COCHRANE CORNER

Antidepressants plus benzodiazepines for adults with major depression: a Cochrane Review†

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†This review is the abstract of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews* 2019, Issue 6, Art. No.: CD001026, doi: 10.1002/14651858.CD001026.pub2. (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.

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See commentary in this issue.

Background

Anxiety frequently coexists with depression and adding benzodiazepines to antidepressant treatment is common practice to treat people with major depression. However, more evidence is needed to determine whether this combined treatment is more effective and not any more harmful than antidepressants alone. It has been suggested that benzodiazepines may lose their efficacy with long-term administration and their chronic use carries risks of dependence. This is the 2019 updated version of a Cochrane Review first published in 2001, and previously updated in 2005. This update follows a new protocol to conform with the most recent Cochrane methodology guidelines, with the inclusion of 'Summary of findings' tables and GRADE evaluations for quality of evidence.

Objectives

To assess the effects of combining antidepressants with benzodiazepines compared with antidepressants alone for major depression in adults.

Search methods

We searched the Cochrane Common Mental Disorders Group's Controlled Trials Register (CCMDCTR), the Cochrane Central Register of Controlled Trials, MEDLINE, Embase and PsycINFO to May 2019. We searched the World Health Organization (WHO) trials portal and ClinicalTrials.gov to identify any additional unpublished or ongoing studies.

Selection criteria

All randomised controlled trials that compared combined antidepressant plus benzodiazepine treatment with antidepressants alone for adults with major depression. We excluded studies administering psychosocial therapies targeted at depression and anxiety disorders concurrently. Antidepressants had to be prescribed, on average, at or above the minimum effective dose as presented by Hansen 2009 or according to the North American or European regulations. The combination therapy had to last at least four weeks.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias in the included studies, according to the criteria of the *Cochrane Handbook for Systematic Reviews of Interventions*. We entered data into Review Manager 5. We used intention-to-treat data. We combined continuous outcome variables of depressive and anxiety severity using standardised mean differences (SMD) with 95% confidence intervals (CIs). For dichotomous efficacy outcomes, we calculated the risk ratio (RR) with 95% CI. Regarding the primary outcome of acceptability, only overall dropout rates were available for all studies.

Main results

We identified 10 studies published between 1978 and 2002 involving 731 participants. Six studies used tricyclic antidepressants (TCAs), two studies used selective serotonin reuptake inhibitors (SSRIs), one study used another heterocyclic antidepressant and one study used TCA or heterocyclic antidepressant.

Combined therapy of benzodiazepines plus antidepressants was more effective than antidepressants alone for depressive severity in the early phase (four weeks) (SMD –0.25, 95% CI –0.46 to –0.03; 10 studies, 598 participants; moderate-quality evidence), but there was no difference between treatments in the acute phase (five to 12 weeks) (SMD –0.18, 95% CI –0.40 to 0.03; 7 studies, 347 participants; low-quality evidence) or in the continuous phase (more than 12 weeks) (SMD –0.21, 95% CI –0.76 to 0.35; 1 study, 50 participants; low-quality evidence). For acceptability of treatment, there was no difference in the dropouts due to any reason between combined therapy and antidepressants alone (RR 0.76, 95% CI 0.54 to 1.07; 10 studies, 731 participants; moderate-quality evidence).

For response in depression, combined therapy was more effective than antidepressants alone in the early phase (RR 1.34, 95% CI 1.13 to 1.58; 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.12, 95% CI 0.93 to 1.35; 7 studies, 383 participants) or in the continuous phase (RR 0.97, 95% CI 0.73 to 1.29; 1 study, 52 participants). For remission in depression, combined therapy was more effective than antidepressants alone in the early phase (RR 1.39, 95% CI 1.03 to 1.90, 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.27, 95% CI 0.99 to 1.63; 7 studies, 383 participants) or in the continuous phase (RR 1.31, 95% CI 0.80 to 2.16; 1 study, 52 participants). There was no evidence of a difference between combined therapy and antidepressants alone for anxiety severity in the early phase (SMD –0.76, 95% CI –1.67 to 0.14; 3 studies, 129 participants) or in the acute phase (SMD –0.48, 95% CI –1.06 to 0.10; 3 studies, 129 participants). No studies measured severity of insomnia. In terms of adverse effects, the dropout rates due to adverse events were lower for combined therapy than for antidepressants alone (RR 0.54, 95% CI 0.32 to 0.90; 10 studies, 731 participants; moderate-quality evidence). However, participants in the combined therapy group reported at least one adverse effect more often than participants who received antidepressants alone (RR 1.12, 95% CI 1.01 to 1.23; 7 studies, 510 participants; moderate-quality evidence).

Most domains of risk of bias in the majority of the included studies were unclear. Random sequence generation, allocation concealment, blinding and selective outcome reporting were problematic due to insufficient details reported in most of the included studies and lack of availability of the study protocols. The greatest limitation in the quality of evidence was issues with attrition.

Authors' conclusions

Combined antidepressant plus benzodiazepine therapy was more effective than antidepressants alone in improving depression severity, response in depression and remission in depression in the early phase. However, these effects were not maintained in the acute or the continuous phase. Combined therapy resulted in fewer dropouts due to adverse events than antidepressants alone, but combined therapy was associated with a greater proportion of participants reporting at least one adverse effect.

The moderate quality evidence of benefits of adding a benzodiazepine to an antidepressant in the early phase must be balanced judiciously against possible harms and consideration given to other alternative treatment strategies when antidepressant monotherapy may be considered inadequate. We need long-term, pragmatic randomised controlled trials to compare combination therapy against the monotherapy of antidepressant in major depression.

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