COCHRANE CORNER

Antidepressants for people with epilepsy and depression: a Cochrane Review[†]

Melissa J. Maguire, Anthony G. Marson & Sarah J. Nevitt

[†] This review is the abstract of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews*, 2021, Issue 4: CD010682, doi: 10.1002/14651858.CD010682.pub3 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

We thank the Cochrane Epilepsy Group for their support in publishing this review.

See Round the Corner in this issue.

Background

Depressive disorders are the most common psychiatric comorbidity in people with epilepsy, affecting around one-third, with a significant negative impact on quality of life. There is concern that people 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 aimed to address these issues, and inform clinical practice and future research.

This is an updated version of the original Cochrane Review published in Issue 12, 2014.

Objectives

To evaluate the efficacy and safety of antidepressants in treating depressive symptoms and the effect on seizure recurrence, in people with epilepsy and depression.

Search methods

For this update, we searched CRS Web, MEDLINE, SCOPUS, PsycINFO, and ClinicalTrials.gov (February 2021). We searched the World Health Organization Clinical Trials Registry in October 2019, but were unable to update it because it was inaccessible. There were no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) and prospective non-randomised studies of interventions (NRSIs), investigating children or adults with epilepsy, who were treated with an antidepressant and compared to placebo, comparative antidepressant, psychotherapy, or no treatment for depressive symptoms.

Data collection and analysis

The primary outcomes were changes in depression scores (proportion with a greater than 50% improvement, mean difference, and proportion who achieved complete remission) and change in seizure frequency (mean difference, proportion with a seizure recurrence, or episode of status epilepticus). Secondary outcomes included the number of participants who withdrew from the study and reasons for withdrawal, quality of life, cognitive functioning, and adverse events.

Two review authors independently extracted data for each included study. We then cross-checked the data extraction. We assessed risk of bias using the Cochrane tool for RCTs, and the ROBINS-I for NRSIs. We presented binary outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) or 99% CIs for specific adverse events. We presented continuous outcomes as standardised mean differences (SMDs) with 95% CIs, and mean differences (MDs) with 95% CIs.

Main results

We included 10 studies in the review (four RCTs and six NRSIs), with 626 participants with epilepsy and depression, examining the effects of antidepressants. One RCT was a multi-centre study comparing an antidepressant with cognitive behavioural therapy (CBT). The other three RCTs were single-centre studies comparing an antidepressant with an active control, placebo, or no treatment. The NRSIs reported on outcomes mainly in participants with focal epilepsy before and after treatment for depression with a selective serotonin reuptake inhibitor (SSRI); one NRSI compared SSRIs to CBT.

We rated one RCT at low risk of bias, three RCTs at unclear risk of bias, and all six NRSIs at serious risk of bias. We were unable to conduct any meta-analysis of RCT data due to heterogeneity of treatment comparisons. We judged the certainty of evidence to be moderate to very low across comparisons, because single studies contributed limited outcome data, and because of risk of bias, particularly for NRSIs, which did not adjust for confounding variables.

More than 50% improvement in depressive symptoms ranged from 43% to 82% in RCTs, and from 24% to 97% in NRSIs, depending on the antidepressant given. Venlafaxine improved depressive symptoms by more than 50% compared to no treatment (mean difference (MD) –7.59 (95% confidence interval (CI) –11.52 to –3.66; 1 study, 64 participants; low-certainty evidence); the results between other comparisons were inconclusive. Two studies comparing SSRIs to CBT reported inconclusive results for the proportion of participants who achieved complete remission of depressive symptoms.

Seizure frequency data did not suggest an increased risk of seizures with antidepressants compared to control treatments or baseline. Two studies measured quality of life; antidepressants did not appear to improve quality of life over control. No studies reported on cognitive functioning.

Two RCTs and one NRSI reported comparative data on adverse events; antidepressants did not appear to increase the severity or number of adverse events compared to controls. The NSRIs reported higher rates of withdrawals due to adverse events than lack of efficacy. Reported adverse events for antidepressants included nausea, dizziness, sedation, headache, gastrointestinal disturbance, insomnia, and sexual dysfunction.

Authors' conclusions

Existing evidence on the effectiveness of antidepressants in treating depressive symptoms associated with epilepsy is still very limited. Rates of response to antidepressants were highly variable. There is low certainty evidence from one small RCT (64 participants) that venlafaxine may improve depressive symptoms more than no treatment; this evidence is limited to treatment between 8 and 16 weeks, and does not inform longer-term effects. Moderate to low evidence suggests neither an increase nor exacerbation of seizures with SSRIs.

There are no available comparative data to inform the choice of antidepressant drug or classes of drug for efficacy or safety for treating people with epilepsy and depression.

RCTs of antidepressants utilising interventions from other treatment classes besides SSRIs, in large samples of patients with epilepsy and depression, are needed to better inform treatment policy. Future studies should assess interventions across a longer treatment duration to account for delayed onset of action, sustainability of treatment responses, and to provide a better understanding of the impact on seizure control.