ROUND THE CORNER

Do we need a more individualised approach to the management of comorbid depression and diabetes?[†]

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SUMMARY

Diabetes and depression have a bidirectional relationship, but some antidepressants (such as the tricyclics) may have detrimental effects in diabetes that are exacerbated by behavioural changes associated with depression. This month's Cochrane Review evaluated the efficacy of psychological and pharmacological treatments of comorbid depression in diabetes and found that such interventions have a moderate and clinically significant effect on depression outcomes in people with diabetes. However, conclusions were limited by significant heterogeneity within examined populations and interventions, and significant risk of bias within trials. This commentary critically appraises the review and aims to contextualise its findings.

KEYWORDS

Depressive disorders; randomised controlled trial; antidepressants; experimental design; statistical methodology.

Depression affects an estimated 16% of UK adults (Office for National Statistics 2022) and its prevalence is projected to rise in the coming years. Depressive disorders can develop in the context of chronic medical conditions such as diabetes mellitus (diabetes, for short) (Moulton 2015). Diabetes is characterised by chronic hyperglycaemia due to impaired insulin secretion, insulin action or both (Petersmann 2019), and is mainly classified into type 1 and type 2. The prevalence of comorbid depression in people with diabetes has reportedly increased over the past three decades (van der Feltz-Cornelis 2020), and the two conditions are known to have a bidirectional relationship. Evidence suggests that some antidepressants, such as tricyclic antidepressants, may contribute to less favourable outcomes for people with diabetes (Alruwaili 2023), which are subsequently exacerbated by behavioural changes associated with depression. Given the greater healthcare costs, utilisation of services and long-term complications that this could cause, effective treatment of depression in people with diabetes is proving to be increasingly important.

This month's Cochrane Review (Baumeister 2012) aimed to evaluate the efficacy of psychological and pharmacological treatments of comorbid depression in people with diabetes.

The Cochrane Review

Search strategy

Randomised controlled trials (RCTs) were utilised, which are deemed among the highest level of evidence in clinical research. The authors conducted a commendable search, where four electronic databases were searched from inception to 2011 (the review was published in 2012). Two further databases were searched for ongoing trials, and reference lists of included trials were also searched.

Who was included?

The study population consisted of adults with diabetes and comorbid depression. However, the review authors did not differentiate between type 1 and type 2 diabetes or depressive disorder subtypes in their search criteria. This is likely to be because only one included trial (Komorousova 2010) exclusively examined people with type 1, and reliable conclusions cannot be drawn from a single trial. Even now, there remains a limited number of trials examining depression in type 1 diabetes (van der Feltz-Cornelis 2020), and we speculate that this is because type 1 is significantly less prevalent than type 2 (National Institute for Health and Care Excellence (NICE) 2022).

Treatment interventions

The study interventions were pharmacological or psychological and were compared with placebo versus 'no intervention' or 'usual care'. However, time points for outcome measurement were not included in search criteria and varied significantly between studies (3 weeks to 12 months). This is clinically significant, as there are guideline-specified treatment times for each intervention (NICE 2009),

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and by not adhering to these, reproducibility of the analysis is limited.

End-points of the study

Primary outcomes were defined as reduction of depressive symptoms or remission of clinically significant depression, and glycaemic control, and were stratified as short term (<1 month), medium term (1–6 months) and long term (>6 months). Secondary outcomes, defined as health-related quality of life, healthcare costs, adherence to a diabetic treatment regimen, diabetes complications and death from any cause, were not analysed in the review as there were insufficient investigations. A possible explanation for this is that most of the defined secondary outcomes necessitate measurement over a longer time period so are more at risk of associated complications such as loss to follow-up and non-adherence to treatment. This could be minimised by utilising patient and public involvement and engagement (PPIE) activities such as focus groups, workshops or interviews prior to trial commencement, which may empower patients by allowing them to share their experiences and viewpoints.

Results: effective interventions?

Regarding the primary outcomes, the review authors found that psychological interventions versus usual care had a moderately beneficial effect on short-term (seven trials, 1032 participants; results were not pooled owing to significant between-study heterogeneity (Box 1)) and medium-term (standard mean difference (s.m.d.) = −0.42, 95% CI −0.70 to −0.14, $n = 504$, three trials) depression severity. Only one study investigated the long-term effect, finding a significant beneficial effect (s.m.d. = −0.31, 95% CI −0.58 to −0.04, $n = 208$).

Regarding depression remission rates, psychological interventions showed a significant beneficial effect in the short term (odds ratio = 2.88, 95% CI 1.58–5.25, $n = 647$, four trials) and medium term (odds ratio = 2.49, 95% CI 1.44–4.32, $n = 296$, two trials). The effect of psychological interventions on glycaemic control was non-significant owing to significant heterogeneity in the short and medium term and no significant effect in the long term (short-term effect: significant heterogeneity, $I^2 = 83\%$, $n = 441$, four trials; medium-term: significant heterogeneity, $I^2 = 78\%$, $n = 346$, three trials; long-term: no significant effect, $n = 49$, one trial).

Pharmacological interventions were evaluated only for short-term primary outcomes and were broadly beneficial versus placebo (short-term depression severity: s.m.d. = −0.61, 95% CI −0.94 to −0.27, $n = 306$, seven trials; short-term depression remission rates: odds ratio = 2.50, 95% CI 1.21–5.15, $n = 136$, three trials; short-term glycaemic control: mean difference for HbA_{1c} of −0.4%, 95% CI −0.6 to −0.1, $n = 238$, five trials).

BOX 1 Heterogeneity

Heterogeneity refers to forms of variability that inevitably exist within studies included in a systematic review. There are different types of heterogeneity:

- Clinical heterogeneity – refers to variability in the participants, interventions or outcomes studied. For example, the use of a mixture of participants with type 1 and type 2 diabetes.
- Methodological heterogeneity – refers to variability in study design or risk of bias. For example, utilisation of different masking (blinding) techniques (double versus single blinding).
- Statistical heterogeneity – refers to variability in the intervention effects being evaluated in each of the different studies and it can arise from clinical or methodological heterogeneity. In other words, how similar are the results between individual trials? And are differences between the results of trials greater than would be expected by chance alone?

Discussion

The quality of evidence

Double-blind RCTs can be considered the gold standard in experimental studies as they minimise the risk of confirmation bias and observer bias (Misra 2012). Four trials included in the review did not report sufficient information regarding masking (blinding) of staff and participants (Xue 2004; Gülseren 2005; Qu 2005; Khazaie 2011) and one trial was single-blind (Paile-Hyvärinen 2003), meaning these trials were at greater risk of confirmation and observer bias.

The review authors' restriction to RCTs may have narrowed sample size. Only 19 RCTs (1592 participants) were subsequently included (11 investigated pharmacological interventions and eight investigated psychological interventions). This could affect the reliability of conclusions drawn. Peinemann et al (2013) recommend that inclusion of multiple study designs is necessary in systematic reviews aiming to evaluate the efficacy of healthcare interventions.

Three trials included in the review (Li 2003; Lu 2005; Simson 2007) did not report any information regarding drop-out and attrition rates and are therefore potentially subject to attrition bias (Box 2).

Generalisability of results

The heterogeneity between diabetes subtypes and lack of subsequent subgroup analysis mean it is

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BOX 2 Attrition bias

Attrition bias is a type of bias that can arise when participants drop out or are lost from a study. If there is a significant systematic difference between the participants who drop out compared with those who remain, the results may not be truly representative of the entire population under study. Bias is more likely to be introduced if drop-out is not random and a high number drop out. For instance, if drop-out occurs because participants experience side-effects from a particular medication, this would not be a random occurrence, and hence there is a likelihood of attrition bias affecting results.

unclear whether the review authors' findings are valid and generalisable to both diabetes subtypes. They did not conduct subgroup analyses (Box 3) following acquisition of results. Overlooking differences between type 1 and type 2 diabetes has a risk of missing subgroup-specific effects, as there are significant differences in metabolic, physiological and demographic parameters (Krause 2023).

Similarly, sensitivity analyses (Box 3) to examine differential effects of interventions on different depression subtypes were not feasible in the present review, owing to the small number of trials per outcome. Thus, conclusions regarding differential treatment effects depending on depression subtypes or severity cannot be drawn.

Furthermore, the use of 1998, 1999 and 2008 diagnostic criteria for diabetes in selected studies may not accurately represent the current diabetes population owing to the later implementation of glycated haemoglobin (HbA_{1c}) as a diagnostic tool (American Diabetes Association 2013). The clinical utility of the results is also uncertain, since important secondary outcomes, such as quality of life, adherence to diabetes treatment and diabetes complications, were not measured.

It was unclear whether participants included in pharmacological intervention trials were taking medications beyond anti-diabetics or antidepressants. This is clinically relevant, since steroids, for example, may affect both blood glucose and mental state (Warrington 2006; Tamez-Pérez 2015). Inclusion of such participants results in a less uniform study population and introduces risk of confounding bias. Conversely, such participants may be more representative of the target population, since people with diabetes often have other comorbidities.

BOX 3 Subgroup analysis versus sensitivity analysis

Subgroup analysis refers to a process whereby participants are split into subgroups (often according to demographic characteristics such as ethnicity, gender, age) and analysis is performed to determine whether the treatment effect is the same or different between the subgroups. For instance, in this Cochrane Review, subgroup analysis could have been performed to determine whether the included interventions showed any differences in efficacy between people with type 1 and type 2 diabetes with depression.

Sensitivity analysis, also known as the 'what if' analysis, is a tool used to assess the robustness of study results, by use of 'what if' questions. If the outcome of this analysis is consistent with the primary analysis, we can be confident that the results are robust enough that they are unaffected by alternative assumptions. For example, the review authors here could have asked 'What if we eliminated data from people with type 1 diabetes – would our results be different?' If the answer is yes, this would imply that the findings were affected by the presence of participants with type 1 diabetes, and therefore less robust.

In summary, subgroup analysis utilises the original research question to examine variations between different subgroups of participants, whereas sensitivity analysis utilises alternative ('what if') questions to examine variations in study results as a whole.

Conclusions

This review found that psychological and pharmacological interventions had moderately beneficial effects on depression outcomes in people with diabetes with comorbid depression. Evidence pertaining to glycaemic control was heterogeneous and inconclusive. The clinical utility of the results is limited owing to significant heterogeneity within examined populations and interventions, significant risk of bias within trials, as well as sparse evidence for secondary outcomes. Additionally, participants were not stratified by diabetes or depression subtypes, and subsequent lack of subgroup and sensitivity analysis further limits clinical applicability.

The NICE guidelines (NICE 2009) for depression in adults with a chronic physical health problem recommend psychological interventions as first line in mild-to-moderate depression. This review was unable to stratify evidence according to depression subtype, and consequently the evidence is difficult to contextualise. Studies comparing psychological and pharmacological interventions would also have been useful, as this would have enabled further exploration of the rationale for current NICE guidelines, thus potentially contributing to the prevention of unnecessary pharmacological treatment.

Consideration of adverse effects is especially important when initiating pharmacological treatment in individuals with comorbid diabetes and depression, as this allows us to determine risk–benefit ratios and is likely to influence clinical

decision-making. However, few trials included in this review addressed this. This is likely because detection of adverse effects often requires long-term observation (Peinemann 2013), whereas the included trials lasted only a maximum of 12 months.

Overall, this review provides a starting point and highlights key areas for further research into an increasingly important field. A similar review has been conducted since (van der Feltz-Cornelis 2020), which examines more recent evidence to determine the effect of psychological and pharmacological interventions on comorbid depression in type 1 and type 2 diabetes. Although its authors did not investigate differences between diabetes subtypes, they were able to estimate differential effects of interventions on depression subtypes and glycaemic control. The paucity of studies investigating comorbid depression in type 1 diabetes remains problematic and makes it difficult to draw definitive conclusions about the generalisability of results in all people with diabetes. Further research in this area may help us understand the mechanisms underpinning the increased efficacy of interventions in certain subgroups of patients, contributing to a more individualised approach for the treatment of depression in those with chronic medical conditions, which would likely be beneficial owing to the heterogeneity in the population of people with diabetes.

Data availability

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

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Author contributions

Both authors are responsible for the ideation and revision of the article. S.M. is responsible for the design and writing of the manuscript. P.P. is responsible for the review of drafts of the article.

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Declaration of interest

None.

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