day, third week 200 mg/day, forth week 300 mg/ day, which was maintained to the end, although, according to the patient's situation, doses could be increased to 400mg/day (Wu 2010). In the last study, zonisamide was started at 100 mg/day, and then increased to 300 mg/day (100 mg, three times a day) within three weeks; the dose during maintenance was 300 mg/day (Zhang 2011).

See Characteristics of included studies for full details of the included studies.

Excluded studies

Shimizu 1988 was excluded as no control group was used (see Characteristics of excluded studies).

Studies awaiting classification

One add-on study compared zonisamide with valproate rather than placebo in a head-to-head trial, which met the inclusion criteria (Anderson 1988). However, only a single-page summary was available, which gave too little information on methods or outcome data. Two further studies compared add-on zonisamide with placebo; however, a full report of these studies was not available (NCT00327717; NCT01546688). Therefore, we are currently unable to include information from these trials in the review (see Characteristics of studies awaiting classification).

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias in the included studies.





Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

Allocation

In three studies, allocation was concealed by dispensing sequentially numbered packages to each participant (Faught 2001; Sackellares 2004; Schmidt 1993), whilst Brodie 2005 used

a telephone randomisation service. In two studies, participants were assigned to groups in blocks of six and four respectively (Brodie 2005; Schmidt 1993). Randomisation codes were generated centrally (Faught 2001), or by the study sponsor (Sackellares 2004).

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Lu 2011 used a process of restricted randomisation as zonisamide and placebo were assigned in a ratio of 1:1.

Participant codes were hidden by use of numbered containers (Lu 2011; Sackellares 2004), or sealed envelopes containing an individual participant code (Faught 2001). However, the appearance of the items used to conceal codes was not explicitly described, so one could not be certain how effective these concealment methods were. One study performed randomisation using a stratified random, segmented random, and random distribution list (Zhang 2011). Allocation concealment and random sequence generation were not specified in one study (Wu 2010).

Blinding

We deemed six of the included studies to be at low risk of performance bias (participants), as placebo and zonisamide tablets were identical in appearance (Brodie 2005; Faught 2001; Lu 2011; Sackellares 2004; Schmidt 1993; Guerrini 2013). Two studies did not specify whether placebo and zonisamide tablets were identical in appearance (Wu 2010; Zhang 2011).

Blinding of outcome assessors was not detailed in any of the included studies, and therefore, we classified this as being at an unclear risk of bias. However, participants self-reported seizure frequency and duration, and therefore, we thought that a lack of detail on the outcome assessors would have a minimal impact overall. One trial report did not provide any detail with regard to blinding of study personnel or outcome assessors, and as such, was classified as being at unclear risk of bias overall (Schmidt 1993).

Incomplete outcome data

We classified Brodie 2005; Lu 2011 as being at a low risk of attrition bias overall, as few participants left the study before completion for any reason, and those who did were reasonably evenly spread across the different intervention groups. We assessed Faught 2001 to be at an unclear risk of attrition bias due to unclear reporting of missing data and study attrition rates. Sackellares 2004 did not clearly report all data in relation to study attrition and missing data. The attrition rate was not clearly reported in Schmidt 1993, and as such, we classified it as being at an unclear risk of attrition bias. Two studies (Wu 2010; Zhang 2011) were at high risk of attrition bias.

All of the trials, including the trials included in this updated version of the review (Guerrini 2013; Wu 2010; Zhang 2011) and not included in the previous one (Carmichael 2013), conducted a modified version of an intention-to-treat (ITT) analysis, while one trial also conducted a second, unmodified ITT analysis (Faught 2001). Three trials failed to include all randomised participants in their ITT analysis, and instead omitted participants who had not completed the trial for any reason (Brodie 2005; Lu 2011; Sackellares 2004). In these three trials, participants were included in the ITT analysis if they had taken at least one dose of the intervention to which they had been allocated. A fourth trial also conducted a modified ITT analysis, but instead included participants who had received at least seven days of treatment (Schmidt 1993).

Selective reporting

We contacted all study authors; some provided additional data, but nobody made their trial protocols available to us. All primary and secondary outcomes outlined in the methods section of each trial were analysed and reported in the results section of each study, so we classified them as being at a low risk of reporting bias.

Other potential sources of bias

One potential source of bias would be the unequal duration of stable-dose phase, depending on which dosage group a participant had been allocated. Specifically, in one study, participants allocated to the 100 mg/day zonisamide dose were on a stable dose for 23 weeks in total, as their titration phase was relatively brief in comparison to those participants in the 300 mg/day and 500 mg/day groups who had a stable-dose phase of 20 and 18 weeks respectively (Brodie 2005).

Five included trials were sponsored by industry (Dainippon or Elan Pharma; Brodie 2005; Faught 2001; Sackellares 2004; Schmidt 1993; Guerrini 2013). No sources of funding were used to assist in the conduct or preparation of Lu 2011, but two different manufacturers of zonisamide provided the drug for the trial (Eisai Co. Ltd and Shenzhen Zifu Co. Ltd). Two studies did not provide details on funding (Wu 2010; Zhang 2011). Only authors of one study explicitly specified their conflicts of interest (Guerrini 2013). Two studies extended the baseline period by four weeks if participants did not experience 15 or more seizures in the first four weeks of baseline, or 30 or more seizures in the first eight weeks of baseline (Sackellares 2004; Schmidt 1993). This manipulation may have artificially inflated the effect of zonisamide on seizure frequency, making any reduction in seizures attributed to zonisamide of a greater magnitude by comparison. Conversely, this extension of the baseline period may have increased the likelihood of regression to the mean. We did not find evidence of any other source of bias in the remaining included trials (low risk of bias; Brodie 2005; Faught 2001; Lu 2011; Wu 2010; Zhang 2011).

Effects of interventions

See: Summary of findings for the main comparison Zonisamide compared to placebo for focal epilepsy

Zonisamide versus placebo

Efficacy: 50% or greater reduction in seizure frequency

Seven studies with 1429 participants contributed to this outcome. Despite different titration schedules and dosages (see Included studies), included studies were clinically and methodologically similar enough to warrant pooling.

Analysis of participants who experienced a 50% or greater reduction in their seizure frequency (responders) included data from the whole treatment period (titration plus stable-dose phase).

There were differences in the median, target, and maximum dose across studies: median dose was 400 mg in Schmidt 1993 and Sackellares 2004; the target dose was 400 mg in Faught 2001, 300 mg in Zhang 2011, and either 300 mg/day or 400 mg/day in Lu 2011; the maximum dose was 400 mg in Wu 2010. Brodie 2005 tested different doses of 100 mg, 300 mg, and 500 mg. Taking into account these differences, our analyses included data from all groups in Brodie 2005, as well as analyses excluding the 100 mg/day group.

We excluded Guerrini 2013 from the analysis, as it did not provide data from the whole treatment period.

Zonisamide add-on therapy for focal epilepsy (Review)

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(1) Whole treatment period analysis

For the analysis using any dose of zonisamide, there was no statistical heterogeneity among trials ($I^2 = 0\%$), and the overall risk ratio (RR) was 1.86 (95% confidence interval (CI) 1.60 to 2.17; 7 RCTs, 1429 participants) indicating a significant effect of zonisamide. Results excluding the 100 mg group from Brodie 2005 were similar (RR 1.90, 95% CI 1.63 to 2.22; 7 RCTs, 1371 participants). Number needed to treat for an additional beneficial outcome (NNTB) calculations showed that approximately six participants (95% CI 4.1 to 6.8) would need to be treated with zonisamide for every additional participant with at least a 50% response.

Both analyses indicated a significant treatment effect (Analysis 1.1).

(2) Best- and worst-case scenarios

We calculated best- and worst-case scenarios using data for the whole treatment period, for all doses of zonisamide. For the bestcase scenario, the overall RR was (RR 2.22, 95% CI 1.92 to 2.57; 7 RCTs, 1429 participants; Analysis 1.2), and for the worst-case, the RR was (RR 1.44, 95% CI 1.26 to 1.64; 7 RCTs, 1429 participants; Analysis 1.3). These results were consistent with a significant effect of zonisamide.

(3) Results for each dose compared to placebo

Brodie 2005 and Faught 2001 provided data for different doses of zonisamide. For Brodie 2005, estimates were as follows: 100 mg/ day (RR 1.70, 95% Cl 0.98 to 2.97; 177 participants), 300 mg/day (RR 1.94, 95% Cl 1.14 to 3.31; 176 participants), and 500 mg/day (RR 2.66, 95% Cl 1.73 to 4.11; 238 participants; Analysis 1.4). Estimates indicated increasing efficacy with increasing dose. For Faught 2001, there was no clear relationship between dose and response: 100 mg/day (RR 1.93, 95% Cl 0.96 to 3.91; 145 participants), 200 mg/day (RR 2.26, 95% Cl 1.15 to 4.48; 143 participants), and 400 mg/day (RR 1.74, 95% Cl 1.11 to 2.75; 203 participants; Analysis 1.5).

Tolerability: treatment withdrawal for any reason

Six studies with 1156 participants contributed to this outcome.

We undertook analyses including and excluding the 100 mg/day group from Brodie 2005. Wu 2010 and Zhang 2011 did not provide data on this outcome. We could not perform an analysis excluding the 100mg/day group from Faught 2001, as the final report of this study provided aggregate data on patients receiving 100mg/ day and 200 mg/day. For both analyses, there was no statistical heterogeneity ($I^2 = 0\%$). For any dose of zonisamide, the RR was 1.44 (95% CI 1.08 to 1.93; 6 RCTs, 1156 participants); and excluding the 100 mg/day group from Brodie 2005, the RR was 1.59 (95% CI 1.18 to 2.13; 6 RCTs, 1099 participants; Analysis 1.6).

Therefore, participants receiving zonisamide were significantly more likely to withdraw than those receiving placebo. Number needed to treat for an additional harmful (NNTH) outcome calculations showed that approximately 15 participants (95% CI 9.3 to 36.7) needed to be treated with zonisamide for every participant who withdrew, compared to placebo.

Adverse effects

In addition to reports of ataxia, dizziness, fatigue, nausea, and somnolence (pre-specified adverse effects; see Secondary outcomes), agitation and anorexia were among the five most common adverse effects, and therefore, we included them in this analysis.

Seven studies with 1429 participants provided data on one or more of the above mentioned adverse effects. Guerrini 2013 did not report data on ataxia, dizziness, or agitation; Wu 2010 did not report data on ataxia, nausea, fatigue, or agitation; and Zhang 2011 did not report data on nausea or agitation.

The confidence intervals for the following adverse effects results did not cross the line of no effect: ataxia (RR 3.85, 99% CI 1.36 to 10.93, P = 0.0009; 4 RCTs, 734 participants), somnolence (RR 1.52, 99% CI 1.00 to 2.31, P = 0.01; 8 RCTs, 1636 participants), agitation (RR 2.35, 99% CI 1.05 to 5.27, P = 0.07; 4 RCTs, 598 participants), and anorexia (RR 2.74, 99% CI 1.64 to 4.60, P < 0.00001; 6 RCTs, 1181 participants), indicating that these effects were more likely to occur in patients receiving zonisamide than in those receiving placebo, and should probably be considered treatment-related adverse effects.

For the following adverse effects, there was no statistically significant difference between the zonisamide and placebo groups in the number of people experiencing these events: dizziness (RR 1.40, 99% CI 0.90 to 2.18, P = 0.05; 7 RCTs, 1429 participants), fatigue (RR 1.41, 99% CI 0.79 to 2.53, P = 0.12; 6 RCTs, 1045 participants), and nausea (RR 1.10, 99% CI 0.58 to 2.10, P = 0.70; 5 RCTs, 805 participants; Analysis 1.7).

Zonisamide versus another antiepileptic drug

We did not find full reports of any studies that conducted studies on zonisamide versus another antiepileptic drug, although three potential studies are awaiting classification.

DISCUSSION

When reading this updated version, please note that we changed the title of the original Cochrane Review from 'Zonisamide addon for drug-resistant partial epilepsy' (Chadwick 2002; Chadwick 2005; Carmichael 2013), to 'Zonisamide add-on therapy for focal epilepsy'. We used the term 'focal' according to the most recent classification of epilepsies of the International League Against Epilepsy (ILAE; Scheffer 2017). We also decided to avoid the term 'drug-resistant epilepsy', because according to the current definition by the ILAE (Kwan 2010), it should be defined as the 'failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies, or in combination) to achieve sustained seizure freedom'. However, some studies included in this review were conducted in participants receiving only one background antiepileptic drug; according to the ILAE definition, these participants would not be classified as having drug-resistant epilepsy.

Summary of main results

We included eight studies (1636 participants) in this update. The intention-to-treat analysis showed that zonisamide reduced seizure frequency in people with drug-resistant focal epilepsy. Two studies were at high risk of attrition bias (Wu 2010; Zhang 2011); they did not provide reasons for differences in the number of patients in ITT and in per protocol set (PPS). However, the conclusions were unchanged following best-case (RR 2.23, 95% Cl 1.93 to 2.58) and worst-case (RR 1.44, 95% Cl 1.26 to 1.64) scenario analysis on 50% responder rate. The data from Brodie 2005

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provided some evidence of a dose-response relationship, although minimal effective or maximal tolerated doses have not yet been defined. Also the study by Faught 2001 performed a dose-response analysis, and found no difference in efficacy at dosage of 100 and 200 mg/day. Treatment in the included trials ranged from 12 to 18 weeks, so no conclusions could be drawn about longer-term efficacy.

Five trials included in this review were sponsored by industry (Dainippon or Elan Pharma; Brodie 2005; Faught 2001; Sackellares 2004; Schmidt 1993; Guerrini 2013). No sources of funding were used to assist in the conduct or preparation of Lu 2011, but the drug was provided for the trial by two different manufacturers of zonisamide (Eisai Co. Ltd and Shenzhen Zifu Co. Ltd). Two studies did not provide details on funding (Wu 2010; Zhang 2011).

All included studies were defined as double-blind and six were at low risk of bias due to having used adequate methods of allocation concealment (Brodie 2005; Faught 2001; Lu 2011; Sackellares 2004; Guerrini 2013; Zhang 2011), while this risk was unclear in two studies (Schmidt 1993; Wu 2010). The detailed internal company report of Schmidt 1993 indicated that 144 participants were randomised into this study, although the published paper indicated that 139 participants were randomised. The numbers of responders differed slightly because for this review, we only considered the eight weeks immediately before randomisation to constitute the baseline, rather than a varied period of between eight to 12 weeks. In the previous versions of this review, the incidence of different types of adverse events differed, as previous review authors used figures derived from a later application of an updated lexicon and correction of previous duplicate reporting (Chadwick 2002; Chadwick 2005; Carmichael 2013).

Results for the outcome withdrawal of allocated treatment indicated that zonisamide was more likely to be associated with withdrawal than placebo, an effect that was likely to be related to a higher incidence of adverse effects with active drug treatment. Ataxia, somnolence, agitation, and anorexia were the common adverse effects that were statistically more likely to occur with zonisamide than placebo. These clinical trials did not provide meaningful information about important safety issues, such as acute idiosyncratic drug reactions, chronic toxicity, or teratogenicity.

Overall completeness and applicability of evidence

While this review offered proof of the efficacy of zonisamide for focal epilepsy as an adjunctive treatment, it did not allow comparison with other AEDs. Prospective, actively controlled studies will be necessary to address this question. Similarly, this review provided no information to support the use of zonisamide as either monotherapy, or in people with other epilepsy syndromes. None of the studies included in this review recruited significant numbers of children, and some caution should be exercised in extrapolating the results from adult studies to children with focal epilepsy.

Quality of the evidence

We assessed six of the included studies to be at unclear or low risk of bias for all domains and two studies were assessed at high risk of attrition bias. Adopting the GRADE methodology, we assessed the quality of evidence as moderate for most outcomes (see Summary of findings for the main comparison).

Potential biases in the review process

There were no major potential biases in the review process.

Agreements and disagreements with other studies or reviews

We found only one other systematic review evaluating the efficacy and safety of add-on zonisamide for focal epilepsy (Marson 2001). This systematic review was conducted by three of the authors who carried out the previous version of this Cochrane Review (AG Marson, JL Hutton, and DW Chadwick), and adopted similar inclusion criteria and methodology. Their review identified and included three studies (total of 499 participants), two of which were published in full (Schmidt 1993; Wilder 1986), and one in an abstract (Padgett 1997). We included two of these studies in this Cochrane Review (Schmidt 1993; Wilder 1986). When the results of Wilder 1986 were published in Sackellares 2004, we included this report. Marson 2001 found that zonisamide reduced seizure frequency (50% of responders who were taking a median dose of 400 mg/day showed a RR of 2.46, 95% CI 1.61 to 3.76). Add-on zonisamide was also more likely to be withdrawn than placebo (RR for treatment withdrawal 1.64, 95% CI 1.02 to 2.62). Overall, the results of Marson 2001 were consistent with our present Cochrane Review.

AUTHORS' CONCLUSIONS

Implications for practice

People with focal epilepsy uncontrolled by one or more concomitant antiepileptic drugs were twice as likely to experience at least a 50% reduction in the frequency of their seizures when they took 300 mg to 500 mg/day of zonisamide compared to a placebo, and were treated over a stable-dose period of up to 18 weeks. For the participants entered into the trials, approximately six participants needed to be treated with zonisamide for every additional participant with a 50% response, compared to placebo, i.e. for the population recruited into the trials, the number needed to treat for an additional beneficial outcome was six.

Ataxia, somnolence, agitation, and anorexia were the most common and statistically significant adverse effects attributable to zonisamide. Participants treated with zonisamide were more likely to withdraw from treatment. For the participants entered into the trials, approximately 15 needed to be treated with zonisamide for every additional participant withdrawing, compared to placebo, i.e. for the population recruited into the trials, the number needed to treat for an additional harmful outcome was 15.

Implications for research

There is a need for studies that more adequately explore the doseresponse relationship for zonisamide in focal epilepsy. Zonisamide should be compared to other new and standard antiepileptic drugs as both add-on and monotherapy. With regards to the design of trials, thought should be given to the dynamics of the baseline period in order to prevent over-estimating the efficacy of the drug.

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Zonisamide add-on therapy for focal epilepsy (Review)

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Zonisamide add-on therapy for focal epilepsy (Review)

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Chadwick 2005

Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD001416.pub2]

Marson 1996

Marson AG, Kadir ZA, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *BMJ* 1996;**313**:1169-74.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brodie 2005

Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and

* Indicates the major publication for the study

tolerability. Epilepsia 1997;38(8):859-80.

Marson 1997

Methods	Randomised, double-blind, placebo-controlled, parallel-group study Allocation concealment using telephone randomisation Random permuted blocks of 6 per participating centre Blinded using identical tablets and packaging 12 week pre-randomisation baseline period, 24-week treatment period including 6-week dose titration			
Participants	Multicentre study, 49 centres in Europe and 5 in South Africa 351 participants. At least 12 seizures during 12-week baseline period, with no period of more than 3 weeks seizure-free Taking 1 to 3 AEDs Aged 12 to 77 51% male			
Interventions	Placebo, 100 mg, 300 m	ng or 500 mg placebo, randomised in 2:1:1:2 ratio		
Outcomes	Reduction in seizure frequency, proportion with a 50% or greater reduction in seizure frequency Adverse events			
Notes				
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Bias Random sequence genera- tion (selection bias)	Authors' judgement	Support for judgement "Patients were randomised sequentially in blocks of six"		
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias)	Authors' judgement Low risk Unclear risk	Support for judgement "Patients were randomised sequentially in blocks of six" Insufficient details were provided		
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias) Blinding of participants and personnel (perfor- mance bias) All outcomes	Authors' judgement Low risk Unclear risk Low risk	Support for judgement "Patients were randomised sequentially in blocks of six" Insufficient details were provided "Treatments were blinded using a double dummy technique throughout the study"		
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias) Blinding of participants and personnel (perfor- mance bias) All outcomes Blinding of outcome as- sessment (detection bias) All outcomes	Authors' judgement Low risk Unclear risk Low risk Unclear risk	Support for judgement "Patients were randomised sequentially in blocks of six" Insufficient details were provided "Treatments were blinded using a double dummy technique throughout the study" Insufficient details about blinding of outcome assessors was provided		

Zonisamide add-on therapy for focal epilepsy (Review)

Brodie 2005 (Continued)

Selective reporting (re- porting bias)	Low risk	This study was deemed to be at a low risk of selective reporting
Funding Source	Low risk	Reported (sponsored by industry)
Conflicts of interest	Unclear risk	Not specified
Other bias	Low risk	Allocation to groups led to different durations of stable-dose phase

Faught 2001	
Methods	Randomised, double-blind, placebo-controlled, parallel-group study. 2 treatment arms: 1 placebo and 1 zonisamide Randomisation concealment by allocated sequentially numbered, sealed packages. Random list gen- erated by random permuted blocks. Blinding by identical packing and tablets All participants received placebo during 28-day prospective baseline. Treatment period was 12 weeks. Participants receiving zonisamide were divided into 2 groups, 1 (group B1) of which received 100 mg/ day during weeks 1 to 5, the second (group B2) of which received 100 mg/day during week 1 followed by 200 mg/day during weeks 2 to 5. Both groups received an escalating dose of zonisamide for weeks 5 to 7 followed by 400 mg/day during weeks 8 to 12
Participants	Multicentre (20) USA study Total randomised: 203 participants between April 1994 and March 1996 with at least 4 partial seizures/ month taking 1 or 2 AEDs, 85 to placebo, 60 to group B1, 58 to group B2 Ages 13 to 68 years, 104 male, 99 female Median monthly seizure frequency for the randomised groups during baseline ranged between 11.2 and 13 seizures/month
Interventions	Zonisamide 400 mg/day or placebo (weeks 8 to 12) Zonisamide 100 mg/day or 200 mg/day or placebo (weeks 1 to 5) All treatments and packaging were identical
Outcomes	Primary: median percentage reduction from baseline of all focal seizures Secondary: proportion of participants showing a 50% reduction in all focal seizures from baseline Adverse events
Notes	Of the randomised participants, 8 failed to complete week 5 in the placebo group, 15 in the zonisamide group By the end of week 12, 13 participants had withdrawn from the placebo group, 23 from zonisamide

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	"Randomization codes were generated centrally, with separate randomization sequences for each site."
Allocation concealment (selection bias)	Low risk	"Each investigator had a sealed copy of the code to be opened in an emer- gency. Otherwise, assignments were not revealed until all patients at all sites had completed the study."
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	Insufficient detail was provided about blinding of personnel

Zonisamide add-on therapy for focal epilepsy (Review)

Faught 2001 (Continued)

Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	Insufficient detail was provided about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The analysis for "the primary populations was a modified ITT" as it included participants who had received at least one dose of study medication
Selective reporting (re- porting bias)	Low risk	No evidence of selective reporting
Funding Source	Low risk	Reported (sponsored by industry)
Conflicts of interest	Unclear risk	Not specified
Other bias	Low risk	No evidence of any other source of bias

Guerrini 2013	
Methods	Randomised, double-blind, placebo-controlled, parallel-group
	2 treatment arms: 1 placebo and 1 zonisamide
	Computer-generated, centrally performed randomisation (pseudo-random number generator), alloca- tion concealed by telephone randomisation service
	Method of blinding: identical appearance of active drug and placebo
	Baseline period: 8 weeks (4 weeks historical + 4 weeks screening)
	Treatment duration: 8 weeks titration + 12 weeks maintenance
Participants	Number of participants:
	Zonisamide: 107; Placebo: 100
	Age of participants, mean (SD); median (range):
	Zonisamide: 11.6 (3.3); 11.0 (6 to 17);
	Placebo: 11.2 (3.2); 11.0 (6 to 17).
	Gender of participants:
	Zonisamide: male 53 (49.5%);
	Placebo: male 55 (55.0%).
	Type of seizures:
	Zonisamide: simple focal with motor signs 40 (37.4%), simple focal without motor signs 11 (10.3%), complex focal 59 (55.1%), secondarily generalized tonic-clonic 29 (27.1%)
	Placebo: simple focal with motor signs 34 (34.0%), simple focal without motor signs 10 (10.0%), com- plex focal 58 (58.0%), secondarily generalized tonic-clonic 33 (33.0%)
	Seizure frequency during the baseline period, mean (SD); median (range):
	Zonisamide: 32.9 (50.3); 10.5 (4 to 261; (number of seizures per 28 days))
	Placebo: 43.8 (126.4); 10.0 (4 to 882; (number of seizures per 28 days))

Zonisamide add-on therapy for focal epilepsy (Review)

Guerrini 2013 (Continued)					
	Number of background	l drugs:			
	Zonisamide: 0 AED: 0; 1	AED: 44 (41.1%); 2 AEDs: 63 (58.9%)			
	Placebo: 0 AED: 1 (1.0%	b); 1 AED: 39 (39.0%); 2 AEDs: 60 (60.0%)			
Interventions	Add-on zonisamide ver	sus add-on placebo			
	Zonisamide drug dose of 1 mg/kg over 8 week the 12-week maintenar	regimen (dosage and infusion rate): 1 mg/kg/day, titrated in weekly increments s to a target dose of 8 mg/kg/day (max 500 mg/day), continued unchanged over nce period.			
Outcomes	Efficacy:				
	Primary outcome: proportion of participants with a ≥ 50% reduction in seizure frequency during the 12- week maintenance period compared to baseline (i.e. the 8 weeks preceding randomisation)				
	Secondary outcomes: r tion of participants wit in seizure frequency of percentage change fror zonisamide plasma leve	nedian percentage change from baseline in 28-day seizure frequency; propor- h ≥ 75% seizure frequency reduction; proportion of participants with an increase ≥ 25%, 25%, and 100%; proportion of participants achieving seizure freedom; n baseline in 28-day seizure frequency by seizure type; relationship between el and responder rate			
	Safety: incidence of treatment emergent AEs (TEAEs), serious TEAEs, and withdrawal due to TEA clinical laboratory parameters; physical and neurologic evaluations; vital signs; height and weig electrocardiography				
Notes					
Risk of bias					
Bias	Authors' judgement	Support for judgement			
Random sequence genera- tion (selection bias)	Low risk	Computer-generated, centrally performed randomisation (pseudo-random number generator)			
Allocation concealment (selection bias)	Low risk	Allocation concealed by telephone randomisation service			
Blinding of participants and personnel (perfor- mance bias)	Low risk	Identical appearance of active drug and placebo			

mance bias) All outcomes		
Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	Insufficient details about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (re- porting bias)	Low risk	No evidence of selective reporting
Funding Source	Low risk	Reported (sponsored by industry)
Conflicts of interest	Low risk	Reported
Other bias	Low risk	No evidence of any other source of bias

Zonisamide add-on therapy for focal epilepsy (Review)



Lu 2011

Methods	Randomised, double-blind, placebo-controlled, parallel trial. 12-week baseline phase, 4-week titration phase, 12-week stable treatment phase. Placebo or zonisamide treatment interventions
Participants	Single centre in China. 104 participants randomised, 53 received zonisamide (29 M:24 F) and 51 re- ceived placebo (32 M:19 F). Mean age in zonisamide group = 36.83 years ± 10.77, and mean age in place- bo group = 29.81 years ± 8.24. All participants had simple focal seizures, complex focal seizures, or sec- ondary generalised seizures
Interventions	Placebo or zonisamide (titrated to 300 mg/day or 400 mg/day)
Outcomes	The following outcomes were measured:
	1. Responder rate (50% or greater reduction in seizures frequency during treatment phase compared to baseline)
	2. Seizure freedom
	3. Adverse effects

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	No information given other than "zonisamide and placebo were assigned to our centre in a ratio of 1:1"
Allocation concealment (selection bias)	Low risk	"Random allocation of patients to their treatment group was concealed via the use of numbered containers"
		Comment: it is not explicitly stated whether the containers were opaque or not
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"Investigators were blind to treatment each patient received until the end of the study" and "Zonisamide and placebo tablets had the same size, colour and shape. The tablets were randomly numbered by the study sponsors"
Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	It is unclear whether the investigators, who were blinded, were also the out- come assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was lost from each group, therefore, missing data were bal- anced between groups
Selective reporting (re- porting bias)	Low risk	No evidence of selective reporting
Funding Source	Low risk	No sources of funding were used to assist in the conduct or preparation of this study, but the drug was provided for the trial by two different manufacturers of zonisamide (Eisai Co. Ltd and Shenzhen Zifu Co. Ltd)
Conflicts of interest	Unclear risk	Not specified
Other bias	Low risk	Both providers of zonisamide were manufacturers of the drug

Zonisamide add-on therapy for focal epilepsy (Review)



Sackellares 2004

Methods	Randomised, double-blind, placebo-controlled, parallel-group study 2 treatment arms, 1 placebo, 1 zonisamide. The initial target dose of zonisamide was 7 mg/kg/day, but when it became apparent that this was associated with a significant incidence of adverse effects, it was titrated over the first 4 weeks to 400 mg/day. Thereafter, a non-blinded observer recommended dose adjustments to obtain plasma levels of 20 µg to 30 µg/mL. Median dosage in this group was 400 mg/day (range 200 to 600 mg/day) Randomisation concealment by allocated sequentially numbered, sealed packages. Random list gen- erated by random permuted blocks. Blinding by identical packing and tablets Baseline was variable, between 8 and 12 weeks, being extended if frequency was below 4 focal seizures/month Treatment period was 12 weeks	
Participants	Conducted at 4 USA centres between August 1983 and July 1986 Total randomised: 152 participants, all with 4 or more focal seizures/month while taking 1 or 2 AEDs. 78 were randomised to zonisamide, 74 to placebo Age 17 to 67 years, 101 male, 51 female Median monthly seizure frequency pre-baseline: 7.5 zonisamide, 11.1 placebo	
Interventions	Zonisamide median dosage 400 mg/day (100 mg capsules) Placebo Treatments and packaging were identical	
Outcomes	Primary: median percentage reduction in seizure frequency of all focal seizures from baseline Secondary: proportion of participants with a 50% reduction in all focal seizures from baseline	
Notes	Because of the variable baseline periods, baseline seizure frequency was recalculated for the 8 weeks immediately before entry into the treatment period 14 people failed to complete the 12-week treatment period in the zonisamide group, 7 in the placebo group	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	"Randomisation codes were generated by the study sponsor". "Each patient who qualified to receive double-blind treatment was assigned a randomisa- tion number and given zonisamide or placebo"

Allocation concealment (selection bias)	Low risk	"Random allocation of patients to their treatment groups was concealed via the use of numbered containers"
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	This study was deemed to be at low risk of performance bias
Blinding of outcome as- sessment (detection bias) All outcomes	Low risk	This study was deemed to be at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient or unclear details were provided with regard to attrition bias
Selective reporting (re- porting bias)	Low risk	No evidence of selective reporting

Zonisamide add-on therapy for focal epilepsy (Review)



Sackellares 2004 (Continued)

Funding Source	Low risk	Reported (sponsored by industry)
Conflicts of interest	Unclear risk	Not specified
Other bias	Low risk	Baseline period was extended if the frequency of seizures did not meet a pre- specified threshold

Schmidt 1993	
Methods	Randomised, double-blind, placebo-controlled, parallel group study 2 treatment arms, 1 placebo, 1 zonisamide. The initial target dose of zonisamide was 7 mg/kg/day, but when it became apparent that this was associated with a significant incidence of adverse effects, it was titrated over the first 4 weeks to 400 mg/day. Thereafter, a non-blinded observer recommended dose adjustments to obtain plasma levels of 20 µg to 30 µg/mL. Median dosage in this group was 400 mg/day Randomisation concealment by allocated sequentially numbered, sealed packages. Random list gen- erated by random permuted blocks. Blinding by identical packing and tablets Baseline was variable, between 8 and 12 weeks, being extended if frequency was below 4 focal seizures/month Treatment period was 12 weeks
Participants	Participants from 10 European centres recruited between June 1984 and October 1986 Total randomised: 144 participants, all with 4 or more focal seizures/month while taking 1 or 2 AEDs. 73 were randomised to zonisamide, 71 to placebo Age 17 to 60 years, 85 male 59 female Median monthly seizure frequency pre-baseline: 11.3 zonisamide, 11.0 placebo
Interventions	Zonisamide median dosage 400 mg/day (100 mg capsules) Placebo Treatments and packaging were identical
Outcomes	Primary: median percentage reduction in seizure frequency of all focal seizures from baseline Secondary: proportion of participants with a 50% reduction in all focal seizures from baseline
Notes	Because of the variable baseline periods, baseline seizure frequency was recalculated for the 8 weeks immediately before entry into the treatment period 7 people failed to complete the 12-week treatment period in the zonisamide group, 2 in the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	"Patients were randomised sequentially in blocks of four"
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	Insufficient details were provided about blinding of personnel
Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not detailed

Zonisamide add-on therapy for focal epilepsy (Review)

Schmidt 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A modified ITT analysis was conducted including participants who had re- ceived "at least 7 days of treatment"
Selective reporting (re- porting bias)	Low risk	This study was deemed to be at low risk of selective reporting
Funding Source	Low risk	Reported (sponsored by industry)
Conflicts of interest	Unclear risk	Not specified
Other bias	Low risk	Baseline period was extended if the frequency of seizures did not meet a pre- specified threshold

Bias	Authors' judgement Support for judgement
Risk of bias	
Notes	
Outcomes	The median of the difference between the frequency of epileptic seizures and baseline value; in com- parison with baseline period, the frequency of epileptic seizures decreased by more than 50%; safety index
Interventions	Add-on zonisamide versus add-on placebo Zonisamide: increment: first two weeks 100 mg/day, third week 200 mg/day, forth week 300 mg/day. Stabilization: 300 mg/day. According to the participant's situation, doses could be increased to 400 mg/day.
	Number of background drugs: 1 to 2
	Placebo: male/female = 63/43
	Zonisamide: male/female = 57/54
	Gender of participants:
	Placebo: 30.7 ± 11.6
	Zonisamide: 32.7 ± 12.2
	Age of participants, mean ± SD:
	Placebo: 120
	Zonizamide: 120
	Number of participants:
Participants	Participants with focal epilepsy
	Duration of study: increment, stabilization, reduction = 4 weeks, 12 weeks, 4 weeks
	Duration of baseline: 12 weeks.
Methods	Multicentre, randomised, double-blind, placebo-controlled study

Zonisamide add-on therapy for focal epilepsy (Review)



Wu 2010 (Continu	ed)
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Random sequence genera- tion (selection bias)	Unclear risk	Insufficient details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	Study defined as double-blind. However, insufficient details were provided.
Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants who were seriously against the treatment program were ex- cluded. FAS include 216 participants (zonisamide group : placebo group = 111:106), PPS include 201 participants (zonisamide group : placebo group=102:99). No reasons for differences in the number of patients in ITT and in per protocol set (PPS) are provided.
Selective reporting (re- porting bias)	Low risk	The study protocol was not available, but it was clear that the published re- ports included all expected outcomes
Funding Source	Unclear risk	Not reported
Conflicts of interest	Unclear risk	Not reported
Other bias	Low risk	No evidence of any other source of bias

Zhang 2011

Methods	Multicentre, randomised, double-blind, placebo-controlled study	
	Stratified block randomisation and block randomisation	
	Duration of baseline period: 12 weeks	
	Duration of treatment: increment, stabilization = 3 weeks, 13 weeks	
Participants	participants with focal epilepsy	
	Number of participants:	
	Zonizamide: 120	
	Placebo: 120	
	Age of participants, mean ± SD:	
	Zonisamide: 30.83 ± 11.68	
	Placebo: 32.47 ± 11.92	
	Gender of participants:	
	Zonisamide: male/female = 42/52	
	Placebo: male/female = 55/52	

Zonisamide add-on therapy for focal epilepsy (Review)



Zhang 2011 (Continued)	Number of background drugs: 1 to 2		
Interventions	Add-on zonisamide versus add-on placebo		
	Zonisamide: at the beginning, 100mg/day, increase to 300mg/day (100 mg, three times a day) within three weeks Stabilization: 300mg/day		
Outcomes	The clinical efficacy at 5 to 16 weeks; the average number of episodes per 4 weeks; drug safety evalua- tion		

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Stratified random, segmented random, random distribution list
Allocation concealment (selection bias)	Low risk	Gave random distribution list to major leadership for safekeeping
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Study defined as double-blind. However, insufficient details were provided.
Blinding of outcome as- sessment (detection bias) All outcomes	Unclear risk	Insufficient details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT included 240 participants (zonisamide group : placebo group = 120:120); PPS included 201 participants (zonisamide group : placebo group = 94:107). No reasons for differences in the number of patients in ITT and in per protocol set (PPS) are provided.
Selective reporting (re- porting bias)	Low risk	The study protocol was not available, but it was clear that the published re- ports included all expected outcomes
Funding Source	Unclear risk	Not reported
Conflicts of interest	Unclear risk	Not reported
Other bias	Low risk	No evidence of any other source of bias

AED: antiepileptic drug F: female FAS: full analysis set ITT: intention-to-treat M: male PPS: per-protocol set SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Zonisamide add-on therapy for focal epilepsy (Review)



Study

Reason for exclusion

Shimizu 1988

No control group was used

Characteristics of studies awaiting assessment [ordered by study ID]

Anderson 1988	
Methods	Five-month titration and stabilisation period followed by a three-month treatment period
	Randomised controlled study (no further details on study design were provided)
Participants	14 adult participants (9 males, 5 females); average age of 35 years
	At least 4 focal seizures
Interventions	Zonisamide add-on versus sodium valproate add-on
Outcomes	No details
Notes	No details

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Methods	Randomized, double-blind, placebo-controlled, parallel-group
	2 treatment arms: 1 placebo and 1 zonisamide
	Duration of baseline period:12 weeks (retrospective, prior to entry)
	Duration of treatment period: 16 weeks (4-week titration period + 12-week fixed-dose phase)
Participants	According to the International League Against Epilepsy (ILAE) classification of seizure type (1981) and international classification of epilepsies and epileptic syndromes (Kwan 2010), definite di- agnosis of focal seizures (with or without secondary generalized seizures) refractory to current antiepilepsy drug (AED) therapy
	Number of participants:
	Zonisamide: 120
	Placebo: 120
	Age of participants, mean (SD):
	Zonisamide: 32.72 (12.18)
	Placebo: 30.69 (11.59)
	Gender of participants:
	Zonisamide: male 57/111
	Placebo: male 63/106
	Number of background drugs:
	At least 1 to 2 concomitant AEDs on a stable dose (for 3 months prior to enrolment)

Zonisamide add-on therapy for focal epilepsy (Review)

NCT00327717 (Continued)								
Interventions	Add-on zonisamide versus add-on placebo							
	Zonisamide drug, dose regimen (dosage and infusion rate):							
	During the 4-week titration period, zonisamide dosing began at 100 mg/day for the first 2 weeks, increased to 200 mg/day for the 3rd week, and to 300 mg/day for the 4th week, reaching 300 mg/ day at the end of the titration period. The 300 mg/day was the target dose in the titration period, and must have been reached. Dose increment was continued to 400 mg/day if this was tolerated by the participant.							
Outcomes	Efficacy							
	Primay outcome: median percent change in seizure frequency from baseline during the fixed-dose phase							
	Secondary outcomes: mean percent change in complex focal seizure frequency from baseline dur- ing the fixed-dose phase; mean percent change in simple focal seizure frequency from baseline during the fixed-dose phase; mean percent change in focal with secondary generalisation seizure frequency from baseline during the fixed-dose phase; responder rate as percentage of participants with ≥ 50% reduction in seizure frequency from baseline; mean number of seizure-free days per 28 day period during fixed-dose phase; mean percentage of change in seizure-free days; mean time- to-first seizure during fixed dose phase; percentage of seizure-free participants during fixed-dose phase; drop-out rate							
	Safety: drop-out rate; incidence of treatment emergent AEs (TEAEs), serious TEAEs, and withdrawal due to TEAEs							

Notes

NCT01546688	
Methods	Randomised, double-blind, placebo-controlled, parallel-group
	2 treatment arms: 1 placebo and 1 zonisamide
	Duration of baseline period: 4 weeks
	Duration of treatment period: 16 weeks (8-week titration period + 8-week maintenance phase)
Participants	Number of participants:
	Zonisamide: 33
	Placebo: 18
	Age of participants, mean (SD):
	Zonisamide: 72.5 (5.63)
	Placebo: 71.1 (4.61)
	Gender of participants, mean (SD):
	Zonisamide: male 14/33
	Placebo: male 7/18
	Number of background drugs (active and control group):
	At least one, but not more than two concomitant AEDs

Zonisamide add-on therapy for focal epilepsy (Review)

NCT01546688 (Continued)								
Interventions	Add-on zonisamide versus add-on placebo Zonisamide at targeted daily doses of 100 mg to 500 mg/day							
	Subjects started the titration period on a total daily dose (TDD) of zonisamide 50 mg (25 mg twice daily) for a total of 8 weeks. Doses increased in 100 mg increments up to a targeted TDD of 300 mg, with a range of 100 mg to 500 mg. Subjects entered the maintenance period on the same dose they were on at the end of the titration phase, taking the dose once daily (in the evening), or twice daily, for a total of 8 weeks. Subjects were withdrawn if they required a TDD outside of the suggested range.							
Outcomes	Primary outcome:							
	change in mean reaction time in computer visual search task of the Ferrum Psyche test, and Bond- Lader Visual Analogue Scale Mood Sub-Scores from baseline, by visits during titration and mainte- nance period (weeks 4, 8, 12, 16).							
	Secondary Outcome:							
	percent change in seizure frequency from baseline to the last 28 days of the maintenance peri- od; percentage of responders (≥ 50% reduction in seizure frequency) during the last 28 days of the maintenance period							
	Safety: incidence of treatment emergent AEs (TEAEs), serious TEAEs, and withdrawal due to TEAEs							
Notes								

DATA AND ANALYSES

Comparison 1. Zonisamide versus placebo

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 50% responder rate - whole treat- ment period	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Any dose	7	1429	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.60, 2.17]
1.2 300 mg to 500 mg/day zonisamide	7	1371	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.63, 2.22]
2 50% responder rate - best-case sce- nario	7	1429	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.92, 2.57]
3 50% responder rate - worst-case sce- nario	7	1429	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.26, 1.64]
4 50% responder rate - dose-effect for Brodie 2005	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 100 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 300 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Zonisamide add-on therapy for focal epilepsy (Review)



Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
4.3 500 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 50% responder rate - dose effect for Faught 2001	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 100 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 200 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 400 mg/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Withdrawal rates	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Any dose	6	1156	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.08, 1.93]
6.2 300 mg to 500 mg/day zonisamide	6	1099	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.18, 2.13]
7 Adverse effects	8		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 Ataxia	4	734	Risk Ratio (M-H, Fixed, 99% CI)	3.85 [1.36, 10.93]
7.2 Dizziness	7	1429	Risk Ratio (M-H, Fixed, 99% CI)	1.40 [0.90, 2.18]
7.3 Fatigue	6	1045	Risk Ratio (M-H, Fixed, 99% CI)	1.41 [0.79, 2.53]
7.4 Nausea	5	805	Risk Ratio (M-H, Fixed, 99% CI)	1.10 [0.58, 2.10]
7.5 Somnolence	8	1636	Risk Ratio (M-H, Fixed, 99% CI)	1.52 [1.00, 2.31]
7.6 Agitation or irritability	4	598	Risk Ratio (M-H, Fixed, 99% CI)	2.35 [1.05, 5.27]
7.7 Anorexia	6	1181	Risk Ratio (M-H, Fixed, 99% CI)	2.74 [1.64, 4.60]

Analysis 1.1. Comparison 1 Zonisamide versus placebo, Outcome 1 50% responder rate - whole treatment period.

Study or subgroup	Zonisamide	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI
1.1.1 Any dose					
Brodie 2005	91/231	21/120	· · · · · · · · · · · · · · · · · · ·	16.44%	2.25[1.48,3.43]
Faught 2001	41/118	16/85	│ ── + ──	11.07%	1.85[1.11,3.06]
Lu 2011	29/53	18/51	+	10.91%	1.55[0.99,2.42]
Sackellares 2004	22/78	12/74	+	7.33%	1.74[0.93,3.26]
Schmidt 1993	19/71	9/68	+	5.47%	2.02[0.98,4.15]
Wu 2010	58/120	30/120		17.85%	1.93[1.35,2.77]
Zhang 2011	90/120	52/120	_ 	30.93%	1.73[1.38,2.18]
Subtotal (95% CI)	791	638	•	100%	1.86[1.6,2.17]
Total events: 350 (Zonisamide), 1	158 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1.96	5, df=6(P=0.92); I ² =0%				
Test for overall effect: Z=7.95(P<	0.0001)				
		Favours placebo	0.5 0.7 1 1.5 2	Favours zonisamide	

Zonisamide add-on therapy for focal epilepsy (Review)



Chudu au aub auaun	Zeniermide	Disasha		Wainha	Diele Detie
Study or subgroup	Zonisamide	Placebo	RISK RATIO	weight	RISK RATIO
	n/N	n/N	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
1.1.2 300 mg to 500 mg/day zor	nisamide				
Brodie 2005	74/173	21/120		15.39%	2.44[1.6,3.74]
Faught 2001	41/118	16/85	+	11.54%	1.85[1.11,3.06]
Lu 2011	29/53	18/51	+	11.38%	1.55[0.99,2.42]
Sackellares 2004	17/78	8/74	+	5.09%	2.02[0.93,4.39]
Schmidt 1993	19/71	9/68	+	5.71%	2.02[0.98,4.15]
Wu 2010	58/120	30/120		18.62%	1.93[1.35,2.77]
Zhang 2011	90/120	52/120	_ 	32.27%	1.73[1.38,2.18]
Subtotal (95% CI)	733	638	•	100%	1.9[1.63,2.22]
Total events: 328 (Zonisamide), 1	54 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2.87	′, df=6(P=0.82); I²=0%				
Test for overall effect: Z=8.15(P<0	0.0001)				
		Favours placebo	0.5 0.7 1 1.5 2	Favours zonisamide	

Analysis 1.2. Comparison 1 Zonisamide versus placebo, Outcome 2 50% responder rate - best-case scenario.

Study or subgroup	Zonisamide	Placebo		Risk Ratio			Weight	Risk Ratio			
	n/N	n/N			M-H, Fi	ixed, 9	95% CI				M-H, Fixed, 95% Cl
Brodie 2005	94/231	21/120								16.44%	2.33[1.53,3.53]
Faught 2001	47/118	16/85				-	+			11.07%	2.12[1.29,3.47]
Lu 2011	29/53	18/51				-	+			10.91%	1.55[0.99,2.42]
Sackellares 2004	36/78	12/74					+			7.33%	2.85[1.61,5.04]
Schmidt 1993	24/71	9/68				-	+			5.47%	2.55[1.28,5.09]
Wu 2010	67/120	30/120								17.85%	2.23[1.58,3.16]
Zhang 2011	116/120	52/120								30.93%	2.23[1.81,2.74]
Total (95% CI)	791	638					•			100%	2.22[1.92,2.57]
Total events: 413 (Zonisamide), 15	8 (Placebo)										
Heterogeneity: Tau ² =0; Chi ² =3.48,	df=6(P=0.75); I ² =0%										
Test for overall effect: Z=10.72(P<0	0.0001)										
		Favours placebo	0.1	0.2	0.5	1	2	5	10	Favours zonisamide	

Analysis 1.3. Comparison 1 Zonisamide versus placebo, Outcome 3 50% responder rate - worst-case scenario.

Study or subgroup	Zonisamide	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl
Brodie 2005	91/231	22/120		13.29%	2.15[1.43,3.24]
Faught 2001	41/118	29/85	+	15.48%	1.02[0.69,1.5]
Lu 2011	29/53	19/51	+	8.89%	1.47[0.95,2.26]
Sackellares 2004	22/78	19/74		8.95%	1.1[0.65,1.86]
Schmidt 1993	19/71	14/68		6.57%	1.3[0.71,2.38]
Wu 2010	58/120	37/120	—•—	16.99%	1.57[1.13,2.17]
Zhang 2011	90/120	65/120		29.84%	1.38[1.14,1.68]
Total (95% CI)	791	638	•	100%	1.44[1.26,1.64]
Total events: 350 (Zonisamide), 205	(Placebo)				
		Favours placebo	0.5 0.7 1 1.5 2	Favours zonisamide	

Zonisamide add-on therapy for focal epilepsy (Review)



Study or subgroup	Zonisamide n/N	Placebo n/N	Risk Rati M-H, Fixed, 9	o 5% Cl	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau ² =0; Chi ² =8.3, df=	6(P=0.22); I ² =27.72%					
Test for overall effect: Z=5.27(P<0.00	001)					
		Favours placebo	0.5 0.7 1	1.5 2	Favours zonisamide	

Analysis 1.4. Comparison 1 Zonisamide versus placebo, Outcome 4 50% responder rate - dose-effect for Brodie 2005.

Study or subgroup	Zonisamide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.4.1 100 mg/day				
Brodie 2005	17/57	21/120		1.7[0.98,2.97]
1.4.2 300 mg/day				
Brodie 2005	19/56	21/120		1.94[1.14,3.31]
1.4.3 500 mg/day				
Brodie 2005	55/118	21/120		2.66[1.73,4.11]
		Favours placebo ^{0.1}	0.2 0.5 1 2 5	¹⁰ Favours zonisamide

Analysis 1.5. Comparison 1 Zonisamide versus placebo, Outcome 5 50% responder rate - dose effect for Faught 2001.

Study or subgroup	Zonisamide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.5.1 100 mg/day				
Faught 2001	15/60	11/85	+	1.93[0.96,3.91]
1.5.2 200 mg/day				
Faught 2001	17/58	11/85		2.26[1.15,4.48]
1.5.3 400 mg/day				
Faught 2001	46/118	19/85		1.74[1.11,2.75]
		Favours placebo 0.1	0.2 0.5 1 2 5	¹⁰ Favours zonisamide

Analysis 1.6. Comparison 1 Zonisamide versus placebo, Outcome 6 Withdrawal rates.

Study or subgroup	Zonisamide	Placebo	Risk	Ratio		Weight	Risk Ratio
	n/N	n/N	M-H, Fixe	ed, 95% CI			M-H, Fixed, 95% Cl
1.6.1 Any dose							
Brodie 2005	59/231	23/120		+		46.61%	1.33[0.87,2.05]
Faught 2001	23/118	13/85	_	+•		23.27%	1.27[0.69,2.37]
Guerrini 2013	14/107	10/100		++		15.92%	1.31[0.61,2.81]
Lu 2011	0/53	0/51					Not estimable
Sackellares 2004	14/78	7/74	-	├-+		11.06%	1.9[0.81,4.44]
		Worse on placebo	0.05 0.2	1 5	20	Worse on zonisamide	

Zonisamide add-on therapy for focal epilepsy (Review)



Study or subgroup	Zonisamide	Placebo		Risk Ratio		Weight	Risk Ratio
	n/N	n/N		M-H, Fixed, 95%	CI		M-H, Fixed, 95% Cl
Schmidt 1993	7/71	2/68			+	3.15%	3.35[0.72,15.57]
Subtotal (95% CI)	658	498		•		100%	1.44[1.08,1.93]
Total events: 117 (Zonisamide), 55 (P	acebo)						
Heterogeneity: Tau ² =0; Chi ² =1.9, df=4	(P=0.75); I ² =0%						
Test for overall effect: Z=2.45(P=0.01)							
1.6.2 300 mg to 500 mg/day zonisar	nide						
Brodie 2005	55/174	23/120				43.98%	1.65[1.08,2.53]
Faught 2001	23/118	13/85		-+		24.41%	1.27[0.69,2.37]
Guerrini 2013	14/107	10/100		-++		16.7%	1.31[0.61,2.81]
Lu 2011	0/53	0/51					Not estimable
Sackellares 2004	14/78	7/74		++		11.61%	1.9[0.81,4.44]
Schmidt 1993	7/71	2/68			+	3.3%	3.35[0.72,15.57]
Subtotal (95% CI)	601	498		•		100%	1.59[1.18,2.13]
Total events: 113 (Zonisamide), 55 (Pl	acebo)						
Heterogeneity: Tau ² =0; Chi ² =1.84, df=	4(P=0.77); l ² =0%						
Test for overall effect: Z=3.09(P=0)							
		Worse on placebo	0.05 0	.2 1	5 20	Worse on zonisamide	

Analysis 1.7. Comparison 1 Zonisamide versus placebo, Outcome 7 Adverse effects.

Study or subgroup	Zonisamide	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 99% Cl		M-H, Fixed, 99% Cl
1.7.1 Ataxia					
Faught 2001	5/118	2/85		31.25%	1.8[0.22,15.06]
Sackellares 2004	14/78	4/74		55.17%	3.32[0.82,13.46]
Schmidt 1993	8/71	0/68	+	6.86%	16.29[0.39,674.41]
Zhang 2011	2/120	0/120	+	6.72%	5[0.09,266.7]
Subtotal (99% CI)	387	347		100%	3.85[1.36,10.93]
Total events: 29 (Zonisamide), 6 (Plac	cebo)				
Heterogeneity: Tau ² =0; Chi ² =1.95, df=	=3(P=0.58); I ² =0%				
Test for overall effect: Z=3.33(P=0)					
1.7.2 Dizziness					
Brodie 2005	10/231	3/120		7.65%	1.73[0.33,9.2]
Faught 2001	20/118	10/85	- +•	22.53%	1.44[0.57,3.64]
Lu 2011	2/53	6/51	+	11.85%	0.32[0.04,2.47]
Sackellares 2004	19/78	13/74	- •	25.86%	1.39[0.61,3.17]
Schmidt 1993	12/71	3/68	+	5.94%	3.83[0.77,19.06]
Wu 2010	12/120	13/120		25.2%	0.92[0.35,2.45]
Zhang 2011	4/120	0/120		0.97%	9[0.2,412.71]
Subtotal (99% CI)	791	638	◆	100%	1.4[0.9,2.18]
Total events: 79 (Zonisamide), 48 (Pla	acebo)				
Heterogeneity: Tau ² =0; Chi ² =8.96, df=	=6(P=0.18); I ² =33.06%	1			
Test for overall effect: Z=1.96(P=0.05)					
1.7.3 Fatigue					
Faught 2001	10/118	11/85	— • +	42.35%	0.65[0.23,1.9]
Guerrini 2013	0/107	3/100		11.98%	0.13[0,6.46]
	V	Vorse on placebo	0.01 0.1 1 10	100 Worse on zonisamide	2

Zonisamide add-on therapy for focal epilepsy (Review)



Study or subgroup	Zonisamide	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 99% Cl		M-H, Fixed, 99% Cl
Lu 2011	1/53	2/51	•	6.75%	0.48[0.02,10.83]
Sackellares 2004	12/78	3/74	+	10.2%	3.79[0.76,18.97]
Schmidt 1993	16/71	8/68		27.07%	1.92[0.69,5.34]
Zhang 2011	5/120	0/120		1.66%	11[0.25,486.97]
Subtotal (99% CI)	547	498	•	100%	1.41[0.79,2.53]
Total events: 44 (Zonisamide), 27	7 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =11.7	74, df=5(P=0.04); I ² =57.429	%			
Test for overall effect: Z=1.54(P=0	0.12)				
1.7.4 Nausea					
Faught 2001	12/118	8/85	_	34.1%	1.08[0.35,3.3]
Guerrini 2013	2/107	4/100	+	15.16%	0.47[0.05,4.22]
Lu 2011	1/53	0/51		1.87%	2.89[0.04,188.16]
Sackellares 2004	14/78	10/74		37.63%	1.33[0.5,3.54]
Schmidt 1993	3/71	3/68		11.24%	0.96[0.12,7.49]
Subtotal (99% CI)	427	378	•	100%	1.1[0.58,2.1]
Total events: 32 (Zonisamide), 25	ō (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1.63	3, df=4(P=0.8); l ² =0%				
Test for overall effect: Z=0.38(P=0	0.7)				
1.7.5 Somnolence					
Brodie 2005	6/231	1/120		2.37%	3.12[0.2,49.6]
Faught 2001	17/118	10/85		20.96%	1.22[0.47,3.19]
Guerrini 2013	5/107	2/100		3.73%	2.34[0.28,19.56]
Lu 2011	2/53	6/51		11.03%	0.32[0.04,2.47]
Sackellares 2004	30/78	10/74		18.51%	2.85[1.23,6.61]
Schmidt 1993	10/71	3/68		5.53%	3.19[0.62,16.43]
Wu 2010	15/120	17/120		30.66%	0.88[0.38.2.06]
Zhang 2011	5/120	4/120	+	7.21%	1.25[0.23.6.81]
Subtotal (99% CI)	898	738	•	100%	1.52[1.2.31]
Total events: 90 (Zonisamide), 53	3 (Placebo)				
Heterogeneity: Tau ² =0: Chi ² =12.7	75. df=7(P=0.08): l ² =45.1%	1			
Test for overall effect: 7=2 56(P=0) 01)				
1.7.6 Agitation or irritability					
Faught 2001	7/118	5/85		43.07%	1.01[0.23,4.36]
Lu 2011	1/53	0/51		3.77%	2.89[0.04,188.16]
Sackellares 2004	18/78	5/74		38.02%	3.42[1,11.72]
Schmidt 1993	7/71	2/68		15.14%	3.35[0.45,25.23]
Subtotal (99% CI)	320	278		100%	2.35[1.05,5.27]
Total events: 33 (Zonisamide), 12	2 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =3.05	5, df=3(P=0.38); I ² =1.63%				
Test for overall effect: Z=2.72(P=0	0.01)				
1.7.7 Anorexia					
Faught 2001	17/118	7/85		25.87%	1.75[0.58,5.24]
Guerrini 2013	7/107	4/100		13.15%	1.64[0.34,7.89]
Sackellares 2004	19/78	6/74	+	19.58%	3[0.97,9.31]
Schmidt 1993	9/71	1/68		3.25%	8.62[0.59,125.69]
Wu 2010	22/120	6/120	 ── + ──	19.08%	3.67[1.17,11.45]
Zhang 2011	16/120	6/120	+	19.08%	2.67[0.81,8.74]
Subtotal (99% CI)	614	567		100%	2.74[1.64,4.6]
	V	Vorse on placebo	0.01 0.1 1 10	¹⁰⁰ Worse on zonisamide	

Zonisamide add-on therapy for focal epilepsy (Review)



Study or subgroup	Zonisamide n/N	Placebo n/N		M-H	Risk Ratio , Fixed, 99	% CI		Weight	Risk Ratio M-H, Fixed, 99% CI
Total events: 90 (Zonisamide), 30 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =3.52,	df=5(P=0.62); I ² =0%								
Test for overall effect: Z=5.03(P<0.0	0001)								
		Worse on placebo	0.01	0.1	1	10	100	Worse on zonisamide	

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialised Register search strategy

- 1 Zonisamid* or Zonegran or Excegran AND INREGISTER
- 2 (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND INREGISTER

3 #1 NOT #2 AND INREGISTER

4 >12/02/2013:CRSCREATED AND INREGISTER

5 #3 AND #4 AND INREGISTER

Appendix 2. CENTRAL via CRSO search strategy

#1 zonisamid*:TI,AB,KY

#2 "1 2 benzisoxazole 3 methanesulfonamide" OR "3 sulfamoylmethyl 1 2 benzisoxazole" OR "benzo d isoxazol 3 yl methanesulfonamide" OR exceglan OR excegram OR excegran OR zonegran

#3 #1 OR #2

- #4 (epilep* OR seizure* OR convuls*):TI,AB,KY
- #5 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
- #6 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
- #7 #4 OR #5 OR #6

#8 #3 AND #7

#9 (monotherap* not (adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*)):TI

#10 #8 NOT #9

#11 31/01/2013 TO 30/09/2017:DL

#12 #10 AND #11

Appendix 3. MEDLINE search strategy

The following search strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials published in Lefebvre 2011.

1. (Zonisamid\$ or Zonegran or Excegran).tw.

- 2. exp Epilepsy/
- 3. exp Seizures/
- 4. (epilep\$ or seizure\$ or convuls\$).tw.

5. 2 or 3 or 4

Zonisamide add-on therapy for focal epilepsy (Review)

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6. exp *Pre-Eclampsia/ or exp *Eclampsia/

7.5 not 6

8. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 1 and 7 and 13

15. (monotherap\$ not (adjunct\$ or "add-on" or "add on" or adjuvant\$ or combination\$ or polytherap\$)).ti.

- 16. 14 not 15
- 17. remove duplicates from 16
- 18. limit 17 to ed=20130212-20170904
- 19. 17 not (1\$ or 2\$).ed.
- 20. 19 and (2013\$ or 2014\$ or 2015\$ or 2016\$ or 2017\$).dc.

21. 18 or 20

Appendix 4. ClinicalTrials.gov search strategy

Zonisamide | Epilepsy | Studies received from 02/12/2013 to 09/04/2017

Appendix 5. ICTRP search strategy

epilepsy in the Condition

zonisamide in the Intervention

Trials registered after 13/02/2013 selected manually

Appendix 6. SCOPUS search strategy

((TITLE-ABS-KEY(Zonisamide or Zonegran or Excegran)) and not (TITLE-ABS-KEY(monotherap* AND NOT (adjunct* or "add-on" or "add on")))) and (((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) and (TITLE-ABS-KEY(refractor* OR resist* OR nonrespons* OR non-respons* OR intractable))) and (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover or cross-over) PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR "parallel group" OR crossover or cross-over) PRE/2 (trial OR method OR procedure OR study))) AND (EXCLUDE(EXACTKEYWORD,"Animal experiment") OR EXCLUDE(EXACTKEYWORD,"Animal model"))

WHAT'S NEW

Date	Event	Description
4 September 2017	New search has been performed	Searches updated 4 September 2017; we included three new studies.

Zonisamide add-on therapy for focal epilepsy (Review)

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Date	Event	Description
4 September 2017	New citation required but conclusions have not changed	Conclusions are unchanged

HISTORY

Protocol first published: Issue 1, 1999 Review first published: Issue 2, 2000

Date	Event	Description
12 February 2013	New citation required and conclusions have changed	One new study has been included. Some adverse effects conclu- sions have changed.
12 February 2013	New search has been performed	Searches updated 12 February 2013.
15 February 2008	Amended	We re-ran our searches on 15 July 2007; several new potentially relevant studies were identified. These have been added to the 'studies awaiting classification' section and will be assessed for inclusion in the near future.
1 August 2005	New citation required and conclusions have changed	We re-ran our searches on 1 August 2005, which identified one new study (Brodie 2005). This has been added to the review.

CONTRIBUTIONS OF AUTHORS

Francesco Brigo and Simona Lattanzi independently assessed trials for inclusion and extracted data. Francesco Brigo carried out the statistical analyses and wrote the updated text of the review. Stanley C Igwe, Nicola L Bragazzi, and Masoud Behzadifar critically revised the text of the review and the accuracy of the analyses.

DECLARATIONS OF INTEREST

FB: Francesco Brigo received speaker's honoraria and travel support from Eisai, UCB Pharma, Italfarmaco and PeerVoice. He also acted as consultant for EISAI.

SL: none known SI: none known MB:none known NLB:none known

SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• National Institute for Health Research (NIHR), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We considered head-to-head drug trials for inclusion in this review update. However, no such trials met the inclusion criteria. We also changed the title from 'Zonisamide add-on for drug-resistant partial epilepsy' to 'Zonisamide add-on therapy for focal epilepsy'. We used the term 'focal', according to the most recent classification of epilepsies of the International League Against Epilepsy (ILAE; Kwan 2010). We also decided to avoid the term 'drug-resistant epilepsy', because according to the current definition by the ILAE, it should be defined as the 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies

Zonisamide add-on therapy for focal epilepsy (Review)

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or in combination) to achieve sustained seizure freedom'. However, some studies included in this review were conducted in participants receiving only one background antiepileptic drug; according to the ILAE definition, these participants would not be considered affected by drug-resistant epilepsy.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [administration & dosage] [adverse effects] [*therapeutic use]; Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination [methods]; Epilepsies, Partial [*drug therapy]; Intention to Treat Analysis; Numbers Needed To Treat; Randomized Controlled Trials as Topic; Treatment Failure; Zonisamide [administration & dosage] [adverse effects] [*therapeutic use]

MeSH check words

Humans