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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 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.