ROUND THE CORNER

Treatment-resistant depression: therapeutic options when first-line treatments fail[†]

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[†]Commentary on… Pharmacological interventions for treatment-resistant depression in adults (Cochrane Corner). See this issue.

SUMMARY

The Cochrane review by Davies et al aimed to address the lack of clarity on the risks and benefits of switching and augmentation strategies in the pharmacological treatment of treatment-resistant depression in adults who did not respond (or partially responded) to at least 4 weeks of antidepressant treatment at a recommended dose. This commentary assesses their review and their conclusion that augmenting the current antidepressant with mianserin or with an antipsychotic improves depressive symptoms over the short-term (8 to 12 weeks). Their results need to be treated with caution owing to the small body of evidence and individual comparisons supported by one, two or three studies, the limited evidence on long-term effects and the significant gaps in the literature (e.g. a lack of studies assessing dose increases).

KEYWORDS

Treatment-resistant depression; depression; antidepressant; augmentation; psychopharmacology.

Depression is a debilitating mental disorder that affects more than 264 million worldwide (World Health Organization 2017). Individuals who experience inadequate response to one or more treatments of adequate dose and duration are often referred to as having treatment-resistant depression (TRD), although currently there is no universally accepted definition of TRD (Box 1). TRD predicts poorer outcomes (Cowen 2015), functional impairments and more persistent suicidal concerns. However, which treatment should be implemented in these cases is still debated and there is no 'standard' approach to treatment for TRD. Therefore, it is imperative to investigate effective strategies and interventions for TRD.

Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial suggest that individuals who do not achieve remission after 2 weeks of treatment may do so by the end of 14 weeks (Trivedi 2006). For those who did not achieve remission by the end of 14 weeks and were progressed to the next level of treatment (switching or augmentation), the likelihood of remission drastically decreased after two treatment levels, indicating that remission probably required a more intensive treatment plan. Notably, the potential risks and benefits of more vigorous dosing with monotherapy agents, augmentation strategies at the earlier stages of treatment and extending the duration of antidepressant trials all require further evidence (Box 2). The primary motivation of the review in this month's Cochrane Corner (Davies 2019) is to address this lack of clarity, as previous systematic reviews of randomised controlled trials (RCTs) investigating pharmacological treatments for TRD have reported weak evidence to guide clinical decision-making.

The Cochrane review

Summary

Ten RCTs, involving a total of 2731 participants and published between 2001 and 2018, were included. Overall, there was evidence that augmenting with a second antidepressant was effective, although this result was not consistent across different antidepressants. Additionally, the authors found moderate- to high-quality evidence (a rating that suggests that the true effect may be different from what the authors found, although findings are likely to be close) that augmenting antidepressants with an antipsychotic significantly reduced depressive symptoms. However, adverse events or limited tolerability were more likely to be associated with the use of antipsychotics.

Included studies, population and outcomes

The review examined the effectiveness of pharmacological interventions for TRD in adults. The review authors defined TRD as depression that did not respond (or had only partially responded) to a minimum of 4 weeks of antidepressant treatment at adequate dose (equivalent to 20 mg/day citalopram or at least 150 mg/day imipramine). This contrasts with the most frequently used definition of TRD as failure to respond to at least two trials of antidepressant of adequate dosage and duration

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BOX 1 Defining treatment-resistant depression

Defining treatment-resistant depression (TRD) can be complex for both major depressive disorder and bipolar disorder. With that in mind, it is unsurprising that there is no universally accepted definition. This creates substantial variability, as some studies will provide valuable information on the sample characteristics such as information on dosage, duration of treatment and number of inadequate treatments, whereas other studies neglect to collect it.

The most common definition of TRD requires a minimum of two failed treatments and evidence of prior adequate dose and duration. According to Gaynes et al (Gaynes 2020), only 17% of intervention studies include samples meeting these specified criteria for TRD.

(Box 1). Although the TRD criteria utilised by the authors provided more inclusive data, it is debatable whether those participants truly had TRD.

Since the review was focusing on treatment for TRD, studies that included participants who had an intolerance to antidepressant medication were excluded. This choice is in line with the focus of the review but leaves an outstanding clinical question regarding treatment options for these patients. As part of the RCTs, continuing antidepressant monotherapy was compared with the following interventions: (a) dose increase of antidepressant monotherapy; (b) switch to a different antidepressant monotherapy; (c) augmentation with another antidepressant; (d) augmentation with a non-antidepressant. In all but one trial, a placebo (Box 3) was given in addition to the continued antidepressant treatment. Trials in which participants could have either unipolar or bipolar depression were excluded unless data were available for the subgroup of with unipolar depression. Trials whose participants also had comorbid physical or psychological conditions (anxiety disorders) were included if the pharmacological therapy was focused on TRD.

Although limiting the external validity of the results, given the size of the samples analysed, the decision to limit the selection to RCTs on TRD for unipolar depression increased power and minimised potential heterogeneity. Although the authors included a series of analyses controlling for the severity of depression and the length of the acute treatment phase prior to trial entry, other potential confounding factors, such as in-patient or outpatient status, were not considered. Further, the populations included in the RCTs were mostly female, but no analysis of the effect of gender was included. Similarly, a subanalysis on the age of the studied populations would have been beneficial. Additionally, the majority of the data analysed was gathered by multisite studies that, despite their potential to generate larger samples, may also lead to potential communication challenges across sites and different statistical approaches.

The review included RCTs with primary outcomes defined by changes on a self-report scale such as the Beck Depression Inventory (Beck 1996). Although self-report measures are valuable and can provide a broad picture of depressive symptoms, they require introspection and do not always allow the disentanglement of different cognitive processes involved in a debilitating, aetiologically complex and heterogeneous disorder such as depression (Box 4). For example, different aspects of anhedonia are more likely to be captured during cognitive tasks (Rizvi 2016).

Drop-out from study or treatment was also included among the primary outcomes. Follow-up was short-term (12 weeks or less), with only one study reporting longer-term outcomes (24–52 weeks). The inclusion of longer follow-up data is of the utmost importance when assessing a pharmacological intervention for TRD, particularly to capture prevention of relapse.

Method of the review and meta-analysis

The authors searched eight medical databases for suitable trials, limiting the inclusion to RCTs and including the relevant arms of cross-over studies, to ensure robust evidence. The quality of the evidence was assessed using GRADE criteria. The

BOX 2 Benefits versus harm of augmentation

It is becoming standard practice to add medications together to treat depression to remission. The ultimate purpose of augmentation strategies is to achieve full remission at a rapid pace otherwise unobtainable with one medication.

One of the most documented augmentation therapies for major depressive disorder is lithium. Lithium has been shown to be effective in improving depressive symptoms and suicidality. Additionally, it shows good tolerability profiles over long periods of time (Barowsky 2006).

Atypical antipsychotics are often associated with side-effects at the cardiovascular, metabolic and endocrine level. Currently, the only antipsychotic approved as adjunctive treatment for major depressive disorder is aripiprazole.

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BOX 3 What does the use of placebo tell us?

Placebo is a term evocatively derived from the Latin verb 'to please' and has been defined by Benedetti as an inert treatment 'with no specific therapeutic properties for the condition being treated' (Benedetti 2016). In research, placebo is commonly used as a comparator in the testing of novel treatments.

BOX 5 Efficacy versus effectiveness

Clinicians distinguish between the efficacy and the effectiveness of an intervention (Gartlehner 2006). Efficacy trials are considered to be exploratory trials and they focus on producing a result under ideal situations, whereas effectiveness trials, also known as pragmatic trials, measure the degree of beneficial effect in real-world clinical settings.

authors identified several limitations with the studies; in particular, many treatment options came from a single large study whereas the results from others came from studies with small samples, thus reducing statistical power and generalisability.

Risk of bias was assessed using the original version of the Cochrane risk-of-bias tool (Higgins 2011). Overall, the authors did not consider any of the included studies to be at a sufficient risk of bias to exclude them from the review, despite some low or unclear risk of selection bias. Heterogeneity was also assessed and no significant heterogeneity was observed for any outcomes for the comparisons of interest. Imprecision was assessed and the authors pointed out that this was one of the key problems with the body of evidence collected for this work. Imprecision is one of five key dimensions in the GRADE approach which relates to the risk of random errors and confidence in the evidence and is one of the dimensions that is commonly associated with downgrading of overall evidence or certainty (Pandis 2015). Last, it is unclear whether the authors distinguished effectiveness from efficacy studies (Box 5).

The review's analysis plan appeared overall compliant with the Cochrane Review standards. The authors reported continuous outcomes by calculating mean differences (MD) between groups where studies used the same outcome measure for comparison. A measure of effect size was also included, facilitating comparison between studies. For dichotomous outcomes, the authors used risk ratios (RR) with 95% confidence intervals (CI) to determine the effect of treatment between the groups of interest. If overall significant risks were identified, the number needed to treat (NNT) or harm (NNH) was calculated by combining the overall RR in the control group – a widely used approach to present results of clinical trials (Balasubramanian 2015).

BOX 4 Perspectives on complementary outcome measures in depression

Combining self-reported measures with other methods, such as behavioural cognitive tasks and/or neuroimaging, offers an opportunity to understand different facets of depression, establish which facets are targeted by specific treatments and identify neurobiological underpinnings associated with maintenance of psychiatric symptoms (Godlewska 2021). Using cognitive tasks to predict or detect reduction in symptoms is relatively nascent, but they have the ability to measure complex aspects of depression such as anhedonia, which encompasses personality, biases and learning (Rizvi 2016; Harmer 2017).

Results

Increasing antidepressant dose

No study increasing the dose of antidepressant monotherapy meeting the inclusion criteria was found.

This result is surprising considering that the guidance published by American Psychiatric Association (2010) and the National Institute for Health and Care Excellence (2009) states that increasing antidepressant dose is a potential next step for those who do not respond to antidepressant medication; despite this, no specific dose efficacy has been established and there remains uncertainty as to the optimal dose for antidepressant monotherapy of major depressive disorder (Furukawa 2019). Although there was no literature meeting the authors' criteria for this treatment approach, their review might have benefited had they included studies that examined dose increases in depression outside of a specific TRD context (e.g. Jakubovski 2016; Furukawa 2019) as these might provide useful information for clinical decisions.

Switching antidepressant

Based on a single study of 71 participants, the authors found no significant difference in depressive symptoms, response or remissions rates when switching from a current antidepressant to another drug (mianserin).

Augmentation with another antidepressant: mianserin and mirtazapine

The authors found moderate-quality evidence that augmentation with mianserin compared with

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placebo significantly reduced severity of depressive symptoms (MD = −4.8, 95% CI −8.18 to −1.42; 1 study, 70 participants) and improved response (RR = 1.70, 95% CI 1.03–2.78) and remission rates (RR = 2.38, 95% CI 1.09–5.16). However, this was not replicated in analysis of self-report outcome measures – this raises questions of whether the finding is less robust or whether the clinician-rated measures are more reliable. The authors also observed a very serious imprecision which suggests that the true effect may be drastically different from the estimate reported in this review paper.

Augmentation with mirtazapine led to no significant difference in depressive symptoms and only weak evidence for treatment response when compared with placebo at 12 weeks, although this was not present at 24–52 weeks (RR = 1.2, 95% CI 0.97–1.54; high-quality evidence, 1 study, 480 participants).

Augmentation with a non-antidepressant

Buspirone was found to lead to no difference in depressive symptom severity. Of the seven studies using antipsychotic medication, all found significant reductions in depressive symptoms from baseline. The difference was modest, with an average group difference between 1.5 and 2.7 on the depression severity scale, equivalent to an effect size of approximately 0.18–0.42 standard deviations. For context, the review notes that NICE guidelines suggest that differences of above 0.33 are clinically significant but the authors suggest that TRD may require larger improvements because of greater baseline impairment. The most robust finding was for quetiapine (standardised mean difference −0.34, 95% CI −0.53 to −0.14), based on three high-quality studies including a total of 977 participants. Although the report found that the other medications were associated with improvements, these comparisons were only supported by one or two studies of lower quality and with small samples (e.g. a single study on olanzapine included only 20 participants).

Discussion

According to this Cochrane review (Davies 2019), the best current evidence for treatment of TRD is augmentation of a selective serotonin reuptake inhibitor (SSRI) with an antipsychotic drug. Nonetheless, this treatment option has limited feasibility: the frequent occurrence of adverse effects and/or the inability to tolerate side-effects, associated with higher rates of drop-out and discontinuation during trials, invites clinicians to carefully consider such drawbacks before selecting these drugs. Their second key finding was that augmentation of antidepressants with an anxiolytic medication (buspirone) led to no significant differences in depressive symptoms – a surprising outcome when considering the frequent comorbidity between anxiety and depression.

As correctly pointed out by the authors, there are significant gaps in the literature for RCTs aiming to address the effectiveness of treatment for TRD. In particular, longitudinal data would improve predictions of long-term prognosis and facilitate individualised treatment of depression. Despite increasing antidepressant dosage being a particularly common practice for clinicians, the authors found no RCTs that met their inclusion criteria; the authors might have benefited from a more inclusive approach to cover studies using the increasing antidepressant dose strategy for individuals with major depressive disorder.

The authors were relatively inclusive in study population, focusing on studies enrolling participants who had failed only one treatment; although this has limitations, including these data provides insight into the potential early stages of TRD and gives clinicians the tools to intervene earlier in the trajectory of depression. On the other hand, the review excluded numerous interventions, such as transcranial magnetic stimulation (TMS) and rapid-acting antidepressants (esketamine, ketamine). Future reviews would benefit from exploring these strategies to provide clinicians with a comprehensive view of available options.

Conclusions

This Cochrane review attempts to address the lack of standardised treatment options for people with TRD, concisely summarising the available evidence from RCTs. Unfortunately, the relatively small sample sizes of the studies analysed, the limited number of replicated results and the lack of long-term data limit the possibility of drawing definite conclusions. The paper gives us an overview of what is currently available, which remains extremely limited.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

Both authors devised the article. C.W. wrote the first draft and both authors commented on all drafts.

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Declaration of interest

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