

Antidepressants for people with epilepsy and depression (Review)

Maguire MJ, Weston J, Singh J, Marson AG



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[Intervention Review]

Antidepressants for people with epilepsy and depression

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ABSTRACT

Background

Depressive disorders are the most common psychiatric comorbidity in patients with epilepsy, affecting around one-third, with a significant negative impact on quality of life. There is concern that patients may not be receiving appropriate treatment for their depression because of uncertainty regarding which antidepressant or class works best and the perceived risk of exacerbating seizures. This review aims to address these issues and inform clinical practice and future research.

Objectives

We aimed to review and synthesise evidence from randomised controlled trials of antidepressants and prospective non-randomised studies of antidepressants used for treating depression in patients with epilepsy. The primary objectives were to evaluate the efficacy and safety of antidepressants in treating depressive symptoms and the effect on seizure recurrence.

Search methods

We conducted a search of the following databases: the Cochrane Epilepsy Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 5), MEDLINE (Ovid), SCOPUS, PsycINFO, www.clinicaltrials.gov and conference proceedings, including studies published up to 31 May 2014. There were no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) and prospective non-randomised cohort controlled and uncontrolled studies investigating children or adults with epilepsy treated with an antidepressant for depressive symptoms. The intervention group consisted of patients receiving an antidepressant drug in addition to an existing antiepileptic drug regimen. The control group(s) consisted of patients receiving a placebo, comparative antidepressant, psychotherapy or no treatment in addition to an existing antiepileptic drug regimen.

Data collection and analysis

We extracted data on trial design factors, patient demographics and outcomes for each study. The primary outcomes were changes in depression scores (proportion with a greater than 50% improvement or mean difference) and change in seizure frequency (mean difference or proportion with a seizure recurrence or episode of status epilepticus, or both). Secondary outcomes included the number of patients withdrawing from the study and reasons for withdrawal, as well as any adverse events. Two authors undertook data extraction

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separately for each included study. We then cross-checked the data extraction. We assessed risk of bias using a version of the extended Cochrane Collaboration tool for assessing risk of bias in both randomised and non-randomised studies. We presented binary outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). We presented continuous outcomes as standardised mean differences (SMDs) with 95% CIs, and mean differences (MDs) with 95% CIs. If possible we intended to use meta-regression techniques to investigate possible sources of heterogeneity however this was not possible due to lack of data.

Main results

We included in the review eight studies (three RCTs and five prospective cohort studies) including 471 patients with epilepsy treated with an antidepressant. The RCTs were all single-centre studies comparing an antidepressant versus active control, placebo or no treatment. The five non-randomised prospective cohort studies reported on outcomes mainly in patients with partial epilepsy treated for depression with a selective serotonin reuptake inhibitor (SSRI). We rated all the RCTs and one prospective cohort study as having unclear risk of bias. We rated the four other prospective cohort studies as having high risk of bias. We were unable to perform any meta-analysis for the proportion with a greater than 50% improvement in depression scores because the studies reported on different treatment comparisons. The results are presented descriptively and show a varied responder rate of between 24% and 97%, depending on the antidepressant given. For the mean difference in depression score we were able to perform a limited meta-analysis of two prospective cohort studies of citalopram, including a total of 88 patients. This gave low quality evidence for the effect estimate of 1.17 (95% CI 0.96 to 1.38) in depression scores. Seizure frequency data were not reported in any RCTs and we were unable to perform any meta-analysis for prospective cohort studies due to the different treatment comparisons. The results are presented descriptively and show that treatment in three studies with a selective serotonin reuptake inhibitor did not significantly increase seizure frequency. Patients given an antidepressant were more likely to withdraw due to adverse events than inefficacy. Reported adverse events for SSRIs included nausea, dizziness, sedation, gastrointestinal disturbance and sexual dysfunction. Across three comparisons we rated the evidence as moderate quality due to the small sizes of the contributing studies and only one study each contributing to the comparisons. We rated the evidence for the final comparison as low quality as there was concern over the study methods in the two contributing studies.

Authors' conclusions

Existing evidence on the effectiveness of antidepressants in treating depressive symptoms associated with epilepsy is very limited. Only one small RCT demonstrated a statistically significant effect of venlafaxine on depressive symptoms. We have no high quality evidence to inform the choice of antidepressant drug or class of drug in treating depression in people with epilepsy. This review provides low quality evidence of safety in terms of seizure exacerbation with SSRIs, but there are no available comparative data on antidepressant classes and safety in relation to seizures. There are currently no comparative data on antidepressants and psychotherapy in treating depression in epilepsy, although psychotherapy could be considered in patients unwilling to take antidepressants or where there are unacceptable side effects. Further comparative clinical trials of antidepressants and psychotherapy in large cohorts of patients with epilepsy and depression are required to better inform treatment policy in the future.

PLAIN LANGUAGE SUMMARY

Antidepressants for people with epilepsy and depression

Background

Depressive disorders occur in approximately one-third of people with epilepsy, often requiring antidepressant treatment. However, depression often goes untreated in people with epilepsy, partly due to fear that antidepressants might cause seizures. There are different classes of antidepressants, however they all aim to increase key neurotransmitters in the brain, thereby alleviating depressive symptoms.

Characteristics of studies

We carried out a search of databases on 31 May 2014. We found eight studies that included 471 patients with epilepsy treated with an antidepressant. Three were randomised controlled trials and five were non-randomised prospective cohort studies. The studies observed the effect of different antidepressants, mainly a class of antidepressant called a selective serotonin reuptake inhibitor (SSRI).

Results

Taking all the evidence into account, the review found that there is very limited evidence demonstrating a significant effect of antidepressants on depressive symptoms in epilepsy. There was limited information on the effect of antidepressants on seizure control, however in the studies reporting this outcome there did not appear to be any significant worsening of seizures.

Quality of the studies

We assessed the studies with regard to bias and quality. Overall the quality of the evidence was rated as moderate for the clinical trials and low for the non-randomised prospective cohort studies. More high quality, larger trials of antidepressants are needed to examine how different classes of antidepressant compare and what impact they are likely to have on seizure control.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Paroxetine compared to doxepin for people with epilepsy and depression						
Patient or population: people with epilepsy and depression Settings: outpatients Intervention: paroxetine Comparison: doxepin						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Doxepin	Paroxetine				
> 50% reduction in depressive symptoms	706 per 1000	819 per 1000 (621 to 1000)	RR 1.16 (0.88 to 1.52)	67 (1 study)	⊕⊕⊕○ ¹ moderate	Only 1 study examined the influence of paroxetine versus doxepin on reduction in depression and it found no significant difference between the 2 drugs
Mean depression scores - HAMD scores		The mean HAMD depression score in the intervention groups was 0.65 higher (-2.15 lower to 3.45 higher)		67 (1 study)	⊕⊕⊕○ ¹ moderate	In the same study no differences were found between mean depression scores in patients taking paroxetine compared to those taking doxepin
Seizure frequency	-	-	-	0 (0 studies)	-	No data contributed to this outcome

Withdrawals (specific reasons)	88 per 1000	13 per 1000 (1 to 242)	RR 0.15 (0.01 to 2.74)	67 (1 study)	⊕⊕⊕○ ¹ moderate	In this study 0 patients withdrew from the paroxetine group and 3 withdrew from the doxepin group. No significant difference was found between the 2 groups
Cognitive functioning	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Quality of life	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Adverse effects	-	-	-	0 (0 studies)	-	No data contributed to this outcome

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

CI: confidence interval; **HAMD:** Hamilton Rating Scale for Depression; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

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

¹Quality downgraded for imprecision due to only one study contributing to the outcomes and it was a small study.

BACKGROUND

Description of the condition

Depressive disorders are the most common psychiatric comorbidity in patients with epilepsy (Tellez-Zenteno 2007), and they are the strongest predictor of poor quality of life (Boylan 2004). Symptoms of depression include low mood, tiredness and apathy. Sleep and cognitive functioning may also be affected. Depressive disorders occur in approximately one-third of patients with epilepsy (Baker 1996; Indaco 1992; Jacoby 1996; Mendez 1986). These disorders are broadly divided into unipolar (depression only) and bipolar disorders (depression associated with mania or hypomania) (American Psychiatric Association 2000). Depressive disorders in epilepsy may be mediated via the interplay of neurobiological, psychosocial and iatrogenic factors (Lambert 1999). Depressive symptoms or episodes may occur inter-ictally (i.e. they appear unrelated to seizures) or peri-ictally (preceding, during or following seizures). This is an important distinction as patients may require modification of their antiepileptic drug regime, commencement of antidepressant drug therapy, or both. In some patients the depressive symptoms may follow a significant period of seizure remission in previously uncontrolled epilepsy, thought to occur via neuro-biochemical changes and termed 'forced normalisation' (Trimble 1998). Studies examining clinical predictors of risk for depression in patients with epilepsy have produced inconsistent results (Lin 2012). There is a perceived greater risk of depression in patients with temporal lobe epilepsy, although elevated rates of depression have been found in generalised and extra-temporal focal epilepsy (Adams 2008). Epilepsy related factors as predictors of risk for depression are inconsistent. Psychosocial factors such as life stress, coping style, social support, perceived stigma and personality are more consistent predictors of depression in patients with epilepsy (Hermann 2000).

In 2008, the Food and Drug Administration issued a health alert about an increased risk of suicidal ideation in patients taking antiepileptic drugs (Hesdorffer 2009). This alert was based on a meta-analysis of approximately 28,000 patients who had participated in randomised controlled trials (RCTs) investigating 11 antiepileptic drugs. There were four completed suicides, all of whom had taken antiepileptic drugs, compared to no cases of suicide in the placebo groups (odds ratio (OR) 1.8; 95% confidence interval (CI) 1.24 to 2.66). Since this alert, a number of observational studies have investigated the association, reporting conflicting results, and a recent consensus statement on risk of suicide with antiepileptic drugs has been published by the International League Against Epilepsy (ILAE) Commission on Neuropsychobiology (Mula 2013). Whilst the exact risk of suicide with antiepileptic drugs is unknown, depression as a treatment-emergent adverse effect is associated with some antiepileptic drugs (GABAergic antiepileptic drugs: benzodiazepines, vigabatrin, gabapentin and also topiramate, levetiracetam and zonisamide) (Mula 2009).

Other antiepileptic drugs appear to have mood-stabilising properties (valproic acid, lamotrigine, carbamazepine, oxcarbazepine), which may benefit patients with epilepsy and depression. Enzyme-inducing antiepileptic drugs (i.e. carbamazepine) may lower plasma levels of antidepressants, thus impacting on their effectiveness.

Case-control studies have shown that patients with depression have a two- to seven-fold higher risk of developing epilepsy, implying a bi-directional relationship (Hesdorffer 2000; Hesdorffer 2006; Hesdorffer 2012). There could be a number of factors to explain this, for example shared pathophysiology involving disturbance in several key neurotransmitter systems (Bagdy 2007), structural lesions (frontal lobe tumours) or a genetic susceptibility. However, there is also the possibility that the use of antidepressants may trigger seizures. This is a common concern for healthcare professionals and may influence decisions to start antidepressant treatment (Cotterman-Hart 2010).

Description of the intervention

Antidepressants are a heterogeneous class of drugs that have been the mainstay of pharmacological treatment in treating depressive disorders. There are 10 classes of antidepressants used to treat depressive disorders, with 60% to 70% of depressive episodes responding to current treatment (Klerman 1990; Sackeim 2006). These are:

1. tricyclic antidepressants;
2. selective serotonin reuptake inhibitors;
3. serotonin-norepinephrine reuptake inhibitors;
4. monoamine oxidase inhibitors;
5. serotonin/antagonist reuptake inhibitors (i.e. trazodone);
6. dopamine and norepinephrine reuptake inhibitors (i.e. bupropion);
7. α -2 antagonists (i.e. mirtazapine);
8. norepinephrine reuptake inhibitors (i.e. reboxetine);
9. selective serotonin reuptake enhancers (i.e. tianeptine); and
10. serotonin 5HT_{2C} receptor antagonists (i.e. agomelatine).

These drugs work by targeting serotonergic and/or noradrenergic and/or dopaminergic neurotransmission, with the aim of increasing their synaptic concentrations (Stahl 2000). Glutamate antagonists represent a novel class of drug currently being tested in refractory depression (Zarate 2006).

The risk of seizures with antidepressants was reported in early studies of the first-generation antidepressants, notably tricyclic antidepressants (Preskorn 1992; Wroblewski 1990). Alper 2007 reviewed the incidence of seizures in 75,000 non-epileptic patients in phase II and phase III trials of antidepressant treatment. It reported lower incidence rates of seizures in those randomised to an antidepressant versus placebo (standardised incidence ratio 0.48; 95% CI 0.36 to 0.61) (Alper 2007). Coupland 2011 examined 60,746 primary care patients aged 65 and over treated for depression with antidepressants between 1996 and 2007 and showed

increased risks of epilepsy/seizures for selective serotonin reuptake inhibitors (hazard ratio (HR) 1.80; 95% CI 1.32 to 2.43) and other antidepressant classes (HR 2.20; 95% CI 1.46 to 3.30) versus tricyclic antidepressants. Venlafaxine was associated with the highest risk of seizures.

How the intervention might work

There appears to be a significant relationship between epilepsy and depression. It is emerging from the studies that they both share common neurobiological substrates involving hyperactivity of the hypothalamic pituitary adrenal axis and disturbance of different neurotransmitter systems, mainly serotonin and norepinephrine (Dell'osso 2013). The density of serotonin receptors is high in the mesial temporal and prefrontal areas (Gilliam 2005b). In critical brain regions, such as the limbic system and prefrontal areas, enforced serotonergic circuits seem to be responsible for increasing seizure threshold (Kondziella 2009).

Antidepressants of the selective serotonin reuptake inhibitor family have been reported not only to be safe in treating depression in patients with epilepsy but to possess antiepileptic properties, as shown in animal models of epilepsy (Hamid 2013). It has been suggested based on clinical data that selective serotonin reuptake inhibitors can decrease the seizure frequency in refractory epilepsy (Kondziella 2009). This is believed to be due to the increase in the concentration of serotonin. The study shows that the concentration of endogenous serotonin (5-HT) and the activity of its receptor subtypes, 5-HT(1A), 5-HT(2C), 5-HT(3) and 5-HT(7), play a significant role in the pathogenesis of epilepsies (Bagdy 2007). Medications with serotonin agonist and antagonist properties can therefore play a significant role in the pathogenesis of epilepsies.

Why it is important to do this review

Depression is common in patients with epilepsy and has a significant negative impact on quality of life (Gilliam 2005b; Kondziella 2009). There is concern that patients may not be receiving appropriate treatment for their depression because of uncertainty regarding which antidepressant or class works best and the perceived risk of exacerbating seizures. This review aims to address these issues and inform clinical practice and future research.

OBJECTIVES

We aimed to review and synthesise evidence from randomised controlled trials of antidepressants and prospective non-randomised studies of antidepressants used for treating depression in patients with epilepsy. The primary objectives were to evaluate the efficacy and safety of antidepressants in treating depressive symptoms and the effect on seizure recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs)
- Prospective non-randomised cohort controlled and uncontrolled studies
 - Prospective non-randomised cohort studies were considered in this review because of the known delayed effect of antidepressants on depressive symptoms which may not be effectively detected in short-term randomised trials. Similarly, prospective non-randomised studies are more likely to recruit populations of patients which better reflect clinical practice since depression can affect any patient with epilepsy.

Types of participants

We considered participants who satisfied all of the following criteria:

1. any age;
2. diagnosis of epilepsy (any type);
3. treated with antidepressants for co-existing depression (including patients with major depressive disorder, adjustment disorder and dysthymic disorder) based on standardised criteria and/or according to participant scores on validated tools (e.g. Hamilton Rating Scale for Depression).

Types of interventions

- Intervention group: patients who received an antidepressant drug in addition to an existing antiepileptic drug regimen.
- Control group(s): patients who received a placebo, comparative antidepressant, psychotherapy or no treatment in addition to an existing antiepileptic drug regimen.

Types of outcome measures

Primary outcomes

- Depression scores
 - The proportion of people with a greater than 50% improvement in depressive symptoms (defined as a 'response')
 - Mean difference in depression scores

If the data allowed, we planned to analyse outcomes at ≤ 12 weeks (short-term), 13 to 26 weeks and ≥ 26 weeks (long-term) however we were unable to perform these analyses.

- Change in seizure frequency
 - The mean difference in seizure frequency
 - The proportion of people with a seizure recurrence

- The proportion of people with an episode of status epilepticus

Secondary outcomes

- Withdrawals
 - For specific reasons
 - For any reasons
- Global state
 - Clinically important change in global state (as defined by the individual studies)
 - Relapse (as defined by the individual studies)
- Mental state score
 - Clinically important change in general mental state score
 - General mental state score (average and endpoint)
 - Clinically important change in specific symptoms (sleep, anhedonia, suicidal ideas)
 - Specific symptom score (average and endpoint)
- General functioning
 - Clinically important change in general functioning
 - General functioning score (average and endpoint)
- Cognitive functioning
 - Clinically important change in overall cognitive functioning
 - Overall cognitive functioning score (endpoint and average)
 - Clinically important change in specific cognitive functioning (attention, concentration, memory, language, executive functioning)
 - Specific cognitive score (average and endpoint)
- Quality of life
 - Clinically important change in quality of life
 - Any change in quality of life score (average and endpoint)
- Behaviour
 - Clinically important change in general behaviour
 - Any important change in general behaviour (average and endpoint)
 - Clinically important change in specific aspects of behaviour
 - Any important change in specific aspects of behaviour score (average and endpoint)
- Adverse effects
 - Death
 - Any non-serious general adverse effects (gastrointestinal effects, anorexia, dizziness, dry mouth, insomnia, sexual dysfunction, hypotension)

- Any serious, specific adverse effects (hypersensitivity reaction)
- Any change in general adverse effect score (average and endpoint)
- Clinically important change in specific adverse effects
- Any change in specific adverse effects score (average and endpoint)

Search methods for identification of studies

Electronic searches

We searched the following databases (search date 31 May 2014):

1. the Cochrane Epilepsy Group Specialised Register;
2. the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 5) ([Appendix 1](#));
3. MEDLINE (Ovid) ([Appendix 2](#));
4. SCOPUS;
5. PsycINFO; and
6. www.clinicaltrials.gov.

We adapted the MEDLINE search strategy for the SCOPUS and PsycINFO databases. There were no language restrictions.

Searching other resources

We checked the reference lists of retrieved studies for additional reports of relevant studies.

We contacted lead authors for any relevant unpublished material. We identified duplicate studies by screening reports according to title, authors names, location and medical institute. We omitted any duplicated studies.

We also identified any grey literature studies published in the last five years by searching:

1. ZETOC database;
2. ISI Proceedings;
3. International Bureau for Epilepsy (IBE) congress proceedings database;
4. ILAE congress proceedings database; and
5. abstract books of symposia and congresses, meeting abstracts and research reports.

Data collection and analysis

Selection of studies

Two authors (MM, JP) independently assessed all citations generated from the searches for inclusion. A third author (JS) re-inspected a random sample of 30% of citations to ensure reliability. Where disputes arose, we acquired the full report for more detailed scrutiny.

Data extraction and management

Two authors (MM, JP) undertook data extraction separately for each included study. We then cross-checked the data extraction. We extracted data using pre-standardised data extraction forms. A third author (JS) re-inspected a random 30% sample to ensure reliability. We discussed any disagreement, documented decisions and, if necessary, contacted trialists for clarification. We extracted the following information from the included studies:

Methodological and trial design

- Year of publication
- Number of study centres
- Language
- Industry funding
- Study design (RCT, prospective cohort study, retrospective cohort study)
 - Blinding
 - Type of control group (placebo, comparative antidepressant, no treatment)
- Sample size
- Follow-up period
- Class of antidepressant as intervention
- Dose range of intervention
- Inclusion and exclusion criteria

Patient demographic information

- Age range
- Number of male/female participants
- Duration of epilepsy
- Previous number of antiepileptic drugs
- Epilepsy type (focal, generalised, unclassified)
- Location of epilepsy (temporal, extra-temporal)
- Baseline mean depression score or severity
- Baseline mean seizure frequency/month

Outcomes

- The number of patients experiencing each outcome recorded per treatment group
- Number of drop-outs

Assessment of risk of bias in included studies

Two authors (JP, MM) assessed risk of bias in each included study separately. We cross-checked the 'Risk of bias' assessment. Due to the observational design of some of the studies, we utilised a version of the extended Cochrane Collaboration tool for assessing risk of bias, currently being developed by the Cochrane Non-Randomised Studies Methods Group. The tool examined selection bias (sequence generation, allocation concealment), performance

bias (blinding), attrition bias (incomplete outcome data), detection bias (blinding, other potential threats to validity), reporting bias (selective outcome reporting) and the influence of confounding variables. We rated the domains of blinding, incomplete outcome data, selective outcome reporting, confounding variables and other bias on a five-point scale ranging from low to high risk of bias according to the risk for the outcome (Appendix 3). The review authors determined the parameters of this scale (Table 1). For RCTs, we assessed all domains of the current Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).

We made an overall summary judgement of risk of bias for each study per outcome, followed by an overall judgement per outcome across studies. We had planned to incorporate the 'Risk of bias' judgements into the analysis using sensitivity analysis in that a secondary analysis of the data including only studies rated as low risk of bias was to be carried out. However; we were unable to do this due to the small amount of studies and lack of data. We presented both results in the Results section of the review. Where applicable, we created 'Summary of findings' tables for outcomes and graded each outcome accordingly using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2008). Outcomes to be reported in summary of findings tables include:- depression scores, seizure frequency, withdrawals, general functioning, cognitive functioning, quality of life and adverse effects as these outcomes are most likely to be measured and reported.

Measures of treatment effect

For binary outcomes (50% or greater improvement in depressive symptoms and % treatment withdrawal), we presented results as risk ratios (RRs) with 95% CIs.

For continuous outcomes (mean change in depression score), we presented results as mean differences (MDs) or standardised mean differences (SMDs) with 95% CIs.

Unit of analysis issues

Studies using a variety of depression measures created issues when combining results in meta-analysis. Where appropriate we used the SMD to allow for these variances.

Dealing with missing data

We sought missing statistics from studies through contact with the study authors. We sought reasons for missing data to determine whether the data were missing at random or not. We found no data missing at random.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important patient factors between studies (age, epilepsy type,

duration of epilepsy, baseline depression score, baseline seizure frequency) and trial factors (study design, type of control group, antidepressant drug class, type of depression disorder). We assessed statistical heterogeneity by using the I^2 statistic, with an I^2 value of 75% or more indicating considerable heterogeneity, 50% to 90% indicating substantial heterogeneity and 30% to 60% indicating moderate heterogeneity. If the I^2 value was 75% or more, we had made an a priori decision not to carry out meta-analysis; the review would then take a narrative form and all comparisons would be discussed according to the findings presented within the studies. We planned meta-regression techniques where possible to investigate possible sources of heterogeneity, however we were unable to investigate this within this review.

Assessment of reporting biases

1. Protocol versus full study

We investigated outcome reporting bias using the ORBIT classification system, allocating studies a letter from A-I if selective outcome reporting bias was suspected to be present (Kirkham 2010).

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Higgins 2011; Sterne 2000). Funnel plots can be used in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes.

Data synthesis

We synthesised data using the RR, the MD or the SMD depending on the measures used in both the controlled and uncontrolled studies. We carried out a sensitivity analysis to check for differences between a random-effects model and fixed-effect model in influencing conclusions. If differences between the models existed, we intended to report outcomes based on the random-effects model, which incorporates an assumption that the different studies are estimating different, yet related, intervention effects.

For controlled studies we intended to carry out meta-analysis using the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. For before and

after studies we used the inverse variance methods for continuous outcomes in meta-analysis.

We did not combine data for outcomes using both randomised and non-randomised studies. We reported combined data on outcomes for randomised and non-randomised studies separately.

Comparisons we expected to carry out included:

1. intervention group versus controls for change in mean depression score;
2. intervention group versus controls on % achieving a 50% improvement in depression scores;
3. intervention group versus controls for change in mean seizure frequency;
4. intervention versus controls on % of patients withdrawing from treatment.

We stratified each comparison by type of control group, study design and/or study characteristics to ensure appropriate combination of study data.

Subgroup analysis and investigation of heterogeneity

We stratified subgroup analysis by antidepressant drug class, epilepsy type and age. For investigation of heterogeneity, please see [Assessment of heterogeneity](#).

Sensitivity analysis

We intended to carry out sensitivity analysis if peculiarities in study quality were found ([Assessment of risk of bias in included studies](#)). We reported the analysis for all studies and then compared this to an analysis only of studies at low risk of bias.

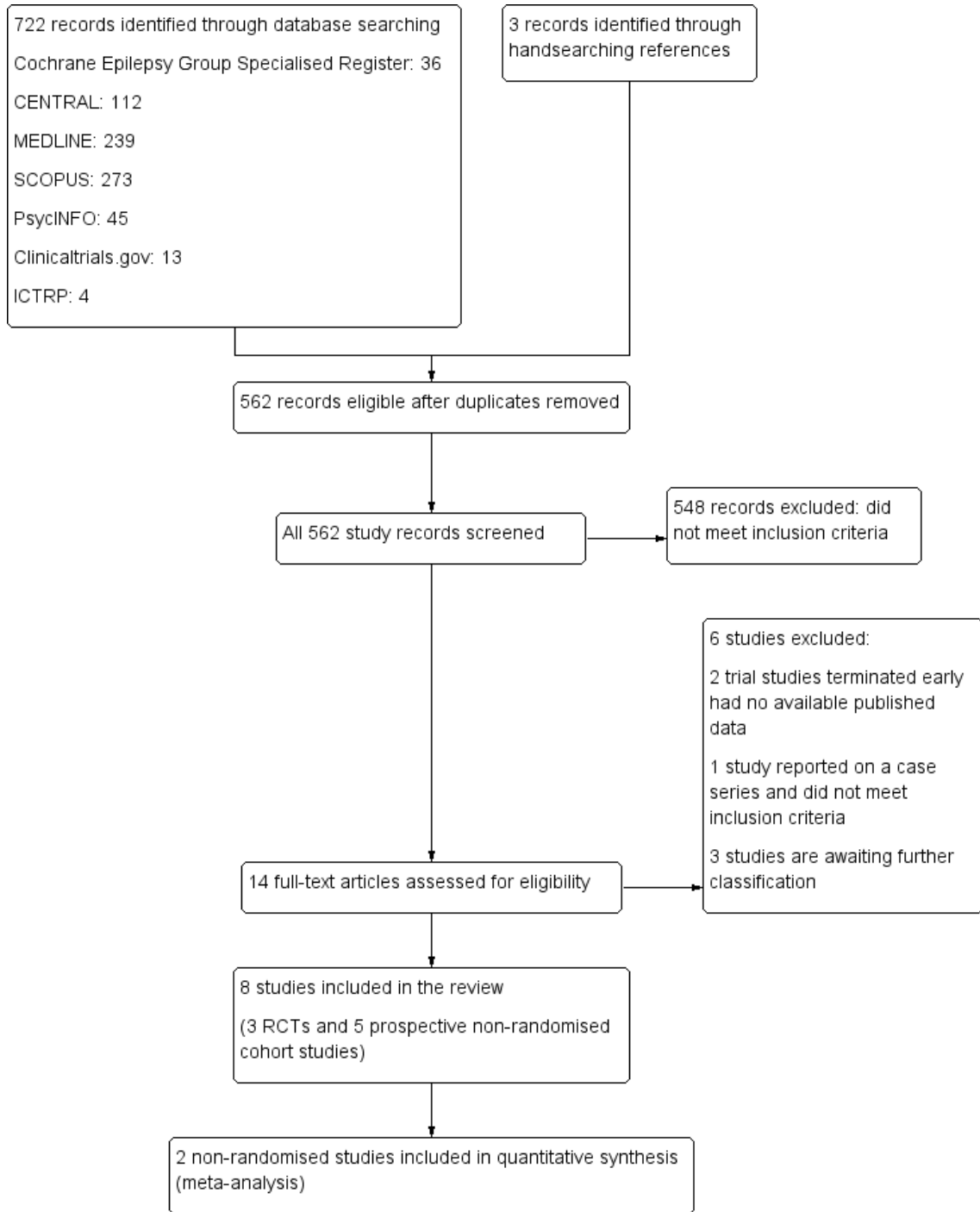
RESULTS

Description of studies

Results of the search

The searches, outlined above, identified 14 eligible studies. [Figure 1](#) outlines the flow diagram of search results, eligible records and study exclusions.

Figure 1. Study flow diagram.



After exclusions 11 studies remained. Three studies are awaiting further classification. Two studies met our inclusion criteria but did not report results for any of the primary or secondary outcomes (Harmant 1990; Machado 2010). We attempted to contact the authors for any further information on outcomes but we have not received a response. A further study, identified through www.clinicaltrials.gov, completed in September 2013 and compared escitalopram versus placebo (Conrad 2013). We attempted to contact the trial author for further information on outcomes but received no response.

Included studies

The eight remaining studies met all of the inclusion criteria. Of these eight reports, we identified three randomised controlled trials and five non-randomised prospective cohort studies examining the effect of antidepressant drugs.

We found three randomised trials of antidepressant versus active control, placebo or no treatment, which reported on the primary efficacy outcome and which met the inclusion criteria (Li 2005; Robertson 1985; Zhu 2004). All were single-centre studies. A total of 173 patients were randomised in these three studies, with 121 patients having partial epilepsy. The remaining five non-randomised prospective cohort studies reported on a total of 298 patients treated with an antidepressant, reported on the primary efficacy outcome and met the inclusion criteria (Hovorka 2000; Kanner 2000; Kuhn 2003; Specchio 2004; Thome-Souza 2007). Two hundred and eighty-two patients had partial epilepsy and were treated with a selective serotonin reuptake inhibitor.

Hovorka 2000 was a published, single-centre, prospective cohort study conducted in the Czech Republic on 43 patients. Two-thirds of patients had focal epilepsy. Patients were between the ages of 12 and 49 years and 35 patients were female. Inclusion criteria were defined as patients with a major depressive illness scoring more than 15 points on the Hamilton Rating Scale for Depression (HAMD). All patients received citalopram (mean daily dose 22.6 mg +/- 8.3 mg) for eight weeks. At four and eight weeks, depression scores and seizure frequencies were measured and compared to an unspecified baseline period. There were no treatment withdrawals and all 43 patients were included in the reported analysis.

Kanner 2000 was a published, single-centre, prospective cohort study conducted in the USA on 100 patients. Patients were aged between 6 and 62 years, 95% had focal onset epilepsy and 49 patients were female. Inclusion criteria were defined as patients with epilepsy and a depressive illness or obsessive compulsive disorder (n = 3). All patients received sertraline (25 mg to 200 mg/day; mean dose of 108 mg +/- 56.9 mg per day) and were followed up for 0.2 to 38 months. Monthly seizure frequencies were compared during the treatment period and compared to a 3- and 12- month retrospective baseline period. No changes in depression scores were

reported. Of the 100 patients, 18 withdrew from the study. All patients were included in the primary efficacy analysis.

Kuhn 2003 was a published, single-centre, prospective cohort study conducted in Germany on 75 patients. All had focal onset epilepsy (temporal lobe). The patients were aged between 19 and 68 years and 45 patients were female. Inclusion criteria were defined as patients having major depression with epilepsy and scoring more than 15 points on the HAMD depression scale. Twenty-seven patients received mirtazepine (mean daily dose 32.2 mg), 33 patients received citalopram (mean daily dose 24.2 mg) and 15 patients received reboxetine (mean daily dose 6.9 mg). Changes in depression scores and treatment responders were measured at four weeks and 20 to 30 weeks, and compared to baseline scores. Changes in seizure frequency were not measured. Forty-two patients dropped out; eight dropped out between baseline and week four, 34 dropped out between week four and weeks 20 to 30. The last observation carried forward was used and all patients were included in the primary efficacy outcomes.

Li 2005 was a published, single-centre, randomised controlled trial conducted in China on 67 patients. Forty-two patients had generalised onset epilepsy. The patients were aged between 14 and 62 years and 35 patients were female. Inclusion criteria were defined as patients having epilepsy defined by the ILAE classification and depressive illness with a HAMD score of more than 18. Thirty-three patients were randomised to paroxetine, which was started at 10 mg/day and titrated up to 40 mg/day depending on response. Thirty-four patients were randomised to doxepin started at 25 mg/day and titrated up according to response (mean 100 mg/day). The HAMD score was measured at eight weeks and compared to the baseline score. Seizure frequency was not assessed. Three patients in the doxepin treatment arm dropped out and were not included in the primary analysis.

Robertson 1985 was a published, single-centre, randomised, placebo-controlled trial conducted in the UK on 42 patients. The majority had focal onset epilepsy. The patients were aged between 18 and 60 years and 26 were female. Inclusion criteria were defined as patients with epilepsy and depression as defined by general criteria and a HAMD score of more than 15. Patients were randomised to amitriptyline, nomifensine or placebo. All treatment arms completed a six-week phase and then both active treatment arms continued the study for a further six weeks. Depression scores were compared to baseline at 12 weeks of treatment. Three patients withdrew from the study. Twenty eight patients within active treatment arms were included in the primary outcome analysis at 12 weeks.

Specchio 2004 was a published, multi-centre, prospective cohort study conducted in Italy on 45 patients. Forty-four patients had focal onset epilepsy. The patients had a mean age of 42.7 years and 31 were female. Inclusion criteria were defined as patients with

epilepsy on a stable regime of antiepileptic medication and with a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or more. All patients received citalopram for four months. Depression scores and seizure frequency were measured at two and four months on citalopram and compared to baseline measures. Six patients withdrew from the study and were omitted from the primary outcome analysis.

[Thome-Souza 2007](#) was a published, single-centre, prospective cohort study conducted in Brazil on 36 patients with focal onset epilepsy. The patients were aged between six and 18 years and 19 were females. Inclusion criteria were defined as patients with epilepsy and a diagnosis of major depressive disorder as per Kiddie SADS score. Twenty-eight patients received sertraline (50 mg to 200 mg/day) and eight patients received fluoxetine (20 mg to 80 mg/day) for a duration of 12 to 78 months. Change in depression scores was measured during the treatment phase and compared to a six-month baseline period. Seizure exacerbation was also observed during the treatment phase. One patient dropped out of the study. All patients were included in the primary outcome analysis.

[Zhu 2004](#) was a published, single-centre, randomised trial of venlafaxine versus no treatment conducted in China on 64 patients. The patients were aged between 7 and 60 years. Inclusion criteria were defined as patients with epilepsy (presumed genetic or cause unknown) and depression. Thirty-two patients were randomised to venlafaxine 25 mg to 75 mg/day and 32 patients received no treatment. Depression scores were measured using the HAMD at eight weeks of treatment and compared to baseline. Seizure frequency as a primary outcome was not reported. There were no drop-outs and all patients were included in the primary outcome analysis.

Clinical heterogeneity

Five studies reported outcomes for adults patient only ([Hovorka 2000](#); [Kuhn 2003](#); [Li 2005](#); [Robertson 1985](#); [Specchio 2004](#)). Three studies reported outcomes for adults and children ([Kanner 2000](#); [Thome-Souza 2007](#); [Zhu 2004](#)). Six studies included patients with focal onset epilepsy, whereas two studies included patients with generalised onset epilepsy ([Li 2005](#); [Zhu 2004](#)). In all trials there was a larger or equal number of female pa-

tients. Six studies evaluated the efficacy of selective serotonin reuptake inhibitors (citalopram, sertraline, fluoxetine) versus no treatment, a tricyclic antidepressant (doxepin), a norepinephrine reuptake inhibitor (reboxetine) or a-2 antagonists (mirtazapine) ([Hovorka 2000](#); [Kanner 2000](#); [Kuhn 2003](#); [Li 2005](#); [Specchio 2004](#); [Thome-Souza 2007](#)). The remaining two studies evaluated a serotonin-norepinephrine reuptake inhibitor (venlafaxine) versus no treatment ([Zhu 2004](#)) and a tricyclic antidepressant (amitriptyline) versus dopamine and a norepinephrine reuptake inhibitor (nomifensine) ([Robertson 1985](#)). Five studies used the Hamilton Rating Scale for depression ([Hovorka 2000](#); [Kuhn 2003](#); [Li 2005](#); [Robertson 1985](#); [Zhu 2004](#)). One study used the Montgomery-Åsberg Depression Rating Scale (MADRS) ([Specchio 2004](#)), one study used the Kiddie SADS depression score ([Thome-Souza 2007](#)), and one study did not report the use of a specific depression rating scale ([Kanner 2000](#)).

Excluded studies

We excluded three studies. Two studies identified through www.clinicaltrials.gov were clinical trials comparing cognitive behavioural therapy versus sertraline and escitalopram versus no treatment, respectively ([Gilliam 2005a](#); [Kocsis 2007](#)). Both trials were terminated early due to problems with recruitment. There were no available published data for either trial and we excluded both. The third study reported on a small case series of patients with epilepsy taking a combined tricyclic antidepressant and SSRI for depression and did not fulfil the inclusion criteria ([Blumer 1997](#)). See [Characteristics of excluded studies](#) for more details of the studies.

Risk of bias in included studies

We rated risk of bias across each domain for each study and then made an overall risk of bias judgement for each study. Overall, we rated four studies as high risk of bias ([Hovorka 2000](#); [Kanner 2000](#); [Kuhn 2003](#); [Thome-Souza 2007](#)), and we rated four as unclear risk of bias ([Li 2005](#); [Robertson 1985](#); [Specchio 2004](#); [Zhu 2004](#)). See [Figure 2](#) for a 'Risk of bias' summary (review authors' judgements about each risk of bias item for each included study).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Confounding variables
Hovorka 2000	-	-	-	-	+	+	+	-
Kanner 2000	-	-	-	-	+	+	-	-
Kuhn 2003	-	-	?	?	?	+	+	-
Li 2005	+	?	+	+	?	-	?	+
Robertson 1985	+	+	+	+	?	+	?	+
Specchio 2004	-	-	?	?	+	+	+	-
Thome-Souza 2007	-	-	-	?	+	+	+	-
Zhu 2004	?	?	?	?	+	+	?	+

Allocation

We rated two RCTs as low risk of bias for sequence generation as they used adequate methods (Li 2005; Robertson 1985). For allocation concealment we rated Li 2005 as unclear and we rated Robertson 1985 as low risk of bias. We rated the other RCT as unclear risk of bias for both sequence generation and allocation concealment (Zhu 2004). (See the 'Risk of bias' tables for more detailed information on methodology).

The prospective cohort studies were non-randomised studies (Hovorka 2000; Kanner 2000; Kuhn 2003; Specchio 2004; Thome-Souza 2007), and therefore we rated them as high risk of bias for these two domains.

Blinding

For the RCTs, we rated two as low risk of bias as study personnel, participants and outcome assessors were blinded (Li 2005; Robertson 1985). There were no clear methods of blinding reported for the third RCT, therefore we rated this study as unclear risk of bias (Zhu 2004).

For the prospective cohort studies, there was either no reported blinding of participants or outcome assessors (Hovorka 2000; Kanner 2000; Thome-Souza 2007), therefore we rated these studies as high risk of bias. For two other non-randomised studies blinding was reported but the methods were unclear and so we rated them as unclear risk of bias (Kuhn 2003; Specchio 2004).

Incomplete outcome data

For the RCTs, two reported missing data and did not perform an intention-to-treat analysis, but they did report both numerator and denominator data (Li 2005; Robertson 1985). We rated these as unclear risk of bias. The third RCT did not report any missing data and an intention-to-treat analysis was carried out, therefore we rated this study as low risk of bias (Zhu 2004). (See the 'Risk of bias' tables for more detailed information on methodology).

For the prospective cohort studies, we rated four as low risk of bias as they either had no missing data or carried out an intention-to-treat analysis (Hovorka 2000; Kanner 2000; Specchio 2004; Thome-Souza 2007). The fifth study reported missing data with 18 patients lost to follow-up and used the last observation carried forward approach in analysis; we therefore rated this study as unclear risk of bias (Kuhn 2003).

Selective reporting

We rated all studies except for one RCT (Li 2005) as low risk of bias as they reported outcomes that were clearly stated in their methods section. For the study by Li 2005, adverse event outcomes were not reported but were stated as an outcome in their methods

section, therefore we rated this study as high risk of bias and this study was allocated the letter E on the ORBIT classification system as it is clear that this outcome was measured but not necessarily analysed.

Other potential sources of bias

One prospective cohort study used an insufficient measure of depression, by looking for "complete resolution of identified target psychiatric symptoms" as a measure of response to treatment; we therefore rated it as high risk of bias (Kanner 2000).

For the RCTs it was unclear whether there were any other potential sources of bias and so we rated all the RCTs as unclear risk of bias for this domain. We rated the other non-randomised studies as low risk of bias (Hovorka 2000; Kuhn 2003; Specchio 2004; Thome-Souza 2007).

Confounding variables

Risk of bias for confounding variables was only assessed in non-randomised studies. All were rated as high risk of bias as no study considered the importance of confounding factors or adjusted for them appropriately within the analyses.

Effects of interventions

See: [Summary of findings for the main comparison](#) Paroxetine compared to doxepin for people with epilepsy and depression; [Summary of findings 2](#) Amitriptyline compared to nomifensine for people with epilepsy and depression; [Summary of findings 3](#) Venlafaxine compared to no treatment for people with epilepsy and depression; [Summary of findings 4](#) Citalopram (before and after) for people with epilepsy and depression

Primary outcomes

(I) Depression scores: proportion with a greater than 50% improvement

All randomised controlled trials (RCTs) reported on the proportion with a 50% or more improvement in depression scores. The RCTs analysed different treatment comparisons and we were unable to combine the data in meta-analysis.

Li 2005 compared paroxetine (20 mg to 40 mg/day) versus doxepin (mean dose 100 mg/day), including a total of 67 patients. The numbers of responders were 27/33 (82%) in the paroxetine group and 24/34 (71%) in the doxepin group. The risk ratio for the proportion with a 50% of more improvement in depression

scores for paroxetine versus doxepin was 1.16 (95% confidence interval (CI) 0.88 to 1.52; P value > 0.05) (Analysis 1.1).

Robertson 1985 compared amitriptyline (75 mg/day) versus nomifensine (75 mg/day) versus placebo, including a total of 42 patients. The number of responders was reported at 12 weeks for active treatment groups. The number of responders for all treatment groups at six weeks is not reported. The numbers of responders at 12 weeks were 6/14 (43%) in the amitriptyline group and 11/14 (79%) in the nomifensine group. The risk ratio for the proportion with a 50% or more improvement in depression scores for amitriptyline versus nomifensine was 0.55 (95% CI 0.28 to 1.06; P value > 0.05) (Analysis 2.1).

Zhu 2004 compared venlafaxine (25 mg to 75 mg/day) versus no treatment and included 64 patients. The numbers of responders were 22/32 (69%) in the venlafaxine group and 6/32 (19%) in the no treatment group. The risk ratio for the proportion with a 50% or more improvement in depression scores for venlafaxine versus no treatment was 3.25 (95% CI 1.19 to 8.90; P value < 0.05) (Analysis 3.1).

Four of five prospective cohort studies reported on the proportion with a 50% or more improvement in depression scores. The fifth study did not use a validated depression scale (Kanner 2000).

Hovorka 2000 observed 28/43 (65%) patients with a 50% or more improvement in depression scores following eight weeks of treatment with citalopram (mean dose 23 mg/day).

Kuhn 2003 observed 17/27 patients (52%) in the mirtazepine group (mean dose 32 mg/day), 12/33 patients (36%) in the citalopram group (mean dose 24 mg/day) and 8/15 patients (53%) in the reboxetine group (mean dose 7 mg/day) with a 50% or more improvement in depression scores following 20 to 30 weeks of treatment. There was no statistical difference between the treatment groups.

Specchio 2004 observed 11/45 patients (24%) with a 50% or more improvement in depression scores following four months of treatment with citalopram (20 mg/day).

Thome-Souza 2007 observed 35/36 patients (97%) with a 50% or more improvement in depression scores following one year of treatment with sertraline (mean dose 111 mg/day) or fluoxetine (mean 46 mg/day).

(2) Depression scores: mean difference

Two of three RCTS reported on the mean difference in depression scores using the Hamilton Rating Scale for Depression (HAMD) depression scale (Li 2005; Zhu 2004). The RCTs compared different treatment groups and we were unable to combine the data in any meta-analysis.

Li 2005 compared paroxetine (20 mg to 40 mg/day) and doxepin (mean dose 100 mg/day), including a total of 67 patients. The effect estimate for the mean difference in depression scores for paroxetine versus doxepin was 0.65 (95% CI -2.15 to 3.45) (Analysis 1.2). There was no significant difference between the

treatment groups.

Zhu 2004 compared venlafaxine (25 mg to 75 mg/day) versus no treatment and included 64 patients. The effect estimate for the mean difference in depression scores for venlafaxine versus no treatment was -7.59 (95% CI -11.52 to -3.66) (Analysis 3.2). There was a statistically significant difference between treatment groups.

Three of five prospective cohort studies reported on the mean difference in depression scores (Hovorka 2000; Kuhn 2003; Specchio 2004).

We were able to perform meta-analysis, pooling data across two uncontrolled studies of citalopram including a total of 88 patients (Hovorka 2000; Specchio 2004). The average doses of citalopram were 22 mg/day and 20 mg/day respectively. The effect estimate for the standardised mean difference (SMD) in depression scores before and after was large, with an estimate of 1.17 (95% CI 0.96 to 1.38) (Analysis 4.1). The I^2 statistic for heterogeneity was 53%, which may reflect differences between the two studies in the treatment period. One study reported outcomes following four months of treatment (Specchio 2004), versus two months of treatment in the other study (Hovorka 2000). Due to the level of statistical heterogeneity we performed a random-effects analysis, which showed no change in significance (SMD 1.17; 95% CI 0.86 to 1.47).

The remaining study reported mean depression scores before and after treatment with mirtazepine, citalopram and reboxetine (Kuhn 2003). Baseline mean depression scores on the HAMD depression scale were 23, 22.5 and 23 respectively. Following 20 to 30 weeks of treatment the mean depression scores decreased to 13.5, 14 and 13.5 respectively. There were no significant differences according to treatment group.

(3) Seizure frequency: mean difference

None of the RCTs reported on mean difference in seizure frequency between baseline and end of treatment period. One RCT reported no increase in seizure frequency in both treatment groups (Li 2005).

Three of five prospective studies reported on changes in mean seizure frequency between baseline and treatment periods (Hovorka 2000; Kanner 2000; Specchio 2004).

We were able to perform meta-analysis, pooling data across two uncontrolled studies of citalopram including a total of 88 patients (Hovorka 2000; Specchio 2004) (Analysis 4.2). The I^2 statistic for heterogeneity in the effect estimate for the standardised mean difference in seizure frequency was 81%. We have therefore not reported the effect estimate. Possible reasons for a high I^2 statistic value include differences in mean baseline seizure frequency, treatment duration and mean age of patients.

Kanner 2000 reported no statistically significant difference in seizure frequency at baseline versus treatment period for the 100 patients treated with sertraline (mean dose 108 mg/day).

(4) Seizure frequency: seizure recurrence or episode of status epilepticus

Only one study reported on one patient with a seizure recurrence (Specchio 2004). There were no reported episodes of status epilepticus reported in any of the eight studies.

Secondary outcomes

(1) Withdrawals: for any reason

Of the RCTs, two reported clearly the number of patients withdrawing for any reason (Li 2005; Robertson 1985).

Li 2005 reported 3/34 patients (9%) withdrawing from the doxepin treatment group versus 0/33 patients from the paroxetine group. The risk ratio for treatment withdrawal for paroxetine versus doxepin was 0.15 (95% CI 0.01 to 2.74; P value = 0.20) (Analysis 1.3). The specific reasons for withdrawal were not reported.

Robertson 1985 reported 1/14 patients (7%) withdrawing from the amitriptyline group, 1/14 from the nomifensine group and 1/14 from the placebo group. The patient withdrew from the nomifensine group because of increased seizures.

All five prospective studies reported on the number of patients withdrawing from the study.

Hovorka 2000 reported no treatment withdrawals from the study. Kanner 2000 reported 18/100 patients (18%) treated with sertraline withdrawing from the study. All withdrew due to adverse events.

Kuhn 2003 reported 20/27 patients (74%) in the mirtazepine group, 16/33 patients (48%) in the citalopram group and 6/15 patients (40%) in the reboxetine group withdrawing from the study after 20 to 30 weeks of treatment. Adverse events accounted for 8/20 withdrawing from the mirtazepine group, 6/16 from the citalopram group and 3/6 from the reboxetine group. Only three patients (two mirtazepine and one citalopram) withdrew due to inefficacy. The remaining 22 patients were lost to follow-up.

Specchio 2004 reported 6/45 patients (13%) treated with citalopram withdrawing from the study. Four withdrew because of adverse events, one due to poor compliance and one due to concurrent illness.

Thome-Souza 2007 reported 1/36 patients treated with a selective serotonin reuptake inhibitor (SSRI) (sertraline) withdrawing because of exacerbation of seizures.

(2) Global State

None of the included studies reported on global state outcomes

(3) Mental State

None of the included studies reported on mental state outcomes

(4) General Functioning

None of the included studies reported on general functioning outcomes

(5) Cognitive Functioning

None of the included studies reported on cognitive functioning outcomes

(6) Quality of life

None of the included studies reported on quality of life outcomes

(7) Behaviour

None of the included studies reported on behaviour outcomes

(8) Adverse effects

Of the RCTs, one reported clearly the number of patients experiencing specific side effects in the treatment groups (Li 2005). Comparing paroxetine versus doxepin, the risk ratio for blurred vision was 0.34 (95% CI 0.09 to 1.32), dizziness 0.21 (95% CI 0.03 to 1.37), dry mouth 0.26 (95% CI 0.06 to 1.20), sleep disorders 0.32 (95% CI 0.08 to 1.20) and urinary retention 0.34 (95% CI 0.01 to 21.99) (see Analysis 1.4). There were no significant differences between treatment groups.

All five prospective cohort studies reported on adverse events. The studies analysed different treatment comparisons and we were unable to combine the data in meta-analysis.

Hovorka 2000 reported 3/43 patients (7%) experiencing nausea and 2/43 patients (5%) experiencing sexual dysfunction following eight weeks of treatment with citalopram.

Kanner 2000 reported 9/100 patients (9%) experiencing sedation, 7/100 patients (7%) experiencing hypomanic symptoms, 1/100 patients (1%) experiencing rheumatic pain and 1/100 patients (1%) experiencing myoclonus following an average 10-month duration of treatment with sertraline.

Kuhn 2003 reported 13/75 patients experiencing side effects; weight gain (5/75), sedation (2/75) and sexual dysfunction (2/75) were the most common side effects.

Specchio 2004 reported 22/45 patients (56%) experiencing side effects; headache (15%), nausea (11%), dizziness (9%), drowsiness (7%) and fatigue (7%) were the most common side effects.

Thome-Souza 2007 reported 1/36 patients (3%) experiencing facial rash and 1/36 patients (3%) experiencing gastrointestinal disorder.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Amitriptyline compared to nomifensine for people with epilepsy and depression						
Patient or population: people with epilepsy and depression Settings: outpatients Intervention: amitriptyline Comparison: nomifensine						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nomifensine	Amitriptyline				
> 50% reduction in depressive symptoms	786 per 1000	432 per 1000 (220 to 833)	RR 0.55 (0.28 to 1.06)	28 (1 study)	⊕⊕⊕⊕ ¹ moderate	1 study compared amitriptyline and nomifensine in reducing seizures and there was no significant difference found between the 2 groups
Seizure frequency	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Withdrawals	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Cognitive functioning	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Quality of life	-	-	-	0 (0 studies)	-	No data contributed to this outcome

Adverse effects	-	-	-	0 (0 studies)	-	No data contributed to this outcome
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

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

¹Quality downgraded for imprecision due to only one study contributing to the outcomes and it was a small study.

Venlafaxine compared to no treatment for people with epilepsy and depression						
Patient or population: people with epilepsy and depression Settings: outpatients Intervention: venlafaxine Comparison: no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Venlafaxine				
> 50% reduction in depressive symptoms	125 per 1000	406 per 1000 (149 to 1000)	RR 3.25 (1.19 to 8.9)	64 (1 study)	⊕⊕⊕○ ¹ moderate	1 study compared venlafaxine to a no treatment control group and found that venlafaxine was more than 3 times more effective in reducing seizures compared to controls
Mean depression scores - HAMD		The mean HAMD depression score in the intervention groups was 7.59 lower (-11.52 to -3.66 lower)		64 (1 study)	⊕⊕⊕○ ¹ moderate	The same study found mean depression scores to be significantly lower in the venlafaxine group compared to the control group
Seizure frequency	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Withdrawals	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Cognitive functioning	-	-	-	0 (0 studies)	-	No data contributed to this outcome

Quality of life	-	-	-	0 (0 studies)	-	No data contributed to this outcome
Adverse effects	-	-	-	0 (0 studies)	-	No data contributed to this outcome

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

CI: confidence interval; **HAMD:** Hamilton Rating Scale for Depression; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

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

¹Quality downgraded for imprecision due to only one study contributing to the outcomes and it was a small study.

Citalopram (before and after) for people with epilepsy and depression

Patient or population: people with epilepsy and depression

Settings: outpatients

Intervention: citalopram (before and after)

Outcomes	Illustrative comparative risks* (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Corresponding risk			
	Citalopram (before and after)			
Mean depression scores - HAMD	The mean HAMD depression score in the intervention groups was 1.17 higher (0.96 to 1.38 higher)	88 (2 studies)	⊕⊕○○ low ^{1,2}	2 before and after studies investigated citalopram and found that depression scores were significantly lower after treatment
Mean monthly seizure frequency		88 (2 studies)	⊕○○○ very low ^{1,3}	2 studies found mixed evidence for the effect of citalopram on seizure frequency. Due to high heterogeneity the overall effect estimate is not presented

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

CI: confidence interval; **HAMD:** Hamilton Rating Scale for Depression

GRADE Working Group grades of evidence

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

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

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

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

¹Across the studies there were concerns about bias with regards to the methods of blinding and methods to deal with confounding variables.

²Large effect found.

³Statistical heterogeneity was significant ($P = 0.02$; $I^2 = 81\%$).

DISCUSSION

Summary of main results

Depression is the most common psychiatric comorbidity in epilepsy and is associated with poor quality of life (Fiest 2013; Taylor 2011). Depression is also a risk factor for refractory epilepsy (Anhoury 2000; Hitiris 2007), suggesting a bidirectional relationship between the two conditions. This may reflect shared pathophysiology, for example changes in serotonin neurotransmission, hyperactivity of the hypothalamic pituitary adrenal axis and imbalances between the excitatory and inhibitory neurotransmitters glutamate and GABA respectively (Kanner 2011). The association may also reflect iatrogenic interplay between antiepileptic drugs and antidepressants used to treat depression and epilepsy.

In this review we synthesised the available data from randomised trials and non-randomised prospective studies of antidepressants used to treat depression in patients with epilepsy. We specifically sought to examine the effect of antidepressants on depressive symptoms and any potential risk of worsening seizures. We included non-randomised studies because of the delayed effect of antidepressants on depressive symptoms and to better reflect effectiveness in populations seen in clinical practice. However, including non-randomised studies within this review may have exposed to selection biases, including publication bias which could lead to unreliable and often inflated estimates of effect (Maguire 2008). Similarly confounding may occur where allocation to treatment is influenced by unmeasured factors which cannot be accounted for within a analysis, for example comorbidities or level of education. The review identified no large, well-conducted randomised controlled trials (RCTs) of antidepressant treatment used in epilepsy patients, and our review included three small RCTs. There were no published trials comparing antidepressant treatment versus psychotherapy in patients with epilepsy. The RCTs showed that venlafaxine significantly improved depressive symptoms when compared to no treatment, and that there was no difference between amitriptyline and nomifensine in improving depressive symptoms. The RCTs did not allow meaningful comparisons among the different classes of antidepressants. We therefore do not know which antidepressant or class of antidepressant is most effective. None of the RCTs reported seizure frequency changes during the trial. Only one RCT reported information on adverse events. We therefore have no randomised data to reliably inform on the likely impact of antidepressants on seizure control. We have limited information on adverse events encountered in clinical trials.

The five prospective cohort studies were of low quality, examining small numbers of patients treated predominantly with SSRIs. The combined meta-analysis of two studies examining citalopram at 20 mg/day showed evidence of an effect on depressive symptoms. We could not combine the data on seizure frequency changes due to marked heterogeneity. However in the three studies reporting seizure frequency changes, none detected a significant increase in

seizures. Only one study reported on one patient with a seizure recurrence on antidepressant treatment (citalopram). Whilst the data are of low quality in terms of impact on seizures, there is broad agreement across the prospective cohort studies of limited or no impact on seizures with selective serotonin reuptake inhibitors (SSRIs).

Patients withdrawing from antidepressants were more likely to do so because of adverse events rather than lack of efficacy. Reported adverse events for SSRIs included nausea, dizziness, sedation, gastrointestinal disturbance and sexual dysfunction. We have no reliable information on the comparative risk of adverse events with different classes of antidepressant treatment.

This review has ascertained that there is very limited evidence of an effect of antidepressants on depressive symptoms in patients with epilepsy. We do not have any reliable high-quality evidence to inform on treatment effect or the best choice of antidepressant drug or class of drug for treating depression with the lowest risk of seizure exacerbation. We do not have any evidence on how antidepressants compare with psychotherapy in patients with epilepsy and depression.

Quality of the evidence

Overall, we rated four prospective cohort studies as high risk of bias (Hovorka 2000; Kanner 2000; Kuhn 2003; Thome-Souza 2007), and four studies (all RCTs and one prospective cohort study) as unclear risk of bias (Li 2005; Robertson 1985; Specchio 2004; Zhu 2004). The 'Summary of findings' tables for each comparison examined shows that the quality of the evidence ranged from moderate quality to low quality. Where data were combined in meta-analysis we rated the quality of evidence as low.

Potential biases in the review process

One potential bias in the review process concerns the extended risk of bias tool for non-randomised studies. The tool is designed for the purpose of primarily assessing cohort-like studies which have control groups. In our study we identified three studies which were uncontrolled and used this risk of bias tool to assess them for risk of bias and this may have brought bias into the review process. There is currently a lack of quality assessment tools which are deemed appropriate for these types of observational studies therefore we took the decision to use the same tool across all included studies. With respect to the same tool, the parameters for assessing risk of bias across all domains except sequence generation and allocation concealment were review author defined and therefore specific to this review only. Although this was part of how the tool was designed to be used, this may have introduced bias into the review process.

AUTHORS' CONCLUSIONS

Implications for practice

Existing evidence on the effectiveness of antidepressants in treating depressive symptoms associated with epilepsy is very limited. Only one small randomised controlled trial (RCT) demonstrated a statistically significant effect of venlafaxine on depressive symptoms, although the study had unclear bias and did not address the impact of seizure control on outcomes. The remaining analyses did not demonstrate a statistically significant effect on depressive symptoms, although the estimates are in the direction of a treatment effect. We have no high quality evidence to inform the choice of antidepressant drug or class of drug for treating depression in people with epilepsy. Two expert consensus statements recommend selective serotonin reuptake inhibitors (SSRIs) as first-line treatment, given better safety and tolerability (Barry 2008;

Kerr 2011). This review provides low-quality evidence of safety in terms of seizure exacerbation with SSRIs, but there are no available comparative data on antidepressant classes and safety in relation to seizures. There are currently no comparative data on antidepressants and psychotherapy for treating depression in epilepsy, although psychotherapy could be considered in patients unwilling to take antidepressants or where there are unacceptable side effects.

Implications for research

Randomised controlled trials of antidepressants and psychotherapy in large cohorts of patients with epilepsy and depression are needed to better inform treatment policy in the future. Quality of life outcomes would be an additional useful measure in evaluating treatment effect.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hovorka 2000

Methods	A single-centre, non-randomised, uncontrolled, prospective before and after study (Prague) Baseline period: 2 months Treatment period: 8 weeks
Participants	43 people with focal epilepsy exceeding 15 points on the HAMD-21 scale for depression 35 females and 8 males Aged 21 to 49 years: mean 33.2 years
Interventions	Citalopram at a flexible dose; the average dose was 19.3 mg +/- 2.6 mg at the end of the first month, 22.62 mg +/- 8.3 mg at the end of the second month
Outcomes	1) Seizure frequency 2) Depressive symptoms measured by the HAMD-21 3) Adverse effects
Notes	No drop-outs and no exclusions from the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomisation methods used
Allocation concealment (selection bias)	High risk	No methods for concealing allocation used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No methods of blinding used. Rated 5 on scale for risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessor not blinded. Rated 5 on scale for risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data. Rated 1 on scale for risk of bias
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available. Rated 2 on scale for risk of bias
Other bias	Low risk	No other risk of bias detected. Rated 1 on scale for risk of bias

Hovorka 2000 (Continued)

Confounding variables	High risk	No confounding variables considered or adjusted for. Rated 5 on scale for risk of bias
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Kanner 2000

Methods	A single-centre, non-randomised, uncontrolled, prospective before and after study (US) Baseline period: Not reported Treatment period: Mean 10.3 months (0.2-38 months)	
Participants	100 people with focal epilepsy, with depressive or obsessive compulsive disorder 51 males and 49 females Aged 6 to 62 years: mean 29.9 years	
Interventions	Sertraline, mean dose of 108 mg +/- 56.9 mg per day	
Outcomes	1) Improvement in depressive symptoms 2) Seizure frequency 3) Adverse effects	
Notes	18 people withdrew due to adverse effects; all included in analysis	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomisation methods used
Allocation concealment (selection bias)	High risk	No methods for concealing allocation used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No methods of blinding used. Rated 5 on scale for risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessor not blinded. Rated 5 on scale for risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data and intention-to-treat analysis carried out. Rated 1 on scale for risk of bias
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available. Rated 2 on scale for risk of bias

Kanner 2000 (Continued)

Other bias	High risk	Measure of depression not an accurate or reliable measure. Rated 4 on scale of risk of bias
Confounding variables	High risk	No confounding variables considered or adjusted for. Rated 5 on scale for risk of bias

Kuhn 2003

Methods	A single-centre, non-randomised, prospective study (Germany) Baseline period: 4 days Observation period: 20 to 30 weeks	
Participants	75 people with temporal lobe epilepsy exceeding 15 points on the HAMD-21 scale for depression 45 females and 30 males Aged 19 to 68 years: mean 40.1 years	
Interventions	Citalopram (n = 33), dose at endpoint: 24.2 mg Mirtazapine (n = 27), dose at endpoint: 32.2 mg Reboxetine (n = 15), dose at endpoint: 6.9 mg	
Outcomes	1) Improvement in depressive symptoms 2) Seizure frequency and severity 3) Adverse effects	
Notes	Large amount of withdrawals from week 4 to weeks 20 to 30. Last observation carried forward approach used	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomisation methods used
Allocation concealment (selection bias)	High risk	No methods for concealing allocation used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Some study personnel blinded; participants not blinded. Rated 3 on scale for risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessor blinded. Rated 3 on scale for risk of bias

Kuhn 2003 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data detected; last observation carried forward approach employed. Rated 3 on scale for risk of bias
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available. Rated 2 on scale for risk of bias
Other bias	Low risk	No other risk of bias detected. Rated 1 on scale for risk of bias
Confounding variables	High risk	No confounding variables considered or adjusted for. Rated 5 on scale for risk of bias

Li 2005

Methods	A single-centre, randomised controlled trial (China) Baseline period: unclear Treatment phase: 8 weeks
Participants	67 patients with epilepsy and depression (meeting CCMD-3 criteria for depression and HAMD-21 score >18)
Interventions	Paroxetine (n = 33): 17 males, 16 females aged 14 to 62 years 10 mg to 40 mg/day Doxepin (n = 34): 15 males, 19 females, aged 16 to 59 years, dose 25 mg/day titrated up according to response (mean dose 100 mg)
Outcomes	1) Change in depression scores (HAMD-21) from baseline 2) Adverse events
Notes	3 patients discontinued study in doxepin arm because of adverse events, with 31 patients analysed for this treatment arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation carried out by flipping of a coin
Allocation concealment (selection bias)	Unclear risk	No details available regarding methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients blinded

Li 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data reported, ITT not employed
Selective reporting (reporting bias)	High risk	Adverse events not reported in results. Rated as letter E in ORBIT tool
Other bias	Unclear risk	Insufficient details in report to judge the influence of other bias
Confounding variables	Low risk	NA

Robertson 1985

Methods	A single-centre, randomised, double-blind, controlled trial (UK) Baseline period: unclear Treatment period: 12 weeks (6 weeks for all 3 arms of trial, then 6 weeks for the 2 antidepressants only)
Participants	42 people with epilepsy exceeding 15 points on the HAMD-21 scale for depression 26 females and 13 males Aged 18 to 60 years
Interventions	Amitriptyline (n = 14) 25mg TDS Nomifensine (n = 14) 25mg TDS Placebo (n = 14)
Outcomes	1) Improvement in depressive symptoms 2) Seizure frequency 3) Adverse effects
Notes	39 people included in the analysis. At 6 weeks non-responders in the active drug arms had dose doubled and those in the placebo arm were withdrawn from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number codes employed, however generation of this randomisation sequence is unclear
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled allocation

Robertson 1985 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel and participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data detected and attrition reported
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available
Other bias	Unclear risk	After 6 weeks, placebo group removed from trial; only active antidepressant treatment groups continued in the trial
Confounding variables	Low risk	NA

Specchio 2004

Methods	A multi-centre, non-randomised, uncontrolled, prospective before and after study (Italy) Baseline period: Not reported Treatment period: 4 months
Participants	45 people with focal epilepsy and exceeding or equal to 20 on the MADRS 31 females and 14 males Mean age of 42.7 years
Interventions	Citalopram 20 mg per day
Outcomes	1) Seizure frequency 2) Improvement in depression measured by MADRS and Zung-SDS 3) Adverse effects
Notes	39 people received intended treatment and analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomisation methods used
Allocation concealment (selection bias)	High risk	No methods for concealing allocation used

Specchio 2004 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given regarding methods of blinding. Rated 3 on scale for risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given regarding methods of blinding. Rated 3 on scale for risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small amount of missing data reported. Intention-to treat-analysis not employed. Rated 2 on scale for risk of bias
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available. Rated 2 on scale for risk of bias
Other bias	Low risk	No other risk of bias detected. Rated 1 on scale for risk of bias
Confounding variables	High risk	No confounding variables considered or adjusted for. Rated 5 on scale for risk of bias

Thome-Souza 2007

Methods	A single-centre, non-randomised, uncontrolled, prospective before and after study (Brazil) Baseline period: Not reported Treatment period: Mean 25.8 months (range 12-78)	
Participants	36 children and adolescents with focal epilepsy and diagnosis of depression 19 females and 17 males Aged 5 to 18 years, mean: 12.7 years	
Interventions	Sertraline up to 200 mg per day, mean dose 111.5 mg per day (50 to 200 mg) Fluoxetine up to 80 mg per day, mean dose 45.7 mg per day (20 to 80 mg)	
Outcomes	1) Seizure severity 2) Improvement in depressive symptoms 3) Adverse effects	
Notes	No drop-outs	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Thome-Souza 2007 (Continued)

Random sequence generation (selection bias)	High risk	No randomisation methods used
Allocation concealment (selection bias)	High risk	No methods for concealing allocation used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded; unclear about other study personnel. Rated 4 on scale for risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available. Rated 2 on scale for risk of bias
Other bias	Low risk	No other risk of bias detected. Rated 1 on scale for risk of bias
Confounding variables	High risk	Some confounding variables considered but not adjusted for in the analysis. Rated 4 on scale for risk of bias

Zhu 2004

Methods	Single-centre, randomised trial of venlafaxine versus no treatment (China) Baseline period: Not reported Treatment period: 8 weeks	
Participants	64 people with epilepsy (presumed genetic or cause unknown) and depression 39 males and 25 females Aged 7 to 60 years (mean 27 years)	
Interventions	Venlafaxine 25 mg to 75 mg/day (n = 32) No treatment (n = 32)	
Outcomes	1) Change in HAMD-21 scores 2) Adverse events	
Notes	No drop-outs	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Zhu 2004 (Continued)

Random sequence generation (selection bias)	Unclear risk	Methods for generation of random sequence are not detailed in the report
Allocation concealment (selection bias)	Unclear risk	Methods for allocation are not detailed in the report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of blinding methods in the report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Outcomes stated in methods section of report are present in the results. No protocol available
Other bias	Unclear risk	Insufficient details in report to judge the influence of other bias
Confounding variables	Low risk	NA

CCMD-3: Chinese Classification of Mental Disorders
HAMD: Hamilton Rating Scale for Depression
ITT: Intention-To-Treat
MADRS: Montgomery-Åsberg Depression Rating Scale
NA: Not Applicable

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Blumer 1997	Case series study not meeting the inclusion criteria
Gilliam 2005a	Trial listed on www.clinicaltrials.gov and recorded as terminated
Kocsis 2007	Trial listed on www.clinicaltrials.gov and recorded as terminated

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

Conrad 2013

Methods	A double-blind, placebo-controlled, randomised trial
Participants	Adults with temporal lobe epilepsy and meeting DSM-IV criteria for depression with a MADRS score greater than or equal to 15
Interventions	Escitalopram versus placebo
Outcomes	1) Change in depressive and anxiety symptoms 2) Seizure frequency 3) Quality of life
Notes	Trial listed on www.clinicaltrials.gov and recorded as complete. We attempted to contact the lead trialist but received no response

Harmant 1990

Methods	Prospective cohort study
Participants	35 patients with epilepsy and depression
Interventions	Fluvoxamine 50 to 200 mg (mean 125 mg)
Outcomes	Seizure frequency
Notes	No available contact details for study authors

Machado 2010

Methods	Prospective cohort study
Participants	42 patients with epilepsy and depression
Interventions	Sertraline 50 to 100 mg/day
Outcomes	Cholesterol levels in responders versus non-responders
Notes	Authors contacted for further data on depression scores and seizure frequency. No response

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV

MADRS: Montgomery-Åsberg Depression Rating Scale

DATA AND ANALYSES

Comparison 1. Paroxetine versus doxepin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 > 50% reduction in depressive symptoms	1	67	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.88, 1.52]
2 Mean depression scores	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 HAMD scores	1	67	Mean Difference (IV, Fixed, 95% CI)	0.65 [-2.15, 3.45]
3 Withdrawals (any reason)	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.74]
4 Adverse effects	1		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
4.1 Blurred vision	1	67	Risk Ratio (M-H, Fixed, 99% CI)	0.34 [0.09, 1.32]
4.2 Dizziness	1	67	Risk Ratio (M-H, Fixed, 99% CI)	0.21 [0.03, 1.37]
4.3 Dry mouth	1	67	Risk Ratio (M-H, Fixed, 99% CI)	0.26 [0.06, 1.20]
4.4 Sleep disorders	1	67	Risk Ratio (M-H, Fixed, 99% CI)	0.32 [0.08, 1.20]
4.5 Urinary retention	1	67	Risk Ratio (M-H, Fixed, 99% CI)	0.34 [0.01, 21.99]

Comparison 2. Amitriptyline versus nomifensine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 > 50% reduction in depressive symptoms	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.28, 1.06]

Comparison 3. Venlafaxine versus no treatment controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 > 50% reduction in depressive symptoms	1	64	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [1.19, 8.90]
2 Mean depression scores - HAMD	1	64	Mean Difference (IV, Fixed, 95% CI)	-7.59 [-11.52, -3.66]

Comparison 4. Citalopram (before and after)

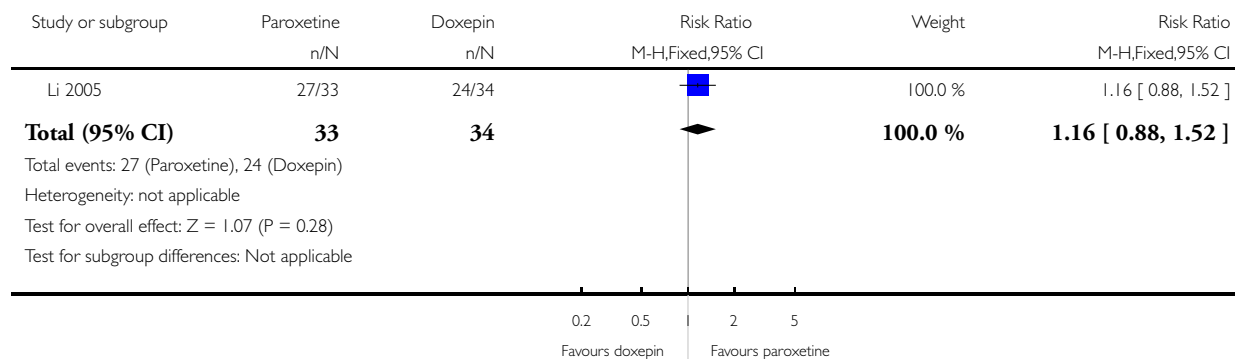
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean depression scores HAMD-21	2	176	Std. Mean Difference (Fixed, 95% CI)	1.17 [0.96, 1.38]
2 Mean monthly seizure frequency	2		Std. Mean Difference (Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Paroxetine versus doxepin, Outcome 1 > 50% reduction in depressive symptoms.

Review: Antidepressants for people with epilepsy and depression

Comparison: 1 Paroxetine versus doxepin

Outcome: 1 > 50% reduction in depressive symptoms

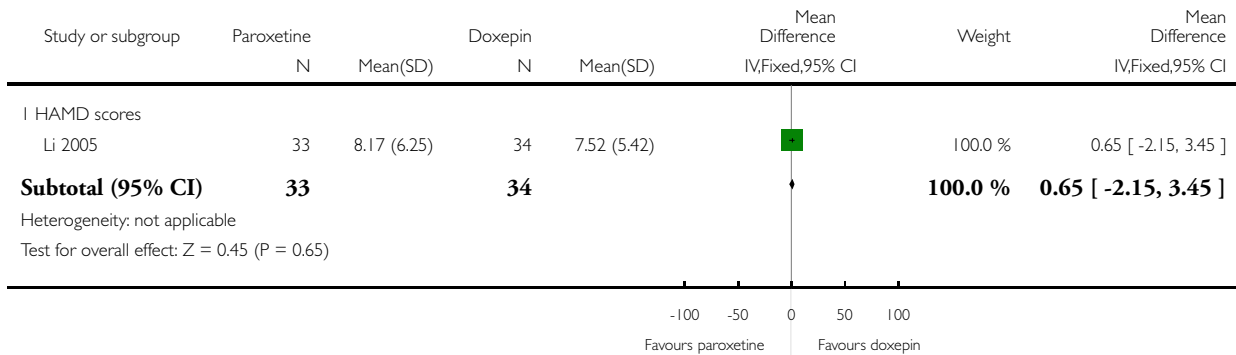


Analysis 1.2. Comparison 1 Paroxetine versus doxepin, Outcome 2 Mean depression scores.

Review: Antidepressants for people with epilepsy and depression

Comparison: 1 Paroxetine versus doxepin

Outcome: 2 Mean depression scores

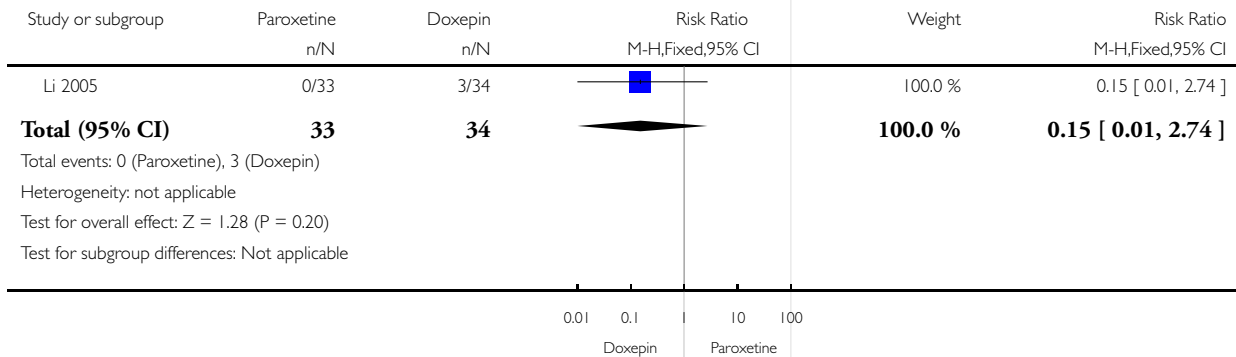


Analysis 1.3. Comparison 1 Paroxetine versus doxepin, Outcome 3 Withdrawals (any reason).

Review: Antidepressants for people with epilepsy and depression

Comparison: 1 Paroxetine versus doxepin

Outcome: 3 Withdrawals (any reason)

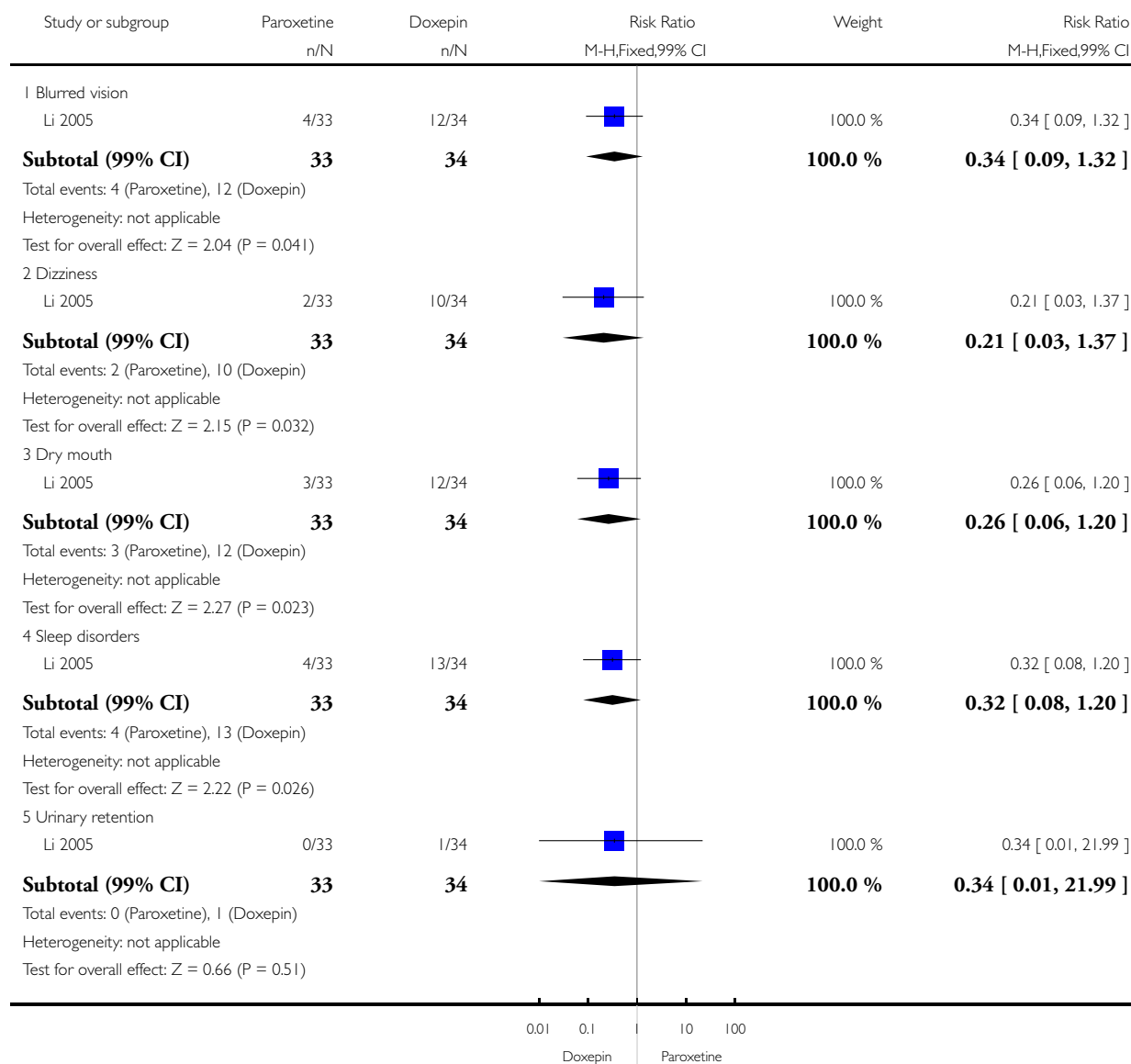


Analysis 1.4. Comparison 1 Paroxetine versus doxepin, Outcome 4 Adverse effects.

Review: Antidepressants for people with epilepsy and depression

Comparison: 1 Paroxetine versus doxepin

Outcome: 4 Adverse effects

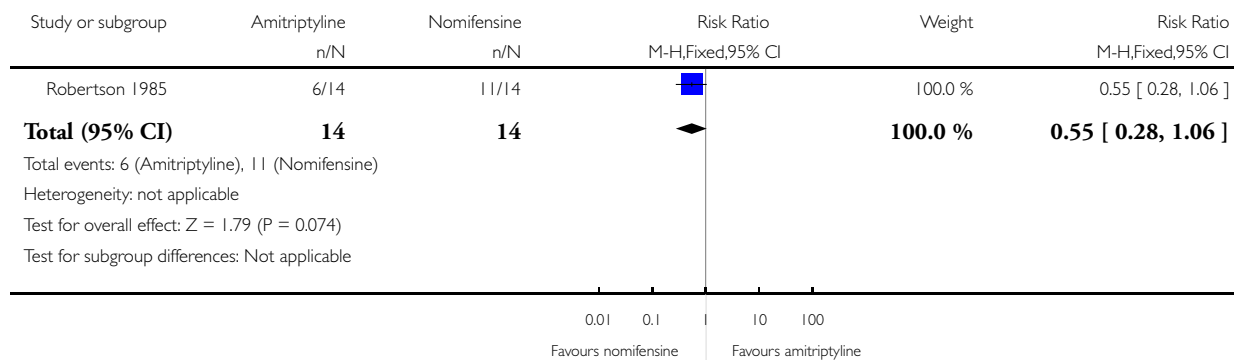


Analysis 2.1. Comparison 2 Amitriptyline versus nomifensine, Outcome 1 > 50% reduction in depressive symptoms.

Review: Antidepressants for people with epilepsy and depression

Comparison: 2 Amitriptyline versus nomifensine

Outcome: 1 > 50% reduction in depressive symptoms

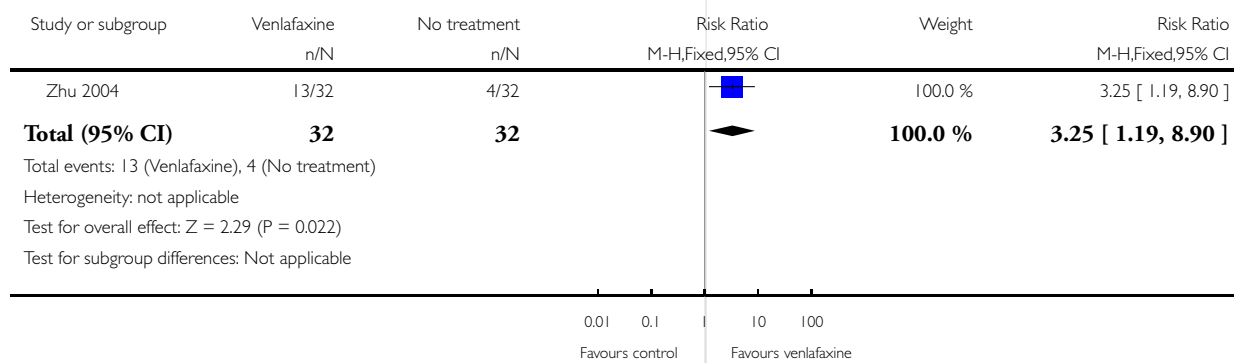


Analysis 3.1. Comparison 3 Venlafaxine versus no treatment controls, Outcome 1 > 50% reduction in depressive symptoms.

Review: Antidepressants for people with epilepsy and depression

Comparison: 3 Venlafaxine versus no treatment controls

Outcome: 1 > 50% reduction in depressive symptoms

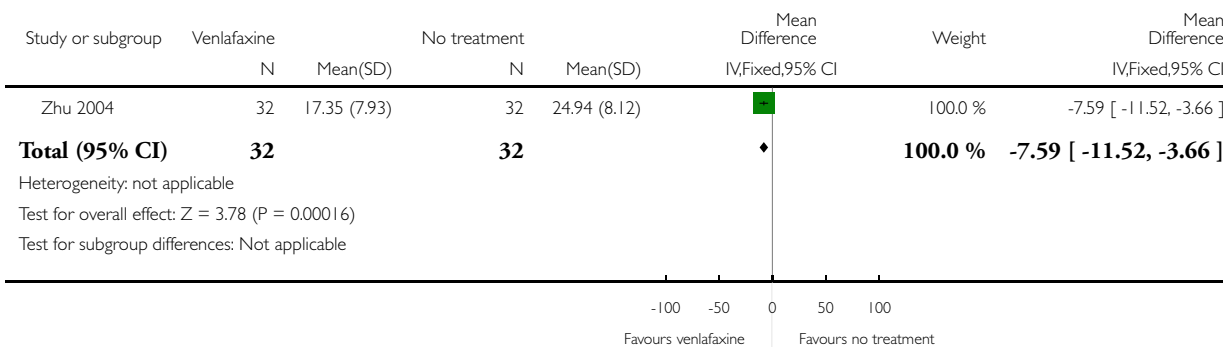


Analysis 3.2. Comparison 3 Venlafaxine versus no treatment controls, Outcome 2 Mean depression scores - HAMD.

Review: Antidepressants for people with epilepsy and depression

Comparison: 3 Venlafaxine versus no treatment controls

Outcome: 2 Mean depression scores - HAMD

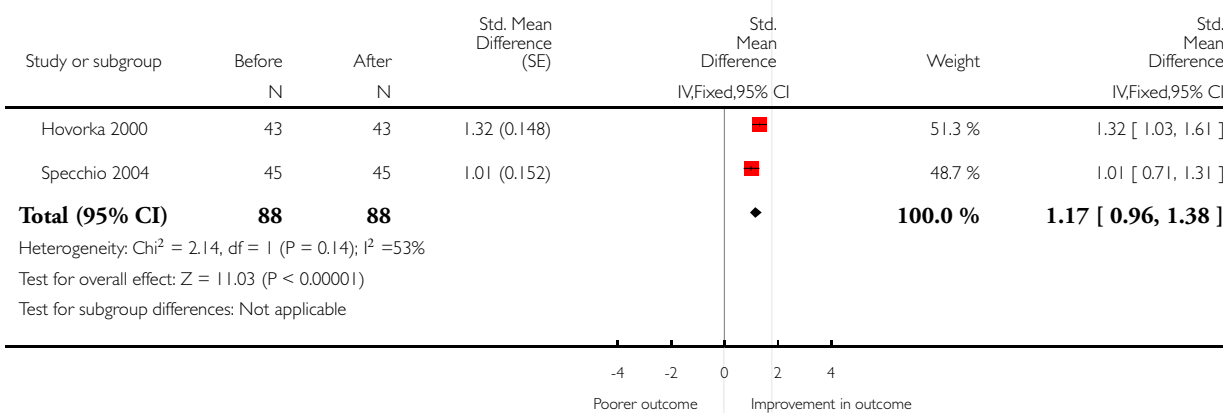


Analysis 4.1. Comparison 4 Citalopram (before and after), Outcome 1 Mean depression scores HAMD-21.

Review: Antidepressants for people with epilepsy and depression

Comparison: 4 Citalopram (before and after)

Outcome: 1 Mean depression scores HAMD-21

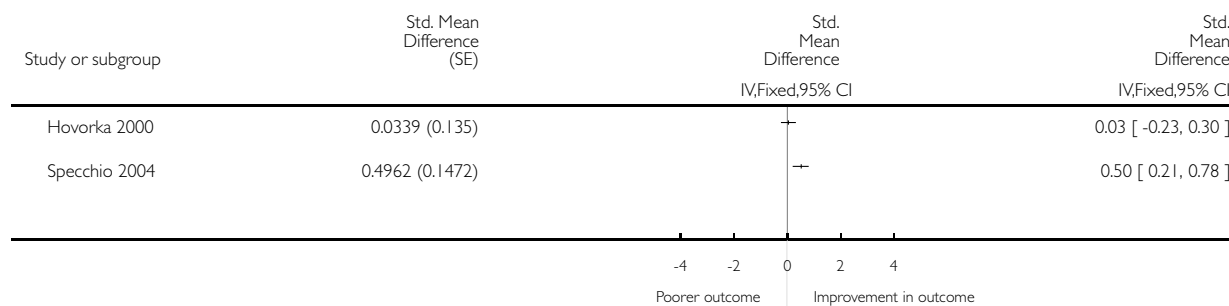


Analysis 4.2. Comparison 4 Citalopram (before and after), Outcome 2 Mean monthly seizure frequency.

Review: Antidepressants for people with epilepsy and depression

Comparison: 4 Citalopram (before and after)

Outcome: 2 Mean monthly seizure frequency



ADDITIONAL TABLES

Table 1. Risk of bias scale parameters

	1 Low risk	2	3	4	5 High risk
Confounding	All important ¹ confounders considered ² and suitable method of adjustment ³ employed. Outcome unlikely to be affected	Most important ⁴ confounders considered and suitable method of adjustment employed. Outcome unlikely to be affected	Some confounders ⁵ considered and full or partial adjustment employed ⁶ . Possible implication for outcome	Some confounders considered and no adjustment employed. Likely to affect outcome	No important confounders considered and no adjustment employed. Likely to affect outcome
Blinding	Assessors blinded to participant's drug regime and participants blinded to drug regime. Outcome unlikely to be affected	Assessors blinded to participant's drug regime. Outcome unlikely to be affected	Partial blinding ⁷ involved in study. Possible implication for outcome	Partial or no blinding involved in study. Outcome likely to be affected	No blinding involved in study. Outcome likely to be affected
Incomplete outcome data	No missing data and/or appropriate analysis ⁸ used to deal with missing data. Unlikely to affect outcome	Smaller amount (< 25%) of missing data with reasons given, balanced across groups. Unlikely to affect outcome	Larger amount of missing data (> 25%) with or without reasons given, balanced across groups. Possible	Larger amount (> 25%) of missing data, imbalance across groups. Outcome likely to be affected	No information provided regarding missing data. Likely to affect outcome

Table 1. Risk of bias scale parameters (Continued)

		come	sible implication for outcome		
Selective outcome reporting	A priori outcomes measured, analysed and reported in main report. Protocol available. Unlikely to affect outcome	A priori outcomes measured, analysed and reported in main report ⁹ . Protocol not available. Unlikely to affect outcomes	Limited information regarding a priori outcomes and measures. Possible implication for outcome	Outcomes measured but not analysed or reported	Outcomes measured but not analysed or reported and clinical judgement infers the presence of an unreported measured outcome ¹⁰
Other bias	No bias identified	Bias identified. Unlikely to affect outcome	Bias identified. Possible implication for outcome	Bias identified. Likely to affect outcome	Bias identified. Extremely likely to affect outcome

¹Important confounders include:

- mean age;
- epilepsy type;
- mean duration of epilepsy;
- location of epilepsy;
- mean baseline seizure frequency;
- mean baseline depression score.

²Reported demographic information and other confounders.

³Matching scores, multiple regression, analysis of co-variance, stratification.

⁴At least four out of six of important confounders including: mean baseline depression score and mean baseline seizure frequency.

⁵At least two out of six of the important confounders.

⁶Full adjustment of confounding variables, e.g. see footnote 2, or partial adjustment, e.g. researchers select limited number of variables to adjust for.

⁷Assessors of outcome are only blinded to certain groups, e.g. blinded to intervention group but not controls.

⁸Intention-to-treat analysis.

⁹An a priori statement is made in the methods section of the main report regarding measurement and analysis of outcome.

¹⁰For example, failure to report full-scale depression score when all other indices are reported.

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Depression] explode all trees
- #2 MeSH descriptor: [Depressive Disorder] explode all trees
- #3 depression* or depressive*:ti,ab,kw (Word variations have been searched)
- #4 “respiratory depression”:ti,ab,kw (Word variations have been searched)
- #5 (#1 or #2 or #3) not #4
- #6 MeSH descriptor: [Antidepressive Agents] explode all trees
- #7 (antidepressant or antidepressive or “af 1161” or “ba 34276” or “bc 105” or “brl 29060” or “brl 29060” or “cl 67772” or “cp 15467 61” or “du 23000” or “fg 7051” or “ici 58834” or “l deprenyl” or “leo 640” or “lilly 110140” or “lu 10 171” or “ma 1291” or “nsc 16895” or “org gb 94” or “r 55667” or “ro 11 1163” or “trans 2 phenylcyclopropylamine” or “ym 35 995” or “ym 992” or “zk 62711” or *amitriptyline or *doxepin or *moclobemide or *nortriptyline or *phenylethylhydrazine or *sertraline or *trimip or *trimipramine or *tripramine or *tryptophan or abilify or adapin or adaptol or adderall or agomelatine or aiglonyl or allegron or altruline or amfebutamone or amineptine or amineurin or amisulpride or amitrip or amitriptylin* or amitrol or amiz?l or amoxapine or amphetamine or anaftranil or anapsique or aponal or ardeydorm or ardeydropin or aremis or arima or aripiprazole or arminol or aropax or asenapine or asendin or astyl or atomoxetine or auror?x or aventyl or axiomin or benactyzine or benzeneacetic acid or besitrans or bolidon or bosnyl or brofaramine or bupropion or buspar or buspirone or butriptyline or carbamazepine or celexa or chlomipramine or chlorgyline or cipralox or cipramil or citalopram or clomipramine or clorgilin* or clorgyline or concerta or cymbalta or cytalopram or dalcipran or damilen or de*methylimipramine or deanol or defanyl or deftan or deman?l or demolox or depakote or deponerton or deprax or deprenorm or deprilept or deptran or desidox or desiflu or desipramine or desisulpid or desitriptyline or desmethylamitriptylin or desmethylloxapine or desvenlafaxine or desyrel or dexedrine or dexmethylphenidate or dextroamphetamine or dibencycladine or digton or dilithium carbonate or dimethylaminoethanol or dimethylethanolamine or dogmatil or dolmatil or domical or doneurin or dosulepin or dothiepin or doxepia or doxepin* or duloxetine or dumirox or edronax or ef*exor or eglonyl or ekilid or elavil or eldepryl or eldoral or emovit or emsam or endep or escitalopram or eskalith or espadox or espiride or etonin or etoperidone or evadene or favarin or fenelzin or feprapax or feraken or fevarin or floxyfral or fluoxetine* or fluvoxadurax or fluvoxamin* or focalin or gam?nil or gladem or guastil or herphonal or hydiphen or imidobenzyle or imipramine or imizin or insidon or iprazid or iprindole or iproniazid or isocarboxazid or ixel or janimine or jatrosom or lamictal or lamotrigine or laroxyl or lebopride or lentizol or lerivon or lexapro or lisdexamfetamine or lithane or lithium or lithobid or lofepramine or lomont or lopramine or lubazodone or lucidil or ludiomil or lustral or luvox or lyphan or manerix or maprolu or maprotilin* or mareen or marplan or melitracen or meresa or meridia or methylphenidate or mianserin or micalith or midalcipran or milnacpra* or mirpan or mirtazapine or moclamine or moclix or moclob?mide or moclobemid* or moclobeta or moclodura or moclonorm or modal or molipaxin or nardelzine or nardil or naturruhe or nefadar or nefazodone or neogama or nialamide or norfenazin or norpramin or nortrilen or norval or novoprotect or olanzapine or opipramol or optimax or oxitriptan or pamelor or parnate or paroxetine or paxil or paxtibi or pertofran* or pertofran or petylyl or phenelzine or phenethylhydrazine or pirazidol or pirlindole or pizotifen or pizotyline or polomigran or pontiride or pramolanserin or priadel or pristin? or prondol or prothiaden or protriptyline or prozac or prudoxin or pryleugan or psicocen or psmion or quetiapine or quilinorm* or quipazine or quitaxon or quomen or r55667 or reboxetine or reductil or remeron or rhotrimine or rimoc or ritalin or ritanserin or rolipram or sandomigran or saphris or sarafem or saroten or sarotex or savella or sealdin or sediel or selegiline or sendis or seroquel or seroxat or serzone or sibutramine or sin*quan or solian or stangyl or strattera or sulp or sulphiride or sulpitil or sulphivert or sulpor or surmontil or sycrest or symbyax or synedil or syneudon or tandospirone or tegretol or tepavil or thombran or tianeptine or tofranil or toledomin or tolvon or tonibril or tradozone or tramadol or tramal or transamine or tranlycypromine or trazodon* or trimepramin* or trimidura or trimineurin or triptafen or tritico or trofan or tryptacin or tryptan or tryptanol or tryptine or tryptizol or tyrima or ultram or valdoxan or valproic acid or venlafaxine or viibryd or vilazodone or viloxazine or vivactil or vivalan or vyvanse or wellbutrin or xepin or yentreve or zelapar or zimelidine or zispin or zolofax or zonalon or zyban or zyntabac):ti,ab,kw (Word variations have been searched)
- #8 #6 or #7
- #9 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)
- #10 MeSH descriptor: [Epilepsy] explode all trees
- #11 MeSH descriptor: [Seizures] explode all trees
- #12 (#9 or #10 or #11) in Trials
- #13 #5 and #8 and #12
- #14 MeSH descriptor: [Electroconvulsive Therapy] explode all trees

Appendix 2. MEDLINE search strategy

1. (validation studies or clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or comparative study or evaluation studies or multicenter study).pt.
2. ((observation\$ or cohort or case\$ or cross?section\$ or "cross section\$" or "time-series" or "time series" or "before and after" or "before-and-after" or retrospective) adj2 (study or trial or method)).mp.
3. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
4. clinical trials as topic.sh.
5. trial.ti.
6. 1 or 2 or 3 or 4 or 5
7. exp animals/ not humans.sh.
8. 6 not 7
9. exp Depression/ or exp Depressive Disorder/ or exp Dysthymic Disorder/ or (depression\$ or depressive\$).tw.
10. "respiratory depression".tw.
11. 9 not 10
12. exp Antidepressive Agents/ or anti?depress\$.tw.
13. ("af 1161" or "bc 105" or "brl 29060" or "cl 67772" or "cp 15467 61" or "du 23000" or "ici 58834" or "leo 640" or "lilly 110140" or "ma 1291" or "nsc 16895" or "org gb 94" or "r 55667" or "ro 11-1163" or "trans 2 phenylcyclopropylamine" or "ym-35,995" or "zk 62711" or abilify or adapin or adaptol or adderall or af?1161 or agomelatine or aiglonyl or allegron or altruline or amfebutamone or amineptine or amineurin or amisulpride or amitrip or amitriptylin\$ or amitrol or amiz?l or amoxapine or amphetamine or anafranil or anapsique or apo?doxepin or apo?moclob?mide or apo?nortriptyline or apo?sertraline or apo?trimip or apoamitriptyline or aponal or ardeydorm or ardeytropin or aremis or arima or aripiprazole or arminol or aronex or asenapine or asendin or astyl or atomoxetine or auror?x or aventyl or axiomin or ba?34276 or bc?105 or benactyzine or benzenoacetic acid or besitrane or beta?phenylethylhydrazine or bolvidon or bosnyl or brl?29060 or brofaramine or bupropion or buspar or buspirone or butriptyline or carbamazepine or celexa or chlomidipramine or chlogyline or cipralext or cipramil or citalopram or cl?67772 or clomipramine or clorgilin\$ or clorgyline or concerta or cp?15467?61 or cymbalta or cytalopram or dalcipran or damilene or de?methylinipramine or deanol or defanyl or deftan or deman?l or demolox or depakote or deponerton or deprax or deprenorm or deprilept or deptran or desidox or desiflu or desipramine or desisulpid or desitriptyline or desmethylamitriptylin or desmethylloxapine or desvenlafaxine or desyrel or dexedrine or dexmethylphenidate or dextroamphetamine or dibencycladine or digton or dilithium carbonate or dimethylaminoethanol or dimethylethanolamine or dogmatil or dolmatil or domical or doneurin or dosulepin or dothiepin or doxepia or doxepin\$ or du?23000 or duloxetine or dumirox or edronax or ef?exor or eglonyl or ekilid or elavil or eldepryl or eldoral or emovit or emsam or endep or escitalopram or eskalith or espadox or espiride or etonin or etoperidone or evadene or favarin or fenelzin or feprapax or feraken or fevarin or fg?7051 or floxyfrol or fluoxetin\$ or fluvoxadura or fluvoxamin\$ or focalin or gam?nil or gen?nortriptyline or gen?sertraline or gladem or guastil or herphonal or hydiphen or ici?58834 or imidobenzyle or imipramine or imizin or insidon or iprazid or iprindole or iproniazid or isocarboxazid or ixel or janimine or jatrosom or lamictal or lamotrigine or laroxyl or l-deprenyl or lebopride or lentizol or lerivon or levo?tryptophan or lexapro or lilly? 110140 or lisdexamphetamine or lithane or lithium or lithobid or lofepramine or lomont or lopramine or l-tryptophan or lu?10?171 or lubazodone or lucidil or ludiomil or lustral or luvox or lyphan or ma?1291 or manerix or maprolo or maprotilin\$ or mareen or marplan or melitracen or meresa or meridia or methylphenidate or mianserin or micalith or midalcipran or milnacipram or milnacipra? or mirpan or mirtazapine or moclamine or moclix or moclob?mide or moclobemid\$ or moclobeta or moclodura or moclonorm or modal or molipaxin or nardelzine or nardil or naturruhe or nefadar or nefazodone or neogama or nialamide or nor?nortriptyline or norfenazin or norpramin or nortrilen or nortriptyline or norval or novo?doxepin or novo?moclob?mide or novo?nortriptyline or novo?sertraline or novo?tripramine or novoprotect or nsc?16895 or nu?moclob?mide or nu?nortriptyline or nu?trimipramine or nu?tripramine or numo?moclob?mide or olanzapine or opipramol or optimax or oxitriptan or pamelor or parnate or paroxetine or paxil or paxtibi or pert? ofran\$ or petylyl or phenelzine or phenethylhydrazine or phenylethylhydrazine or pirazidol or pirlindole or pizotifen or pizotyline or pms?moclob?mide or pms?nortriptyline or pms?tryptophan or polomigran or pontiride or pramol or priadel or pristin or prondol or prothiaden or protriptyline or prozac or pradoxin or pryleun or psicocen or psymion or quetiapine or quilinorm?retard or quipazine or quitaxon or quomen or r55667 or r-55667 or ratio?nortriptyline or ratio?sertraline or ratio?tryptophan or reboxetine or reductil or remeron or rhotrimine or rhoxal?sertraline or rimoc or ritalin or ritanserin or ro-11-1163 or rolipram or sandomigran or saphris or sarafem or saroten or sarotex or savella or sealdin or sediel or selegiline or sendis or seroquel or seroxat or sertraline or serzone or sibturamine or sin?quan or solian or stangyl or strattera or sulp or sulphiride or sulphitil or sulphivert or sulpor or surmontil or sycrest or

symbyax or synedil or syneudon or tandospirone or tegretol or tepavil or thombran or tianeptine or tofranil or toledomin or tolvon or tonibril or tradozone or tramadol or tramal or trans-2-phenylcyclopropylamine or transamine or tranlycypromine or trazodon\$ or trim?pr?min\$ or trimidura or trimineurin or trimip or tripramine or triptafen or tritico or trofan or tryptacin or tryptan or tryptanol or tryptine or tryptizol or tryptophan or tyrima or ultram or valdoxan or valproic acid or venlafaxine or viibryd or vilazodone or viloxazine or vivactil or vivalan or vyvanse or wellbutrin or xepin or yentreve or ym-992 or zelapar or zimelidine or zispin or zk?62711 or zoloft or zonalon or zyban or zyntaxac).mp.

14. 12 or 13

15. exp Epilepsy/

16. exp Seizures/

17. (epilep\$ or seizure\$ or convuls\$).tw.

18. 15 or 16 or 17

19. exp Pre-Eclampsia/ or exp Eclampsia/

20. 18 not 19

21. 8 and 11 and 14 and 20

22. exp Electroconvulsive Therapy/

23. 21 not 22

24. 23 not case reports.pt.

Appendix 3. Extended 'Risk of bias' tool for non-randomised studies

Studies for which the 'Risk of bias' tool is intended

Only suitable for 'cohort-like' studies, individually or cluster-allocated. This can include secondary analyses of clinical databases providing the analysis is clearly structured as a comparison of control and intervention participants:

Individually allocated study designs

- Randomised controlled trial
- Quasi-randomised controlled trial
- Non-randomised controlled trial
- Controlled before and after study (not common use of this label, see controlled cohort before and after study below)
- Prospective cohort study
- Retrospective cohort study

Cluster-allocated study designs

- Cluster randomised controlled trial
- Cluster quasi-randomised controlled trial
- Cluster non-randomised controlled trial
- Controlled interrupted time series
- Controlled cohort before and after study

Assessment of risk of bias

Issues when using the modified 'Risk of bias' tool to assess cohort-like non-randomised studies:

- Follows principle for existing Cochrane Collaboration tool for risk of bias: score judgement and provide information (preferably direct quote) to support judgement.
- Modified 'Risk of bias' tool includes an additional item on confounding.
- Five-point scale for some items (to distinguish 'unclear' from intermediate risk of bias).
- Keep in mind the general philosophy - assessment is not about whether researchers could have done better but about risk of bias; the assessment tool must be used in a standard way whatever the difficulty/circumstances of investigating the research question of interest and whatever study design features were used.

- Use of a five-point scale is uncharted territory
- Anchors for five-point scale: '1/No/low risk' of bias should correspond to a high quality RCT. '5/high risk' of bias should correspond to a risk of bias that means the findings should not be considered (too risky, too much bias, more likely to mislead than inform).

Sequence generation

- Low/high/unclear risk of bias item.
- Always high risk of bias (not random) for a non-randomised study.
- Might argue that this item is redundant for non-randomised studies since they are always at high risk of bias - but important to include in 'Risk of bias' table ('level playing field' argument).

Allocation concealment

- Low/high/unclear risk of bias item.
- Potentially low risk of bias for a non-randomised study, e.g. quasi-randomised (high risk of bias due to sequence generation) but concealed (author judges that the people making decisions about including participants did not know how allocation was being done, e.g. odd/even date of birth/hospital number).

Risk of bias from confounding (additional item for non-randomised studies; assess for each outcome)

- Assumes a prespecified list of potential confounders defined in the protocol for the systematic review.
- Low (1) / 2 / 3 / 4 / high (5) / unclear risk of bias item.
- Judgement needs to factor in (see 'worksheet'):
 - proportion of confounders (from pre-specified list) that were considered;
 - whether most important confounders (from pre-specified list) were considered;
 - resolution/precision with which confounders were measured;
 - extent of imbalance between groups at baseline;
 - care with which adjustment was done (typically a judgement about the statistical modelling carried out by authors).
- Low risk of bias requires that all important confounders are balanced at baseline, i.e.:
 - not primarily/not only a statistical judgement; or
 - measured 'well' and 'carefully' controlled for in the analysis.

We have provided an optional 'worksheet' to help reviewers to focus on the task (rows = confounders and columns = factors to consider). Authors should make a risk of bias judgement about each factor first and then combine these (by eyeballing rather than quantitatively) to make the judgement in the main 'Risk of bias' table.

Risk of bias from lack of blinding (assess for each outcome, as per the existing risk of bias tool)

- Low (1) / 2 / 3 / 4 / high (5) / unclear risk of bias item.
- Judgement needs to factor in:
 - nature of outcome (subjective/objective; source of information);
 - who was/was not blinded and the risk that those who were not blinded could introduce performance or detection bias.

Risk of bias from incomplete outcome data (assess for each outcome, as per the existing risk of bias tool)

- Low (1) / 2 / 3 / 4 / high (5) / unclear risk of bias item.
- Judgement needs to factor in:
 - reasons for missing data;
 - whether amount of missing data balanced across groups, with similar reasons;
 - whether group comparison appropriate (e.g. 'analysed in allocated group' issue).

Risk of bias from selective reporting (assess for each outcome)

- More wide-ranging than existing assessment recommendation. Key issue is whether outcomes were clearly defined, and methods of analysis were pre-specified and adhered to.
- Low (1) / 2 / 3 / 4 / high (5) / unclear risk of bias item.
- Judgement needs to factor in:
 - existing risk of bias guidance on selective outcome reporting;
 - also, extent to which analyses (and potentially other choices) could have been manipulated to bias the findings reported, e.g. choice of method of model fitting, potential confounders considered/included;
 - look for evidence that there was a protocol in advance of doing any analysis/obtaining the data (difficult unless explicitly reported); non-randomised studies are very different from RCTs. RCTs must have a protocol in advance of starting to recruit (for research ethics committee/institutional review board/other regulatory approval); non-randomised studies need not (especially older studies);
 - hence, separate yes/no items asking reviewers whether they think the researchers had a prespecified protocol and analysis plan?

Appendix 4. Assessment of confounding variables

Assessment of how researchers dealt with confounding
Method for *identifying* relevant confounders described by researchers: Yes No
If yes, describe the method used:

Relevant confounders described: Yes No

List confounders described below

Method used for controlling for confounding
At design stage: matching by characteristics of subjects (see below for matching by propensity score)

Variables on which subjects matched:
.....
.....
.....

At analysis stage: stratification
 multivariable regression
 propensity scores (matching)
 propensity scores (multivariable regression)
Describe confounders controlled for below

Confounders described by researchers
Enter/preprint prespecified list of confounders (rank order in importance? Important in bold?)
Tick (yes/no judgement) if confounder considered by the researchers [Cons'd?]
Score (1 to 5) precision with which confounder measured
Score (1 to 5) imbalance between groups
Score (1 to 5) care with which adjustment for confounder was carried out

Confounder	Considered	Precision	Imbalance	Adjustment

CONTRIBUTIONS OF AUTHORS

MM, JP and JS have written the review protocol. MM holds responsibility for managing the review process. AM has provided supervision throughout the development of the protocol and provided comments on drafts.

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MM, JP, JS and AM have no declarations of interest.

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