COCHRANE CORNER

Pharmacological interventions for treatment-resistant depression in adults: 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 12: CD010557, doi: 10.1002/14651858.CD010557.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.

We thank the Cochrane Common Mental Disorders Group for their support in publishing this review. Cochrane Common Mental Disorders: contact@ccdan.org

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Background

Although antidepressants are often a first-line treatment for adults with moderate to severe depression, many people do not respond adequately to medication, and are said to have treatment-resistant depression (TRD). Little evidence exists to inform the most appropriate 'next step' treatment for these people.

Objectives

To assess the effectiveness of standard pharmacological treatments for adults with TRD.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (March 2016), CENTRAL, MEDLINE, Embase, PsycINFO and Web of Science (31 December 2018), the World Health Organization trials portal and ClinicalTrials.gov for unpublished and ongoing studies, and screened bibliographies of included studies and relevant systematic reviews without date or language restrictions.

Selection criteria

Randomised controlled trials (RCTs) with participants aged 18 to 74 years with unipolar depression (based on criteria from DSM-IV-TR or earlier versions, International Classification of Diseases (ICD)-10, Feighner criteria or Research Diagnostic Criteria) who had not responded to a minimum of four weeks of antidepressant treatment at a recommended dose. Interventions were:

(1) increasing the dose of antidepressant monotherapy;
(2) switching to a different antidepressant monotherapy;
(3) augmenting treatment with another antidepressant;
(4) augmenting treatment with a non-antidepressant.

All were compared with continuing antidepressant monotherapy. We excluded studies of non-standard pharmacological treatments (e.g. sex hormones, vitamins, herbal medicines and food supplements).

Data collection and analysis

Two reviewers used standard Cochrane methods to extract data, assess risk of bias, and resolve disagreements. We analysed continuous outcomes with mean difference (MD) or standardised mean difference (SMD) and 95% confidence interval (CI). For dichotomous outcomes, we calculated a relative risk (RR) and 95% CI. Where sufficient data existed, we conducted meta-analyses using random-effects models.

Main results

We included 10 RCTs (2731 participants). Nine were conducted in outpatient settings and one in both in- and outpatients. Mean age of participants ranged from 42–50.2 years, and most were female.

One study investigated switching to, or augmenting current antidepressant treatment with, another antidepressant (mianserin). Another augmented current antidepressant treatment with the antidepressant mirtazapine. Eight studies augmented current antidepressant treatment with a non-antidepressant (either an anxiolytic (buspirone) or an antipsychotic (cariprazine; olanzapine; quetiapine (3 studies); or ziprasidone (2 studies)). We judged most studies to be at a low or unclear risk of bias. Only one of the included studies was not industry-sponsored.

There was no evidence of a difference in depression severity when current treatment was switched to mianserin (MD on Hamilton Rating Scale for Depression (HAM-D) = –1.8, 95% CI –5.22 to 1.62, low-quality evidence)) compared with continuing on antidepressant monotherapy. Nor was there evidence of a difference in numbers dropping out of treatment (RR 2.08, 95% CI 0.94 to 4.59, low-quality evidence; dropouts 38% in the mianserin switch group; 18% in the control).

Augmenting current antidepressant treatment with mianserin was associated with an improvement in depression symptoms severity scores from baseline (MD on HAM-D –4.8, 95% CI –8.18 to –1.42; moderate-quality evidence). There was no evidence of a difference in numbers dropping out (RR 1.02, 95% CI 0.38 to 2.72; low-quality evidence; 19% dropouts in the mianserin-augmented group; 38% in the control). When current antidepressant treatment was augmented with mirtazapine, there was little difference in depressive symptoms (MD on Beck Depression Inventory (BDI-II) –1.7, 95% CI –4.03 to 0.63; high-quality evidence) and no evidence of a difference in dropout numbers (RR 0.50, 95% CI 0.15 to 1.62; dropouts 2% in mirtazapine-augmented group; 3% in the control).

Augmentation with buspirone provided no evidence of a benefit in terms of a reduction in depressive symptoms (MD on Montgomery and Asberg Depression Rating Scale (MADRS) –0.30, 95% CI –9.48 to 8.88; low-quality evidence) or numbers of drop-outs (RR 0.60, 95% CI 0.23 to 1.53; low-quality evidence; dropouts 11% in buspirone-augmented group; 19% in the control).

Severity of depressive symptoms reduced when current treatment was augmented with cariprazine (MD on MADRS –1.50, 95% CI –2.74 to –0.25; high-quality evidence), olanzapine (MD on HAM-D –7.9, 95% CI –16.76 to 0.96; low-quality evidence; MD on MADRS –12.4, 95% CI –22.44 to –2.36; low-quality evidence), quetiapine (SMD –0.32, 95% CI –0.46 to –0.18; I^2 = 6%, high-quality evidence), or ziprasidone (MD on HAM-D –2.73, 95% CI –4.53 to –0.93; I^2 = 0, moderate-quality evidence) compared with continuing on antidepressant monotherapy.

However, a greater number of participants dropped out when antidepressant monotherapy was augmented with an antipsychotic (cariprazine RR 1.68, 95% CI 1.16 to 2.41; quetiapine RR 1.57, 95% CI: 1.14 to 2.17; ziprasidone RR 1.60, 95% CI 1.01 to 2.55) compared with antidepressant monotherapy, although estimates for olanzapine augmentation were imprecise (RR 0.33, 95% CI 0.04 to 2.69). Dropout rates ranged from 10% to 39% in the groups augmented with an antipsychotic, and from 12% to 23% in the comparison groups. The most common reasons for dropping out were side effects or adverse events.

We also summarised data about response and remission rates (based on changes in depressive symptoms) for included studies, along with data on social adjustment and social functioning, quality of life, economic outcomes and adverse events.

Authors' conclusions

A small body of evidence shows that augmenting current antidepressant therapy with mianserin or with an antipsychotic

https://doi.org/10.1192/bja.2021.66 Published online by Cambridge University Press

(cariprazine, olanzapine, quetiapine or ziprasidone) improves depressive symptoms over the short-term (8 to 12 weeks). However, this evidence is mostly of low or moderate quality due to imprecision of the estimates of effects. Improvements with antipsychotics need to be balanced against the increased likelihood of dropping out of treatment or experiencing an adverse event. Augmentation of current antidepressant therapy with a second antidepressant, mirtazapine, does not produce a clinically important benefit in reduction of depressive symptoms (high-quality evidence). The evidence regarding the effects of augmenting current antidepressant therapy with buspirone or switching current antidepressant treatment to mianserin is currently insufficient.

Further trials are needed to increase the certainty of these findings and to examine long-term effects of treatment, as well as the effectiveness of other pharmacological treatment strategies.