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ROUND THE CORNER

Adjunctive benzodiazepines in depression: a clinical dilemma with no recent answers from research†

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SUMMARY

Comorbid anxiety symptoms are common in depression, and adding benzodiazepines to antidepressant treatment may seem a rational clinical solution. Benzodiazepines also have potential to reduce the initial anxiety that may be caused by early antidepressant treatment (owing to their inhibitory effect via $GABA_A$ receptor binding). This month's Cochrane Corner review examines the evidence behind combination treatment versus antidepressants alone in major depressive disorder, in terms of both the clinical and neuroscientific context. The review provides evidence that, in the first 4 weeks of treatment, additional medication with a benzodiazepine may lead to greater improvements than antidepressant alone on ratings of severity, response rates and remission rates for depression, but not on measures of anxiety.

KEYWORDS

Depressive disorders; anti-anxiety drugs; antidepressants.

Depression is a common and disabling disorder affecting more than 250 million people globally (Malhi 2018). Anxiety and depression often co-occur in individuals at different times as well as simultaneously, with each contributing variable amounts to the overall disease burden (Wetzler 1989). Antidepressants are the mainstay of treatment for both disorders (National Institute for Health and Care Excellence 2009, 2019), but there is a delay in therapeutic outcome perhaps partly due to the time taken to desensitise presynaptic 5-HT_{1A} autoreceptors (Duman 2007), and antidepressant treatment can acutely increase anxiety as an early side-effect (Sinclair 2009; Rahn 2015). Therefore, the idea of adjuncts to reduce this early anxiety and provide support while waiting for the antidepressant therapeutic effect may be well-grounded.

Benzodiazepines are an important class of anti-anxiety and hypnotic medication. In broad terms, they work by binding the $GABA_A$ receptors in the central nervous system, thus reducing the excitability and communication between neurons. However, they also interact with peripheral receptors mainly involved in immunological functions (Zavala 1997). Such pleiotropy could be relevant when considering that the neurobiological basis of depression is likely to be diverse and involve several neurotransmitter pathways (including GABA) as well as the immune system (Duman 2019).

Antidepressants are known to be clinically superior to benzodiazepines alone in treating major depression (Birkenhager 1995), but national guidelines in the UK suggest a role for benzodiazepines as a combination therapy for a limited period if anxiety or insomnia are also present (National Institute for Health and Care Excellence 2009). In other words, people with depression and comorbid anxiety, and potentially also insomnia, may benefit from co-prescription of a benzodiazepine, particularly to relieve symptoms of anxiety and poor sleep. From a psychopharmacological perspective, such a combination appears reasonable, since most currently available antidepressants act at the level of the monoaminergic system, whereas benzodiazepines would mediate different effects on the GABAergic system. Indeed, supplementing antidepressant with benzodiazepine treatment has the potential to immediately reduce anxiety symptoms via the enhancement of action at $GABA_A$ receptors (Leonard 1993). However, benzodiazepines bring their own problems. Even when used at controlled doses, benzodiazepines desensitise and downregulate GABA receptors and sensitise the excitatory (glutamate) neurotransmitter system, thus resulting in tolerance and potential dependence syndrome (Allison 2003). Moreover, the development of tolerance may thwart

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longer-term benefits (Schweizer 1998), although this might not include anti-anxiety effects. There is also a possible increased risk of falls and motor vehicle accidents (Neutel 1995), potentially due to detrimental effects on cognition, alertness and motor skills.

Uncertainty regarding the mixed nature of evidence for the use of benzodiazepines as an adjunct in depression provided the motivation for the first Cochrane Review on this topic, published in 2001 (Furukawa 2001) and involving nine studies with 679 patients. This was updated in 2005, and then again in 2019. This 2019 review (Ogawa 2019) is in this month's Cochrane Corner.

Summary of the Cochrane Review

The review authors conducted a systematic review of randomised control trials where either antidepressants or antidepressants plus benzodiazepines had been randomly allocated to individuals with major depression (Ogawa 2019). Ten studies, involving a total of 731 participants, published between 1978 and 2002 were included in the meta-analysis and the review uses the same data as the 2005 review, but with minor changes in methodology. Overall, combined antidepressant and benzodiazepine therapy was more effective and tolerable than antidepressants alone in the early phase, but these effects were not maintained in later phases.

Updated methods…

The study population

The study population comprised adults with major depression as defined by diagnostic criteria according to the main classification systems (such as DSM, ICD or the Research Diagnostic Criteria) who were part of a randomised controlled trial comparing antidepressant with combined antidepressant and benzodiazepine treatment. Given the considerable overlap between anxiety and depression, it was particularly important that participants with comorbid anxiety disorders were included. Participants in studies with other comorbid physical or psychological disorders were not excluded automatically, unless the comorbidity itself was the focus of the study. Allowing participants with disorders outside depression to be included increases the potential generalisability of the review to provide findings applicable to typical clinical populations, but as the study population becomes less uniform it can introduce bias and reduce scientific integrity.

There is a lack of clarity regarding concurrent medications: for example, were participants excluded if they were also taking other non-psychiatric medications that can potentially affect mental state, such as anti-inflammatories and steroids? This uncertainty also extends to participants potentially starting concurrent medications during the study. This sort of detail is unlikely to be recorded in the often historic study reports, and so was outside the control of the Cochrane authors. However, it remains important when considering the potential applicability and clinical utility of the review, as other medications might improve or hinder the action of antidepressant medication.

The study and comparison interventions

The study intervention was an antidepressant plus benzodiazepine for a minimum of 4 weeks at a minimum effective dose according to international guidelines. The breadth of included antidepressants and benzodiazepines listed is a strength of the review and improves the clinical generalisability of the findings. The European guidelines used by the authors are not clarified, which could affect the reproducibility of their analysis. The study comparison was an antidepressant (as for the intervention) but prescribed alone.

Outcomes

Primary outcomes were defined as effect on depression severity and acceptability of treatment and were grouped depending on duration of administration: early (≤4 weeks), acute (5–12 weeks), continuous (>12 weeks). We will not discuss secondary outcomes in this commentary owing to space constraints. The review authors were prepared to combine data from observer-rated and self-reported outcomes across studies for inclusion in the meta-analysis (Box 1); in fact, all studies had observer-rated data available, negating the need for self-report in the analysis.

The search strategy and quality of evidence

The review authors examined only the highest levels of individual study evidence: randomised controlled trials, including the relevant arms of cross-over studies. To maximise the systematic nature of the search, they searched the Cochrane Common Mental Disorders Group's Controlled Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, the World Health Organization (WHO) trials portal, ClinicalTrials.gov and reference lists, and contacted principal investigators to identify any additional unpublished or ongoing studies, with no restrictions for language. Despite this very comprehensive strategy, from inception to May 2019, no new data emerged as published after 2002. It is perhaps surprising that no new studies were found since the

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BOX 1 Self-reported and observer-rated outcomes

Self-reported outcomes: rapid and relatively easy to obtain, but subject to several biases. For example, participants may exaggerate/minimise responses because of their subjective state at the time of assessment, to receive the promised service once enrolled in the study, or out of a natural tendency to respond in a way that is viewed favourably by others. Participants may also forget/misinterpret details of their clinical history and presentation (recall bias).

Observer-rated outcomes: more time-consuming, but arguably more objective than self-reported measures. Some researchers dispute the latter, as these outcomes still rely on the participant's memory and current circumstances, while also introducing potential biases related to the observer's experience and assumptions.

Combining data from different forms of report (for example, self-reported and observer-rated questionnaires) increases the available data for pooling but should be performed only when it is known that changes in effect sizes across studies are comparable. Even when performed carefully, results from combined outcomes can be contended by regulatory agencies.

2005 update (literature searched up to 2004). However, this might indicate that clinical practice may recently have moved away from the use of benzodiazepines in general owing to the concerns about iatrogenic harm, most particularly fostering dependence.

The authors used the GRADE criteria (Schünemann 2013) to evaluate the quality of the evidence; this was one of the updates they made to the review methods used in the 2005 version. Bias was classified as 'unclear' from examining the reports of most studies, probably because many of the studies included date from a time when reporting guidelines were less prevalent, and no studies had an available protocol (Box 2).

The authors also noted particular problems regarding attrition of participants (Box 3) in nine studies, four of which (Feighner 1979; Dominguez 1984; Yamoaka 1994; Smith 2002) were of particular concern as attrition was greater than 33%. This may increase bias and therefore concern about the validity of the findings. However, as the drop-out rate appeared to be similar across both arms, the authors reported that they have some confidence in their findings in this respect.

The meta-analysis

The analysis was appropriately conducted according to Cochrane Review standards. For meta-analysis, the authors combined continuous outcome variables of depression and anxiety severity using standardised mean differences (SMD) with 95% confidence intervals (CI) and calculated the risk ratio (RR) with 95% CI for dichotomous efficacy outcomes. This allowed them to synthesise data from different measures assessing the same outcome. Regarding the primary outcome of treatment acceptability, only overall drop-out rates were available for all studies.

Authors included both continuous measures of depression severity and dichotomous measures of depression response and remission for data clarity and availability reasons. They stated that response and remission data may be more available and also easier to understand. There is no equivalent justification for assessing continuous measures of severity. The authors also combined dichotomous outcome variables at what they term 'approximately the same time-point' using RRs with 95% CIs, although to allow replication this should be better explained. They also justify using empirical data combining different definitions for response as these produce similar RRs (Furukawa 2011).

…similar results

The review authors found moderate-quality evidence that the combination of antidepressants plus benzodiazepines compared with antidepressants alone significantly reduced severity of depressive symptoms (SMD = –0.25, 95% CI –0.46 to –0.03;

BOX 2 Study protocols

A study protocol is a structured document describing all the aspects of a research study.

Pre-registered/published protocols ensure that authors pre-specify methods and analyses to prevent changing these in the context of results (selective-reporting bias), thus increasing transparency of research.

Pre-registering/publishing a study protocol (for example on clinicaltrials.gov or BMJ Open) has become increasingly important and several major medical journals no longer accept studies that have not been previously registered.

BOX 3 Attrition bias

Attrition bias is due to participants leaving a study (dropping out), regardless of the reason.

Drop out may be due to chance and be randomly distributed among study groups; however, systematic differences between participants leaving the study and those who continue can introduce bias.

Attrition always occurs to some extent: it is difficult to control but can be accounted for at the analysis level (for example through intention-to-treat analysis). Studies with longer follow-ups are more likely to incur significant attrition; unfortunately, this often happens.

BOX 4 Forest plots

Forest plots are named after their graphs, which resemble a forest of lines. Forest plots are the most commonly used way to represent the results of a meta-analysis. An article's readers may gauge the most significant meta-analysis results by just glancing at the forest plots.

Figure 1 shows a forest plot of findings from five fictitious studies measuring the number dropping out of treatment (a common measure of treatment's acceptability) for participants taking antidepressants (ADs) versus antidepressants plus benzodiazepines (ADs + BDZ).

Each study included in the meta-analysis is usually reported with the first author's name and date of publication (Study or Subgroup column). The comparison and intervention columns then follow – in this example, ADs and ADs + BDZ. For each of these columns, the number of outcomes of interest (Events) and the number of participants per group (Total) are reported – in this example, for 'Study A 2015' 60 out of 100 participants in the ADs arm dropped out and 50 out of 100 participants in the ADs + BDZ arm.

Each study has a different impact on the pooled result of the meta-analysis depending on how much information it contains (Weight); the weight is calculated by the statistical software and is proportional to the total number of participants and the total number of events for each study – in this example, 'Study D 2018' has much more weight than 'Study C 2016' (41.2% *v.* 1.4% respectively) because the former has several more participants and counts several more events than the latter.

Finally, an effect size measure (for example, a risk ratio, a mean difference, etc.) with 95% confidence interval (CI) is computed by the statistical software for each study. The effect size and the 95% CI are also illustrated by the graphs: the square boxes show the estimated effect size and the horizontal lines the 95% CIs; the larger the square box, the greater the weight of the study. The vertical line of the graph is the line of no effect – in this example measuring a risk ratio, the line of no effect corresponds to 1. If the horizontal line representing the 95% CI touches the vertical line of no effect, the individual study result is not statistically significant.

At the bottom of the graph, a pooled effect size with 95% CI is depicted by the diamond box: the centre corresponds to the estimated effect size, and the lateral tips of the diamond are the limits of the 95% CI. Again, if the 95% CI touches the vertical line of no effect, the pooled estimate is not statistically significant, whereas if the diamond is placed clearly on the right or left of the vertical line of no effect, either the intervention or the comparison is favoured – in this example, the combination of antidepressants and benzodiazepines is better than antidepressants alone in terms of acceptability (RR = 1.10, 95% CI 1.03–1.18) and the diamond box is on the right side of the vertical line of no effect (Favours ADs + BDZ). The pooled result is also reported numerically in the line in bold just below all the included studies. At the bottom of the forest plot, other numerical values are reported: it is important to notice the measure of heterogeneity across all the included studies – the lower, the better.

10 studies, 598 participants), and improved response (RR = 1.34, 95% CI 1.13–1.58; 10 studies, 731 participants) and remission (RR = 1.39, 95% CI 1.03–1.90; 10 studies, 731 participants). Importantly, in all cases this was only in the early period (up to 4 weeks). For the remainder of the results, we refer readers to the Cochrane summary. There were no data on frequency of dependence on benzodiazepines.

The forest plots (Box 4, Fig. 1) of the Cochrane Review, demonstrating pooled data subdivided for short-acting and long-acting benzodiazepines, showed that any potential clinical benefit of early use of combination therapy in terms of depression severity is limited to longer-acting benzodiazepines. This is not clearly stated in the review summary. However, the number of studies assessing short-acting benzodiazepines was small (two), which may explain why the authors did not explore this further in the report. Confidence intervals were generally broad in all analyses, thus limiting the precision of findings. Heterogeneity was moderate for several outcomes, which implies that there are substantial differences between studies and that meta-analyses should be conducted with caution.

In the results section, rather than the summary, the authors state that no new studies were included in this 2019 review compared with the previous 2005 review. They note that they had brought the review processes up to date in the most recent publication, but that this had had little impact on the review findings.

Sensitivity analyses were added in 2019 to check results with and without the inclusion of self-reported data and to check results with and without the same definition of response as a 50% reduction in depression scores. The authors report that results were consistent within and outside of the sensitivity analyses. This helps the reader to understand that the authors' decisions regarding inclusion did not affect the results. Other differences in the 2019 review included addition of secondary outcomes such as remission and improved clarity regarding time periods, which were divided into early, acute and continuous. The authors explain why they added remission as an outcome, but their reasons for the selection of time periods for analysis are less obvious. Taking into account these changes, the findings from the review appear broadly similar.

To add (or not to add) benzodiazepines to antidepressants: the dilemma stands

Weak external evidence in light of changing prescribing practices

The major problem with the external validity of this review update is the lack of recent evidence. Many of the background references used in the review were

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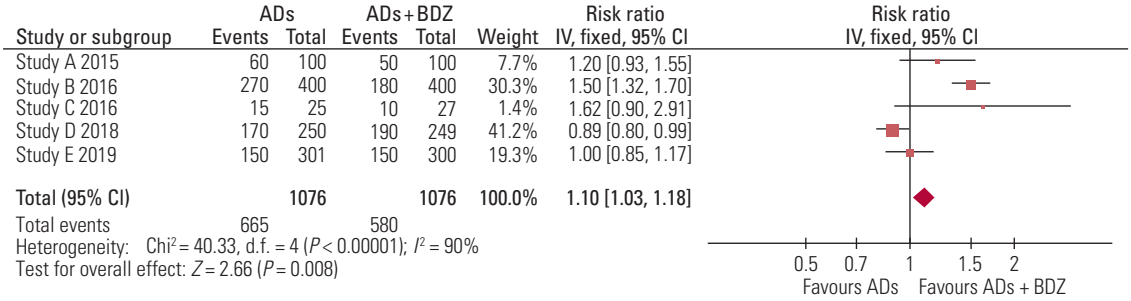

FIG 1 Forest plot of findings from five fictitious studies of treatments for depression, showing drop-out numbers for participants taking antidepressants (ADs) versus antidepressants plus benzodiazepines (ADs + BDZ).
IV, independent variable.

published before 2000, which likely relates to the age of the original review. This is in line with a lack of included studies in the review since the last update in 2005 (none published since 2002), indicating that the evidence in this field has not substantially changed in the past 15–20 years. However, clinical practice in psychiatry has changed significantly even since the most recently published study in 2002. A large epidemiological study (765 130 adults with depression in the USA) identified that the proportion of patients with concurrent new antidepressant and benzodiazepine use increased from 6.1% in 2001 to 12.5% in 2012–2014 (Bushnell 2017). This is concerning considering the apparent lack of data regarding longer-term outcomes for the combination of benzodiazepines and antidepressants, alongside the potentially positive data regarding short-term use of this combination therapy. Considering the conclusions of this Cochrane review, it is possible that any clinical benefit of benzodiazepines as an adjunct in depression is limited to very early use, but this is not yet clear from the randomised data included.

It is possible that undertaking randomised controlled trials examining longer-term outcomes of benzodiazepines when used as combination therapy in depression is difficult in view of the potential risks of dependence/withdrawal, and cognitive and motor impairments. The review authors suggest that more pragmatic randomised trials may be necessary. An alternative is to agree as a community that randomised trials may no longer be possible to help us answer this clinical question, and to systematically assess observational data regarding longer-term use of benzodiazepines as adjuncts in depression instead. From a neuroscientific angle, and as often occurs, exciting findings in basic science (in this case, the potentially important role of the GABAergic system in the aetiology of depression (Luscher 2015)) may fail to be translated at the human research and clinical level.

Benzodiazepine dependence and future research

Dependence is a common concern with benzodiazepines (Marsden 2019), but there is little evidence regarding this in the review, which is important when considering the clinical applicability of its findings. Despite the potential positive findings in terms of combination therapy and a reduction in early depression severity in this review, it remains difficult to know whether clinicians should consider adding a benzodiazepine to an antidepressant acutely if we are unclear about the potential harms of dependence with such an intervention.

The authors suggest that longer-term trials with a pragmatic design (to ensure recruitment of more typical populations and to allow for expected variations in clinical practice) are required to improve the current evidence base, particularly in terms of the potential for benzodiazepine dependence and withdrawal for short- and longer-term prescriptions. As the authors acknowledge, only one included study (Smith 2002) followed up individuals for longer than 8 weeks and could be included in the longer-term assessment of combination treatment. High drop-out rates (attrition bias, Box 3) were a major problem for most of the included trials and would be worth further exploring. This was reported in the review's discussion but less so in its summary.

Conclusions

In all likelihood, this Cochrane Review has limited applicability owing to the paucity of recent studies that could be included, as well as the limited length of follow-up and quality for included studies, and the few studies examining particular areas of concern such as benzodiazepine dependence. Considering that the clinical problem underpinning the review remains as pertinent as ever, we need to remain open to exploring alternative methods of research, such as pragmatic randomised studies, observational data and experimental medicine.

Author contributions

Both authors devised the article. A.N.d.C. wrote the first draft of the article, apart from the boxes and figure, which were drafted by R.D.G. Both authors commented on drafts of the article.

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Declaration of interest

None.

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