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ROUND THE CORNER

Are antidepressants really safe and effective in people with epilepsy and depression?†

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SUMMARY

This commentary gives a very brief overview of depression in epilepsy (prevalence, risk, associations between the two conditions, antidepressant medication) and assesses the quality and results of a Cochrane Review comparing antidepressants with placebo and psychotherapy in managing the condition. Although antidepressants were not shown to be more effective than other interventions and no link between antidepressants and increased seizure frequency was observed, the low-quality evidence obtained cannot provide conclusive answers.

KEYWORDS

Depressive disorders; antidepressants; drug interactions and side-effects; anticonvulsants; individual psychotherapy.

The prevalence of depression in people with epilepsy is estimated to be 23%, which is at least 14% higher than in the general population (Craig 2020). In drug-resistant epilepsy, the prevalence is 55% (Mula 2019). Despite such high figures, little is known regarding the pathophysiology and treatment of depression in epilepsy. Hesitation still exists when prescribing antidepressants owing to the fear of lowering the seizure threshold, which may result in suboptimal treatment (Jackson 2005).

Antidepressants have previously been correlated with an increased risk of seizures; however, findings were mostly obtained from single case studies and in the context of several confounding factors (Duncan 1995).

An observational trial of individuals with depression in the UK revealed a 0.09% individual risk of new-onset seizures per year with the use of antidepressants. After 5 years, 0.037% of those taking antidepressants had experienced a first-time seizure (Craig 2020).

The association between epilepsy and depression involves a complex and bidirectional interaction between neurobiological, chemical, environmental and genetic factors (Mula 2019). Thinning of the frontal cortex and decreased hippocampal volumes may be seen in both depression and temporal lobe epilepsy (Mula 2019). Abnormal serotonin transmission as well as the hypothalamic–pituitary–adrenal axis may also be involved (Mula 2019).

Only a few antidepressants have relatively high dose-related proconvulsant effects; they include amoxapine, bupropion, amitriptyline and clomipramine (Tallian 2017). For the remainder, the risk is low and sertraline may even have anticonvulsant effects (Brennecke 2020).

According to the National Institute for Health and Care Excellence (2009), a selective serotonin reuptake inhibitor (SSRI) such as sertraline or citalopram should be considered as first-line treatment in chronic medical conditions owing to its low propensity to cause unwanted drug interactions.

There is uncertainty regarding the efficacy and risk of seizures of antidepressants, which motivates the necessity for the review in this month's Cochrane Corner (Maguire 2021).

Summary of the Cochrane Review

The review by Maguire et al is updated version of a Cochrane Review first published in 2014. It includes 4 randomised controlled trials (RCTs) and 6 non-randomised prospective cohort studies (non-randomised studies of interventions, NRSIs) involving 626 participants with epilepsy and comorbid depression on antidepressants, mainly SSRIs. A comparison is made between various classes of antidepressant, placebo and psychotherapy. Unfortunately, a meta-analysis depicting the statistical significance of the results could not be conducted owing to a high level of heterogeneity between studies.

Was a clearly focused question addressed?

Many journals today request that the study title should reveal pertinent details of the review, such as intervention strategies and study aims, in a succinct way to facilitate a more efficient search during data collection (Ware 2021). Although this

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was not evident in this review, the missing information was clearly highlighted in the abstract.

Addressing the PICO/PECO

The research question in evidence-based medicine is often developed using the population, intervention, comparator and outcome (PICO) framework (otherwise known as population, exposure, comparator and outcome, PECO).

Population

The high level of heterogeneity between studies is not an unexpected finding, given that the population of interest included people of all ages diagnosed with any type of epilepsy and depression (and on antidepressants). The range of diversity between individual studies (e.g. differences in population group, interventions and study design) is too large for a meaningful comparison to be made. Although the inclusion of dysthymia and adjustment disorder in the study population enhances the generalisability of the data to clinical practice, it may also skew the results, because of variation in antidepressant response in these conditions (Griffiths 2000). In the review, it was noted that standardised criteria were used to diagnose depression, although the same rating scale was not used for each study, which may have introduced variation in the results.

Several key confounders were addressed, such as age and type of epilepsy, but other confounders and co-interventions were not addressed, such as social factors, comorbid mental illness or treatment with other medication, which may have been associated with better or worsening outcomes in depression and antidepressant response. It was also clearly noted that participants were all on antiepileptic medications, which also pose a risk for depression (Mula 2019).

Interventions/exposures

The intervention/exposure groups consisted of participants who received antidepressants alongside their anticonvulsant medication. The minimum duration of treatment was 8 weeks, with each study using different follow-up periods. Further, a range of effective doses were used.

Comparators

Comparators included participants who received placebo, another antidepressant, psychotherapy or no treatment in combination with anticonvulsants.

Outcomes

The response to antidepressants was assessed using rating scale changes on approved questionnaires for depression, such as the Hamilton Rating Scale for Depression. Overall, there was limited evidence that antidepressants improve depression scores more than the other interventions included in the review, namely psychotherapy, placebo or no treatment. No worsening of seizures was observed, which was measured by evaluating change in seizure frequency, mean difference, recurrence and incidence of status epilepticus. Owing to word constraints in this commentary, I will not discuss secondary outcomes, which included loss to follow-up, quality of life, cognitive functioning and adverse events (Box 1).

Study methods

A thorough method and search strategy were outlined in the review. CRS Web, MEDLINE, Scopus (Box 2), PsycInfo, the World Health Organization Clinical Trials Registry and ClinicalTrials.gov were searched. Two review authors collected material, which was then cross-checked. Articles from reference lists were explored. Databases and authors were also contacted for unpublished studies, also known as grey literature (Box 3). Grey literature databases were searched, for example Zetoc, ISI Proceedings, International Bureau for Epilepsy congress proceedings and International League against Epilepsy congress proceedings. The inclusion of these studies helps to reduce publication bias and strengthens the certainty of results (Box 4), as the

BOX 1 What are adverse events?

Adverse events refer to disadvantageous outcomes that occur mostly unexpectedly during a research study after the use of an intervention but are not necessarily directly related to it (Higgins 2022). Examples of adverse events are deaths and drug-related complications. Adverse events may result in drop-out from the study. Examples of adverse effects in the review include mania, psychosis, worsening of depression and sudden unexpected death in epilepsy.

Adverse events are sometimes considered to be different from adverse effects, which are directly caused by the study interventions, i.e. side-effects. Examples of these from the review include nausea, dizziness, headaches and sedation – although they were listed as adverse events. Only three studies reported on adverse events and effects and antidepressants were not thought to be more harmful than placebo. However, there some participants dropped out because of various well-known antidepressant side-effects.

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BOX 2 The Scopus database

Scopus is a citation and abstract database created in 2004 by Elsevier, described by Kulkarni (2009) as the largest for peer-reviewed literature. It is behind a paywall and is especially useful for citation chaining, which encompasses a network of articles that cite each other and refers to either forward searching (identifying sources that have referenced the article at hand) or backward searching (skimming through references listed by the article) (Burnham 2006).

BOX 3 What is grey literature?

Grey literature is a collection of material (e.g. academic, government and business policies) that is covered by intellectual property rights but not by commercial publishing rights (Schöpfel 2011). The material may be more current, informative and relevant owing to fewer limitations posed by publishers. However, it is not peer reviewed, which may result in lower-quality evidence (Higgins 2022).

information may be more relevant or current than commercially published data.

Risk of bias

One RCT was rated as low risk of bias and the remaining nine studies were either high or unclear, mainly owing to difficulties with masking ('blinding') of participants, recall bias and lack of adjustment for confounders for the NRSIs. NRSIs (Box 5) and RCTs were both included, most likely because of the limited availability of relevant information but also to reduce publication bias.

Risk of bias was thoroughly reviewed using the Cochrane risk of bias tool for RCTs and the ROBINS-I tool for NRSIs (Fig. 1). Outcome reporting bias was assessed using the Outcome Reporting Bias in Trials (ORBIT) classification system, a method of appraising outcome evaluation (Norris 2012).

Study results

The search identified a total of 1458 studies and only 18 were potentially eligible as they met inclusion criteria. However, a further 8 were then excluded because they were either terminated early or still ongoing, which are unusual reasons for exclusion. In addition, one study was excluded for being a 'very small pilot study'. These reasons for exclusion all contribute to reporting bias.

Overall, there was limited evidence that antidepressants improve depression scores more than the other interventions included in the review, namely psychotherapy, placebo or no treatment. The RCTs compared antidepressant with all modalities of treatment and the NRSIs explored outcomes before and after treatment with an antidepressant, mainly SSRIs. The primary outcome measure, change in depression scores from antidepressants, revealed that a greater number of participants in the RCTs and NRSIs showed >50% improvement when compared with various comparator groups. However, the results are difficult for readers to interpret as some comparator outcomes were merely labelled as inconclusive without raw data being recorded. Venlafaxine showed the only statistically significant finding of >50% improvement in depressive symptoms versus no treatment between 8 and 16 weeks (mean difference −7.59; 95% CI −11.52 to −3.66), in an RCT of low power because it included only 64 participants.

BOX 4 The GRADE approach to certainty of evidence

GRADE (Grading of Recommendations Assessment, Development and Evaluations) is a popular tool developed in 2000 by the GRADE Working Group and widely used by several organisations to measure how much the results of a systematic review can be trusted by researchers. In other words, are the study outcomes close to the measurement of interest? Although it is a structured approach with clear guidelines for use, it also has an element of subjectivity (Higgins 2022).

Different aspects of the GRADE framework include: indirectness of evidence, inconsistency of results, imprecision of results and risk of bias (Higgins 2022). In the review, the certainty of evidence ranged between low and moderate, mainly owing to high risk of bias and low precision of data associated with a small sample size.

In the review, reasons for excluding studies were appropriately addressed. However, excluding studies mainly because they did not report results of an outcome they have measured poses a risk of bias (Higgins 2022). In the review, three studies were excluded for this reason. The quality of the included studies was rated in a transparent manner using the GRADE approach.

BOX 5 Non-randomised studies of interventions

Non-randomised studies of interventions (NRSIs) are observational studies, so as the name suggests, they involve little to no interference by the researchers, and no randomisation to study arms occurs. Advantages include the following: they may be used to assess rare events or adverse effects, where RCTs would be difficult to design, and they may include larger, unselected population groups which are more likely to reflect real-life practice.

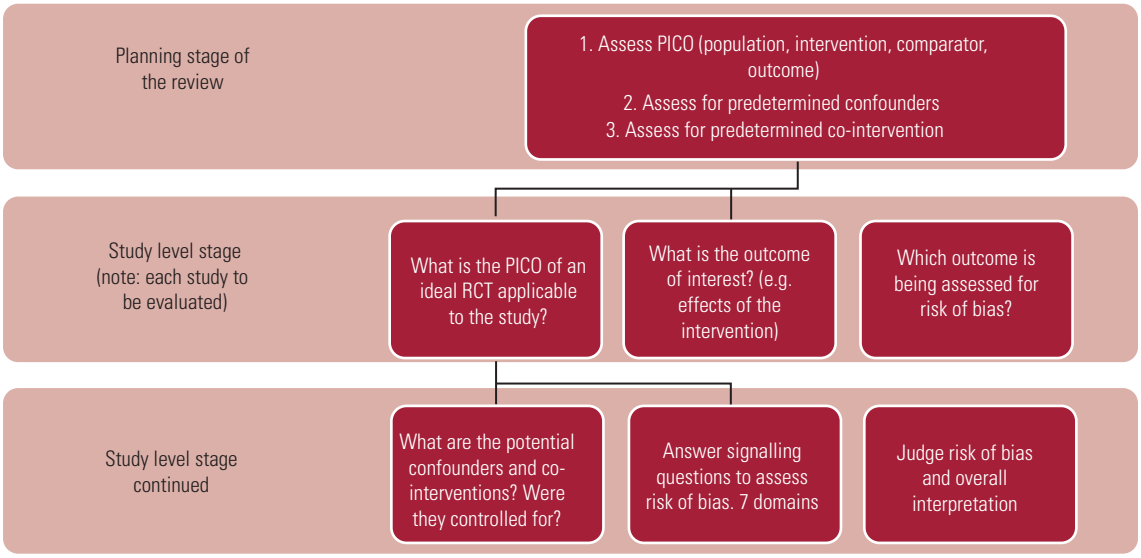

FIG 1 The ROBINS-I (Risk of Bias in Non-Randomised Studies of Interventions) is a recent tool developed by research experts to measure the extent to which we can believe the results of non-randomised studies (Sterne 2016). A systematic approach is used and requires that users have a sound understanding of epidemiology. Confounders are extra variables in the study that influence the outcome, whereas co-interventions are extra interventions the study population receive that might influence the outcome (Higgins 2022).

Heterogeneity (variation in results) in the RCTs was calculated by comparing participant, epilepsy and intervention characteristics (e.g. age), and the I^2 statistic generated was >75%, which was considered too high to perform a meta-analysis and sensitivity analysis. Therefore, not enough information was available to determine which class of antidepressant was most effective.

Can the results be extrapolated to the general population?

This review has limited applicability to the real world, mainly owing to the poor-quality evidence available. Most studies were conducted before 2015, with only two new additions since the original review. Also, studies with longer follow-ups to assess long-term effects of placebo, antidepressant and psychotherapy are needed.

Discussion

One may argue that non-randomised studies in addition to RCTs were included to allow for a larger amount of data in this limited area of research. However, the review authors noted that they chose to include NRSIs to monitor long-term effects of SSRIs when short-term RCTs fail to do this, for example one cohort study observed antidepressant response at 78 months, which is the longest treatment period in the review. Moreover, the participants are more reflective of clinical practice than in RCTs, but the main pitfall of non-randomised controlled trials is the struggle to determine a causal relationship between exposure and outcome (Higgins 2022). The biases that largely exist in NRSIs include confounding bias, selection bias, information bias and reporting bias (Higgins 2022).

Despite this exhaustive search and 732 more records having been identified, only one additional RCT and one NRSI were included in this updated review. This demonstrates that attempts have been made to seek clarity on this issue; however, many studies have been excluded for the reasons reported above.

The review authors had planned to analyse outcomes at ≤12, 13–26 and ≥26 weeks, but this was not possible. Over the included studies, outcomes were assessed at different time points/periods, which caused problems with comparing data, for example

outcomes for different studies were recorded at 6 weeks, 8 weeks, 16 weeks, 20–30 weeks, and so on.

As regards the efficacy of antidepressants in epilepsy, no recent studies could be identified other than the two ongoing studies cited in the review. This is most likely explained by the practical and financial limitations in conducting high-quality studies concerning this area of research.

As regards seizures, the review revealed inconclusive results, but mainly no significant risk of seizures was reported for antidepressants versus comparator groups or pre- and post-antidepressant treatment. According to the literature, the risk of seizures depends on the characteristics of the population studied (Craig 2020), for example clomipramine carries a 0.7% risk of seizures according to the US Food and Drug Administration, however a 3% risk has been observed in developmental disorders (Brodkin 1997). A large cohort study found that sertraline, mirtazapine and escitalopram did not lead to increased seizure risk (Hill 2015).

Conclusions

Overall, this well-conducted review aimed to assess the safety profile and efficacy of antidepressants in managing depression in epilepsy. Owing to the low-quality evidence found, it was unable to provide conclusive answers. Further large-scale epidemiological and interventional studies with long follow-ups are recommended to produce clearer guidelines and advise clinicians.

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Declaration of interest

None.

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