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Repositioning of diabetes treatments for depressive symptoms: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Depression is a common comorbidity in diabetes but conventional antidepressant treatments do not consistently improve outcomes. We tested whether established diabetes treatments can also improve depressive symptoms and examined biological correlates of response. We performed a multi-database systematic search of all clinical trials, which measured the effect of licensed diabetes treatments on depressive symptoms using a validated questionnaire. Results of randomised controlled trials (RCT's) were pooled for meta-analysis. Data were also collected on insulin resistance (HOMA-IR), C-reactive protein (CRP) and fasting blood glucose (FBG) as correlates of response. Nineteen studies (n = 3369 patients) were included in the qualitative synthesis, 9 testing thiazolidenediones, 5 metformin, 2 thiazolidenediones against metformin, 2 incretin-based therapies and 1 insulin. Most studies were of good quality. In random-effects meta-analysis of RCT's, pioglitazone improved depressive symptoms compared to controls (pooled effect size = −0.68 (95% C.I. −1.12 to −0.24), p = .003, $N_{studies}$ = 8, I^2 = 83.2%). Conversely, metformin was comparable to controls overall (pooled effect size = +0.32 (95% C.I. −0.23 to 0.88), p = .25, $N_{studies}$ = 6, I^2 = 94.2%), although inferior to active controls (pooled effect size = +1.32 (95% C.I. 0.31–2.34), p < 0.001, $N_{studies}$ = 3, I^2 = 90.1%). In random-effects meta-regression, female sex (β = −0.023, (95% C.I. −0.041 to −0.0041), p = .016, $N_{studies}$ = 8) predicted reduction in depressive symptoms with pioglitazone, but baseline HOMA-IR, FBG and severity of depressive symptoms did not. In conclusion, pioglitazone was associated with improvement in depressive symptoms, an effect more marked in women and poorly explained by effects on glycaemia and insulin resistance. Metformin had no consistent benefit on depressive symptoms. Further mechanistc trials of diabetes treatments as potential antidepressants are needed, stratified by sex and including serial measures of innate inflammation.

1. Introduction

Depressive symptoms are twice as common in people with type 2 diabetes compared to the general population and are associated with increased risk of diabetes complications and premature mortality (Anderson et al., 2001; Winkley et al., 2012). However, this association is inadequately explained by behavioural and psychological factors alone (Moulton et al., 2015). Conventional treatments for depressive symptoms in type 2 diabetes, such as antidepressant medication and psychological therapies, are associated with high rates of treatment failure and frequent non-adherence to treatment (Rush et al., 2006; Sawada et al., 2009). Understanding the biological mechanisms underlying depressive symptoms in type 2 diabetes could lead to identifying new targets and development of novel treatments.

At least three potential (though not mutually exclusive) biological pathways have been implicated in the link between the two conditions. Firstly, increased concentrations of circulating inflammatory markers are seen in people with depressive symptoms and type 2 diabetes compared to people with type 2 diabetes alone (Hayashino et al., 2014; Laake et al., 2014). Secondly, higher insulin resistance is consistently associated with increased depressive symptoms in cross-sectional studies, even after adjustment for confounders (Kan et al., 2013), and insulin resistance is likewise associated with elevated inflammation (Donath, 2014). Thirdly, hyperglycaemia is associated with increased depressive symptoms in cross-sectional studies (Lustman et al., 2000), although the association is weaker when tested prospectively (Fisher

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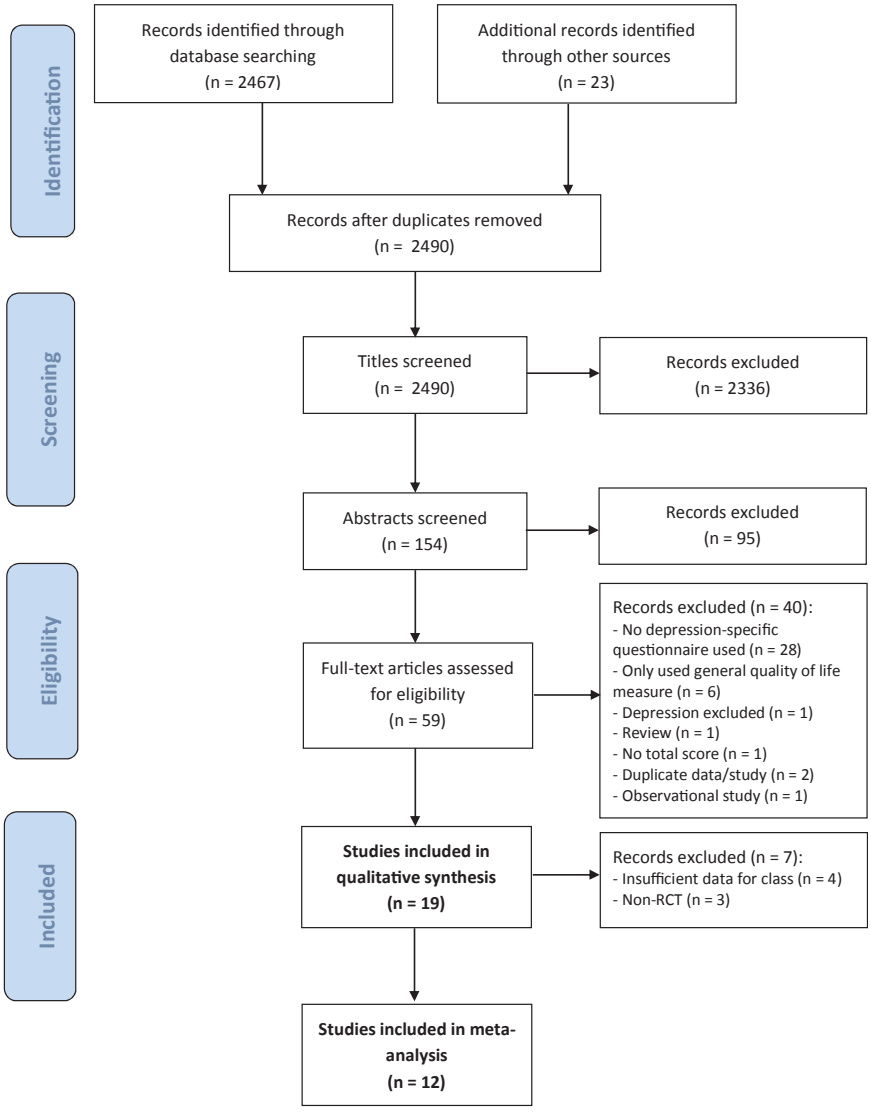

Fig. 1. PRISMA flow diagram of literature search.

et al., 2010b). Importantly, conventional antidepressants have inconsistent effects on glycaemic control, insulin resistance and inflammation (Katon et al., 2004; Kauffman et al., 2005), whereas many diabetes treatments have potent effects on these three pathways (Makdissi et al., 2012; Reynolds et al., 2007; Yki-Jarvinen, 2004). Meanwhile, many diabetes treatments, including metformin, glucagon-like peptide-1 (GLP-1) and thiazolidenediones, have been found to cross the blood-brain barrier (Heneka et al., 2005; Kastin et al., 2002; Labuzek et al., 2010). As well as reducing polypharmacy, this suggests that established diabetes treatments could be repurposed to improve both depressive symptoms and diabetes concurrently. In addition to possible central actions, such antidepressant effects could be driven by the modification of biological pathways common to both depressive symptoms and diabetes. To date, however, the potential antidepressant properties of diabetes treatments have not been systematically evaluated.

We have conducted a systematic review and meta-analysis of diabetes treatments and their effects upon depressive symptoms. Our primary aim was to test whether specific pharmacological classes of diabetes treatments are associated with improvements in depressive symptoms compared to controls. Our secondary aim was to test for potential correlates of treatment response, specifically inflammation, insulin resistance and glycaemic control.

2. Methods

2.1. Design

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, in which studies that meet review criteria are examined and those that were RCTs and with sufficient data pooled for meta-analysis.

2.2. Literature search

We systematically searched PubMed, EMBASE and Web of Science from 1st January 1900 to 1st March 2018. A Boolean search was conducted, cross-referencing licensed pharmacological treatments of diabetes with depressive symptoms and related terms, with exclusion of non-human studies and limiting to clinical trials only. Notably, we included randomised- and non-randomised trials in the qualitative synthesis but only RCT's in the meta-analysis. The search strategy was as follows:

(sglt-2 inhibitor OR dapagliflozin OR canagliflozin OR empagliflozin OR metformin OR incretin OR dpp-iv inhibitor OR dpp-4 inhibitor OR linagliptin OR saxagliptin OR alogliptin OR sitagliptin OR nateglinide OR repaglinide OR albiglutide OR glp-1 OR dulaglutide OR