Review Article

Systematic Review of Psychological and Educational Interventions Used to Improving Adherence in Diabetes and Depression Patients

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Abstract

Diabetes is a life-long chronic condition that is an established risk factor for the development of comorbid depression and possibly affecting medication adherence. Psychological and educational interventions are reported efficacious by the National Institute for Health and Care Excellence (NICE) in treating depression associated with a comorbid condition. As depression is associated with low adherence rates to treatment regimens, improving depression outcomes could improve adherence and therefore glycaemic control. A search strategy was conducted on search engines Google Scholar, PubMed, and Cochrane library for clinical trials. A total of 10 Randomised controlled trials (RCTs) were identified which investigated the effects of psychological and educational interventions on Type 2 diabetic patients with comorbid depression. Outcomes measured were depression and glycaemic control. Evidence from the 10 RCTs with 5759 participants suggests that psychological and educational intervention improved depression outcomes substantially and glycaemic control to an extent. Depression outcomes results were significant: standard mean deviation (SMD) was -0.39 (95% CI -0.62, -0.15); I^2= 81%) p<0.001. Diabetes outcomes were not seen to be significant, SMD was -0.14 (95% CI -0.32, 0.03); I^2= 44%) p=0.12. Psychological and educational interventions are effective in improving depression symptoms significantly and may assist in glycaemic control. Further research is required using larger sample sizes that could be generalized and representative of the whole population.

Keywords: Psychological intervention, Educational intervention, Collaborative care, Depression, Type 2 diabetes, Non-adherence

Introduction

Diabetes is a common condition with a prevalence of 4.7 million in the UK, with type 2 diabetes accounting for 90% of that [1]. Type 2 diabetes arises due to the body ineffectively using the insulin produced otherwise known as insulin resistance and/or an inability to produce sufficient insulin [2, 3]. It is characterized by the inability to metabolize glucose which leads to high blood sugar.

Managing diabetes is a lifelong process requiring devotion from patients as most of the treatment centers on self-management, patients and their families are the key to maintaining their disease control. Poor management leads to serious diabetes complications in the future such as diabetic retinopathy and diabetic foot disease [4].

Depression is defined as persistent low mood combined with a loss of pleasure in most activities including a variety of emotional, cognitive, and behavioral symptoms. It has a prevalence of 4.5% in the UK and it is the leading cause of disability and premature death [5]. Other possible causes such as genetic vulnerability, life events, medication, and medical problems [5].

Pharmacists' Role in the Management of Diabetes and Depression

Pharmacies play a major role in the management of diabetes and depression as they increasingly offer many services including screening, foot health checks and influenza vaccination for diabetes, and general well-being advice for depression. Early detection of both conditions may reduce morbidity and mortality rates. Pharmacists can play a major role, particularly with depression as they are often trained to suspect any early symptoms associated with depression [6]. It is expected that people with chronic illnesses are at a higher risk of developing mental health issues [7].

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Adherence and Non-adherence

Adherence is defined as the extent to which the patient's behavior matches agreed-on recommendations from the prescriber. It highlights how patients have freedom of choice whether to adhere to their prescriber's recommendations [8]. This ultimately suggests that since patients have full autonomy in their treatment, they are responsible and play a major role in adherence to treatment. Non-adherence is defined as resistance to adhering correctly to treatment. This could be in the form of missed doses, skipping routine check-ups, or completely not taking medication [9]. Non-adherence can be grouped under two different types, one being unintentional which refers to factors such as forgetfulness or potential physical disabilities of which the patient may not be in total control. Whilst intentional non-adherence is a personal choice made by the patient to deliberately not take their medication [10]. Recent data has shown that adherence to long-term treatment in patients with chronic conditions is below 50% [11]. This could be linked to diabetes which is a long-term condition, and patients' neglect in adherence to diabetes treatment therapy.

Psychological and Educational Intervention

Cognitive behavior therapy is a type of treatment that focuses on helping people manage their problems by changing the way they think and behave through teaching coping skills [12]. Educational interventions can differ depending on what the healthcare professional assesses the patient requires most and often include methods such as counseling and one-to-one support in understanding their management plan from healthcare professionals [13]. Such interventions have been used, and have proven effective in improving medication adherence provided that specific strategies that are best suited to the individual are identified and put into practice [14]. NICE CG91 guideline (2009) states that treating depression in chronic conditions has the potential to increase the quality of life (QoL) and has recommended a stepped care model which provides an outline that helps healthcare professionals to identify the most effective interventions which include psychological (CBT) and educational collaborative care [15]. Considering diabetes is a chronic life-long condition, a link has been identified between diabetes and the development of comorbid depression. It has been shown that depression worsens an individual's mental state and consequently self-care, as depressed individuals tend to not prioritize treatment and can be resistant to taking medication. Depression and certain antidepressant medications also cause weight gain which can increase blood glucose levels or undereating which can lead to hypoglycemia which also affects diabetic control. This has a direct effect on the management of diabetes and leads to complications that cannot be as easily treated [16]. Interestingly, depression and diabetes share some similar symptoms such as lethargy and excessive sleeping. This can be difficult to distinguish between the two conditions which can lead to undiagnosed depression in some patients. A relationship can be made here between depression and uncontrolled diabetes since, as previously mentioned, diabetes management relies heavily on patient compliance [17]. This implies that efficiently managing depression in diabetic patients could significantly improve diabetic control.

Limited research has examined the link between the two conditions. Randomized controlled trials have explored the impact of an intervention on the improvement of depressive symptoms. However, there has been little evidence to support that interventions improve diabetic control compared to usual care [18]. This analysis examines RCTs looking at psychological and educational interventions and the impact of depression on diabetes control, and whether this approach is feasible in practice.

Materials and Methods

Overview

This meta-analysis analyses existing RCTs and comparing whether there is an improvement in clinical outcomes with interventions such as CBT and educational programs.

Aim

Patients with diabetes are more prone to experience depression than those without diabetes. Diabetes with comorbid depression has been associated with poorer QoL, an increase in hyperglycemia, and an increase in depressive symptoms. This review aims to investigate how combating depression symptoms with the psychological intervention will have a positive impact on diabetes and depression outcomes. This was done by analyzing RCTs of diabetic patients with comorbid depression, where the comparison between treatment intervention in these patients, versus usual care, is studied to determine the impact on adherence.

Objectives

- Use RevMan 5 software to assess and analyze data from the RCTs.
- Apply a critical appraisal skills programme (CASP)(2021) to assess the credibility of the RCT papers used in this analysis [19].
- Use search engines to find suitable RCTs for analysis.
- Apply PRISMA (2021) to display search strategy for papers used in this analysis [20].
- Discuss and explore the link if any, between treatment intervention on clinical outcomes in depression and diabetes.

Design and Protocol

This study was a meta-analysis that combined quantitative as well as qualitative information from several studies and derives conclusions on whether interventions in depression and diabetes treatment have an impact on adherence and whether it will improve clinical outcomes.

The PICO model was used for a focused approach to clinical questions on this analysis and to help in the search for papers that include all these factors [21].

Population or Problem- Diabetic patients with comorbid depression focusing on type 2 diabetes

Intervention or Exposure intervention is analyzing if the psychological and educational interventions will improve adherence and therefore clinical outcomes in diabetes and depression

Comparison- Comparing intervention in adherence improvement to usual care with no intervention measures.

Outcome- Outcomes measured were diabetes by measuring glycaemic control and depressive symptoms determined using different psychometric measures.

Keywords

The following keywords were used in the search strategy as outlined in **Figure 1**: Type 2 diabetes; Adherence; Psychological intervention; Collaborative care; Randomised clinical trial; Comorbid depression

Selection Criteria

A literature search was conducted to identify RCTs on this topic. The search was carried out from December 2020 to March 2021 on databases such as Google® scholar™, PubMed©, and Cochrane© library. It looked at published RCTs from 2000-2021. The inclusion and exclusion criteria are detailed in the **Table 1** below.

Table 1. Inclusion and Exclusion criteria for researched studies.

	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials Primary studies	Non-primary studies e.g., meta-analysis and systematic reviews
Date	Between 2000-2021	Outside 2000-2021 range
Accessibility	Full study available to read	Preview only studies
Measured outcomes	Diabetes control Depression control	If they did not include diabetes control and/or depression control outcomes or reference to adherence
Age	Over 18 years	Under 18 years
Condition	T2D with comorbid depression	Other mental illnesses Non-diabetic conditions

Search Strategy

The search strategy found a total of 1725 papers which contained 1329 duplicates that were excluded. The remaining 396 papers were briefly screened for title and PICO and were found to be irrelevant to this study and therefore 202 were excluded which left 125 papers that were screened further according to measured outcomes and a final quantity of 10 studies were selected and quality assessed using CASP (2021). **Figure 1** shows a PRISMA (2021) flow diagram of the series of events in the search strategy.

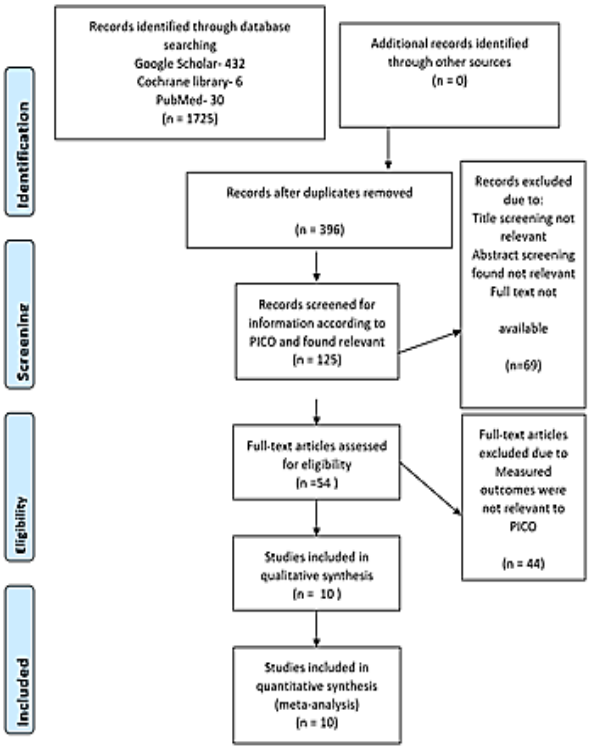

Figure 1. PRISMA diagram showing search strategy

Risk of Bias

The risk of bias analysis can help to explain variations in results. In this case, the risk of bias was created using RevMan© version 5.3 software [22]. To complete this, different tables were made for each study where the characteristics of the studies were declared using authors' judgments on the different areas of bias. The tables can be analyzed using the labels given in RevMan© of "High risk, low risk, and unclear risk". **Figure 2** show the resulting graphs following this method.

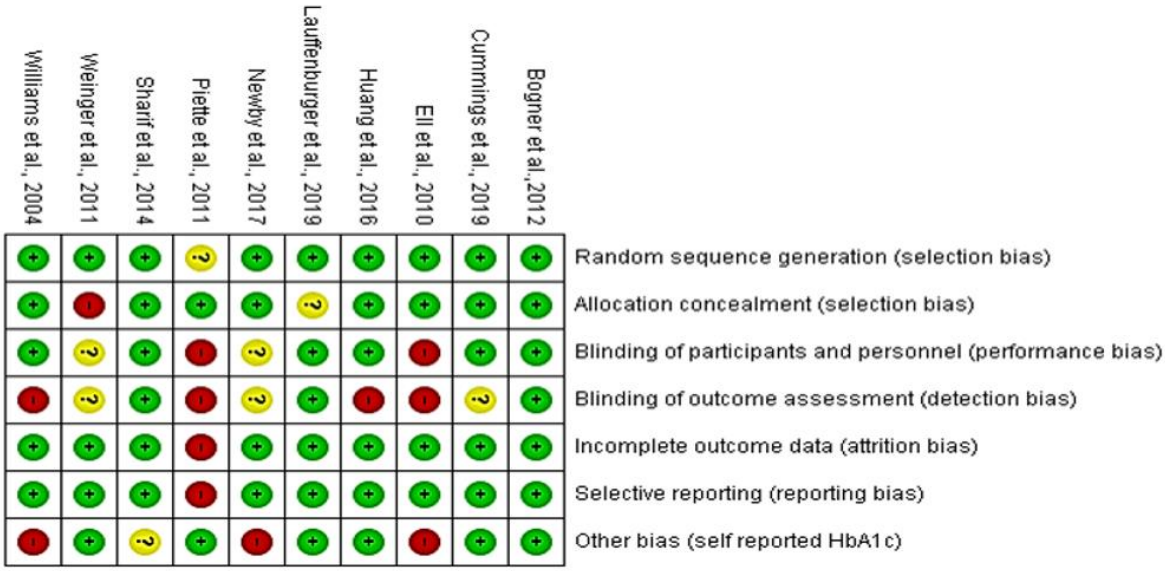

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Table 2. Summary of studies analyzed

Study	Study design	Number of patients	Summary of results	Measured outcomes	Type of intervention	Conclusion
Bogner *et al*., 2012	RCT	180	Intervention and usual care groups did not differ statistically on baseline measures. Patients who received the intervention were more likely to achieve HbA1c levels of less than 7% (intervention 60.9% vs usual care 35.7%; P <.001) and remission of depression (PHQ-9 score of less than 5: intervention 58.7% vs usual care 30.7%; P <.001)	Glucose control (HbA1c) Depression (PHQ-9 score)	Integrated care intervention where a care manager collaborated with physicians to offer education and guide patients to improve and monitor adherence.	Brief intervention integrating treatment of type 2 diabetes and depression was successful in improving outcomes in primary care. An integrated approach to depression and type 2 diabetes treatment may facilitate its deployment in real-world practices with competing demands for limited resources.
Cummings *et al*.,	RCT	139	Using intent-to-treat analyses, patients in the intervention experienced marginally significant improvements in HbA1c (20.92 6 1.81 vs. 20.31 6 2.04; P = 0.06) compared with usual care. However, intervention patients experienced significantly greater improvements in RRD (21.12 6 1.05 vs. 20.31 6 1.22; P = 0.001), depressive symptoms (23.39 65.00 vs. 20.90 6 6.17; P = 0.01), self-care behaviours (1.10 6 1.30 vs. 0.58 6 1.45; P = 0.03), and medication adherence (1.00 6 2.0 vs. 0.17 6 1.0; P = 0.02) versus usual care. Improvement in HbA1c correlated with improvement in RRD (r = 0.3;P = 0.0001) and adherence (r = 20.23; P = 0.007).	Glucose control (Hba1c) Depressive symptoms Self-care behaviours and medication adherence	CBT plus lifestyle counselling	Tailored CBT with lifestyle counselling improves behavioural outcomes and may improve HbA1c in rural patients with T2D and comorbid depressive and/or RRD symptoms.

Lauffenburger *et al.*, 2019	RCT	6000	Among 6000 participants, mean (SD) age was 55.9 (11.0) years and 3344 (59.8%) were male. Compared with arm 1, insulin no persistence did not differ in arm 2 (relative risk, 0.88; 95% CI, 0.75-1.03) or arm 3 (relative risk, 0.91; 95% CI, 0.77-1.06). Glycaemic control was similar in arm 2 and arm 1 (absolute HbA1c level difference, –0.15%; 95% CI, –0.34% to 0.05%) but was better in arm 3 (absolute HbA1c level difference, –0.25%; 95% CI, –0.43% to –0.06%).	Insulin persistence Changes in HbA1c levels Health care utilisation	High intensity intervention of weekly text message and tailored pharmacist assistance of 12 follow up calls, consultations, and counselling	Highly targeted high-intensity intervention did not improve insulin persistence but improved mean glycaemic control
Piette *et al.*, 2011	RCT	291	Baseline A1c levels were good and there was no difference in A1c at follow-up. Intervention patients experienced a4.26 mmHg decrease in systolic blood pressure relative to controls (p=.05). Intervention patients had significantly greater increases in step-counts (mean difference 1,131 steps/day; p=.0002) and greater reductions in depressive symptoms (58%remitted at12 months versus 39%; p=.002). Intervention patients also experienced relative improvements in coping and HRQL.	Diabetes control HbAc1. Blood pressure Depression Quality of life (SF-12)	Telephone CBT programme delivered by nurses for 12 weeks followed by 9 monthly booster sessions	This program of telephone delivered CBT combined with a pedometer-based walking program did not improve A1c values but significantly decreased patients' blood pressure, increased physical activity, and decreased depressive symptoms. The intervention also improved patients' functioning and quality of life.
Shariff *et al.*, 2014	RCT	60	Both groups were demographically homogeneous with no statistically significant difference. The trend in depression scores before as well as 2 weeks, 4 weeks, and 2 months after the intervention was statistically significant in the experimental group ($P \leq 0.001$), but not in the control group ($P = 0.087$). The results showed that HbA1c variation was statistically significant before and after the intervention in both groups ($P \leq 0.001$)	Depression scores HbAc1 change	CBT	Cognitive-behavioural group therapy was effective in reducing depression in patients with diabetes. Therefore, this method can be recommended for such patients.
Ell *et al.*, 2010	RCT	387	INT patients had significantly greater depression improvement (50% reduction in Symptom Checklist-20 depression score from baseline; 57, 62, and 62% vs. the EUC group's 36, 42, and 44% at 6, 12, and 18 months. no intervention effect on A1C or self-care management was found.	Depression (SF-12 Financial situation Number of social stressors Diabetes (HbA1c	Problem solving therapy and/or antidepressant medication with relapse prevention	Sociocultural adapted collaborative depression care improved depression, functional outcomes, and receipt of depression treatment in predominantly Hispanic patients in safety-net clinics.
Newby *et al.*, 2017	RCT	90	A total of 27 participants (66%; 27/41) completed the iCBT program. Analyses indicated between-group superiority of iCBT over TAU at posttreatment on PHQ-9 (g=0.78), PAID (g=0.80), K-10 (g=1.06), GAD-7 (g=0.72), and SF-12 mental well-being scores (g=0.66), but no significant differences in self-reported HbA1c levels (g=0.14), SF-12 physical well-being, or PHQ-15 scores (g=0.03-0.21). Gains were maintained at 3-month follow-up in the iCBT group, and the 87% (27/31) of iCBT participants who were interviewed no longer met criteria for MDD. Clinically significant change following iCBT on PHQ-9 scores was 51% (21/41) versus 18% (9/49) in TAU.	Self-reported depression (PHQ-9) Diabetes related stress Self-reported glycaemic control	iCBT programme with a therapist support provided by phone and email	iCBT for depression is an efficacious, accessible treatment option for people with diabetes. Future studies should explore whether tailoring of iCBT programs improves acceptability and adherence, and evaluate the long-term outcomes following iCBT
Weinger *et al.*, 2011	RCT	222	Linear mixed modelling found that all groups showed improved HbA1c levels (P.001). However, the structured behavioural arm showed greater improvements than the group and	HbAc1 Depression Coping style Quality of life Self-efficacy	CBT with educator led structured group intervention	A structured, cognitive behavioural program is more effective than 2 control interventions in improving glycemia in adults with long-duration diabetes. Educators can

			individual control arms (3- month HbA1c concentration changes: −0.8% vs −0.4% and −0.4%, respectively (P=.04 for group time interaction). Participants with type 2 disease showed greater improvement than those with type 1.Quality of life, glucose monitoring, and frequency of diabetes selfcare did not differ by intervention over time.			successfully use modified psychological and behavioural strategies.
Williams *et al*., 2004	RCT	1801	At baseline, mean (±SD) haemoglobin A1c levels were 7.28% ± 1.43%; follow-up values were unaffected by the intervention (P > 0.2). Intervention had less severe depression (range, 0 to 4 on a checklist of 20 depression items; between-group difference, –0.43 [95% CI, –0.57 to –0.29]; P < 0.001) and greater improvement in overall functioning (range, 0 [none] to 10 [unable to perform activities]; between-group difference, –0.89 [CI, –1.46 to –0.32]) than did participants who received usual care	Depression Functional impairment Diabetes self-care behaviours	offered education, problem-solving treatment, or support for antidepressant management by the patient's primary care physician; diabetes care was not specifically enhanced.	Collaborative care improves affective and functional status in older patients with depression and diabetes; however, among patients with good glycaemic control, such care minimally affects diabetes-specific outcomes.
Huang *et al*., 2016	RCT	61	The experimental group showed a significant reduction in glycosylated haemoglobin, fasting glucose, and depressive symptoms and a significant increase in physical quality of life and mental quality of life at T2 and T3, while patients in the control group with usual care showed no changes.	Depressive symptoms Diabetes control HbAc1 Mental and physical quality of life.	Motivational enhancement therapy with CBT	Conclusion The behavioural intervention facilitated a significant improvement in psychological adjustment and glycaemic control, thus strengthening diabetes control skills and leading to healthy outcomes. It is feasible that nurses and psychiatrists can deliver the behavioural intervention for diabetes patients to decrease their depressive symptoms

Selected Studies Summary

A summary of the 10 studies included in this analysis is provided in **Table 2**. All were RCTs and in total had 5759 participants with diabetes and comorbid depression. Out of the 10 studies, 6 studies explored CBT as an intervention whereas the remaining 4 looked at educational and collaborative care interventions.

Results and Discussion

The 10 RCTs were analyzed using RevMan© by formulating forest plots that calculated the standard mean difference for depression outcomes. The data was continuous and was measured in different methods e.g., different psychometric measures: PHQ-9 score [23], BDI® (Becks depression inventory) score [24], and QoL© index score so that the results are standardized and can be compared [25]. The mean difference effect measure was used for diabetes outcomes as all data was in HbA1c (%) values. The random-effects analysis model was used for both measured outcomes as the heterogeneity was over 50%.

Measurable Outcomes

Measured outcomes were; depression control measured with PHQ-9©, QoL© scores, and BDI® scores. Additionally, Diabetes was measured with HbA1c (%) values.

Diabetes Clinical Outcome

All 10 studies investigated diabetic control measured through HbA1c (%) values which are displayed in **Figure 3**. Only 6 of these studies [26-31] explored T2DM, with the remaining 4 exploring both T1DM and T2DM [32-36]. For this reason, a sub-group analysis was conducted and separated those two sets of studies to determine if that could have been a cause of increased heterogeneity. Only data for T2DM was used in this analysis.

Overall, the combined results for HbA1c values were not significant (p=0.12) and a standard mean difference of -0.14 (95% CI -0.32, 0.04). Out of the 10 trials, only 2 completely crossed the line of null effect which was Huang *et al.* [26] (2015) mean difference (MD) -1.33 (95% CI -2.03, - 0.63) and Lauffenburger *et al.*, [27] MD -0.14 (95% CI -0.23, -0.05) with the latter having the highest weighting of 28.8%. The remaining 8 trials all had confidence intervals (CI) that crossed the line of null effect which shows that the study result no significant differences between the intervention and usual care groups.

Two of the trials [29, 30] had confidence intervals evenly distributed between the intervention group and the usual care group. This was because the HbA1c value did not change between the two groups for all those 4 studies which show no significant results.

The averaged results, symbolized by the diamond on the forest plot show not significant.

The heterogeneity of the first T2DM sub-group was $I^2 = 64\%$ which is higher than the suggested range as it is above 50%. The T1DM and T2DM subgroups have heterogeneity of 0%.

Overall, the heterogeneity was 44% with p= 0.06 which indicates no significant differences and that the studies are relatively consistent with little bias, and any differences can be assumed to be due to chance.

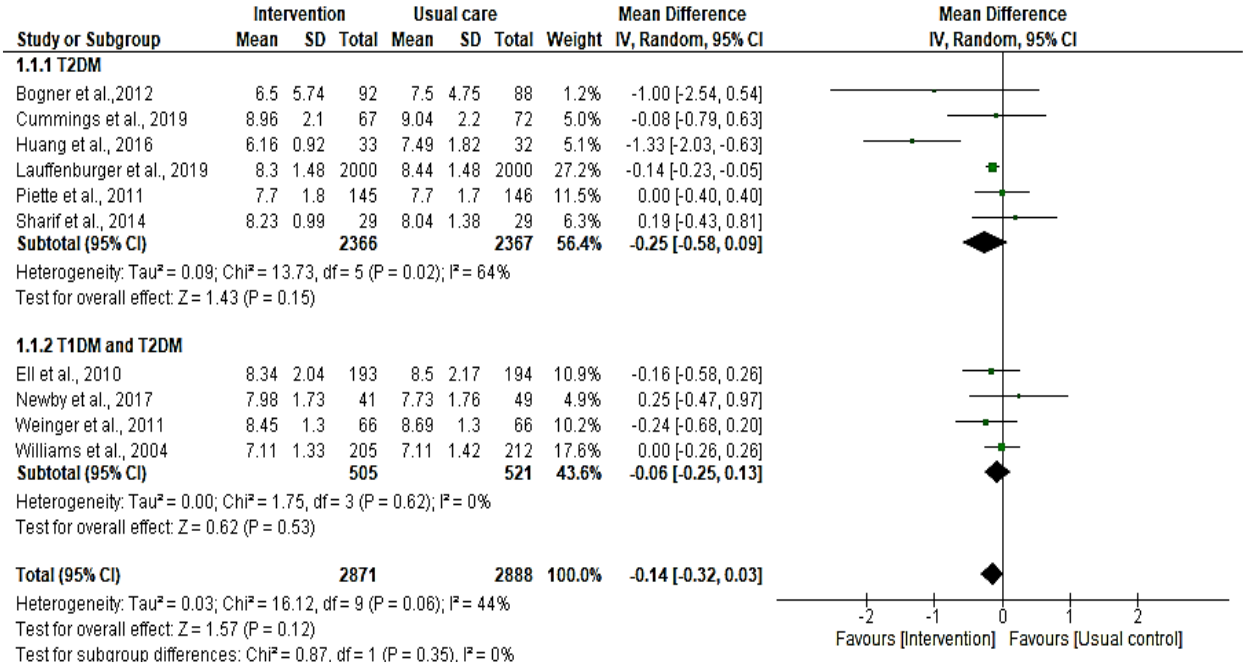

Figure 3. Forest plot showing diabetes clinical outcomes (HbA1c values) Intervention versus usual care [24-29].

Depression Clinical Outcomes

Out of the 10 studies, 9 of the trials studied depression outcomes in a way that was measurable using RevMan©. A sub-group analysis was conducted as 4 of the studies measured depression using PHQ-9© scores, 4 used QoL© scoring, and 1 used BDI®. This was done to see if any differences in heterogeneity were important.

Figure 4 represents the standard mean difference in depression clinical outcomes between intervention and usual care groups. This forest plot confirms that intervention with CBT [37] or education improved the depression outcomes greatly in terms of the PHQ-9© scores sub-group (SMD -0.63, 95% CI -1.05, -0.21) p=0.003. The forest plot was on the intervention side showing these studies significantly supported the hypothesis of intervention improving depression outcomes. The overall effect was SMD -0.39 (95% Cl -0.62, -0.15) p=0.001 which is highly significant.

In the QoL© subgroup, a high score indicated a higher QoL©concerning depression [25]. This is not reflected in the forest plots produced from RevMan© as a higher score in the intervention group indicates usual care favored result. For this reason, the results were reversed to showcase a more accurate representation of the results which showed 3 studies favoring intervention [27-29] with only one favoring the usual care group [30].

Notably, five of the trials [26, 31-34] were completely to the left of the null effect and showcase an unequivocal positive effect for the intervention. Weinger *et al.* [35] was the only trial that completely crossed the line of null effect line.

The heterogeneity measured was relatively high for this outcome at 81% indicating diversity in the studies regarding this outcome. It is higher than 50% indicating differences may be due to factors other than chance. For this reason, sub-group analysis was conducted to see if this influenced the heterogeneity. This showed the subgroup differences were 43.5% (P=0.17) which was a small difference and not highly significant. This could be due to the different methodology being used in the different studies especially since the psychometric measurements for depression were different as well as differences in the patients' baseline characteristics and results for depression measures. Due to the high value of the heterogeneity, it can be assumed that there is the bias associated with this outcome which can range from publication bias to differences in randomization in those trials.

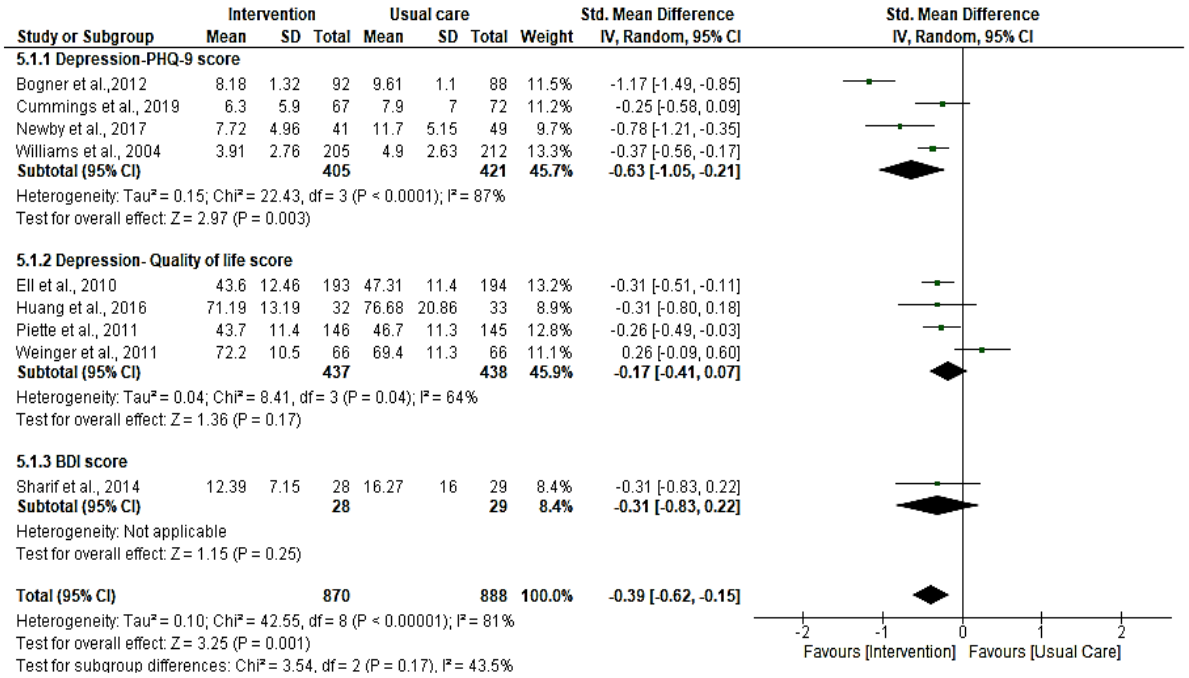

Figure 4. Forest plot showing depression outcomes (PHQ-9© score, QoL©score, and BDI® score) intervention vs usual care [24, 28, 33-35].

Collaborative care, associated with the psychological intervention and educational programs for patients with diabetes and comorbid depression, has been an area that has not been thoroughly explored, with limited evidence on the effects it has on clinical outcomes and adherence. This meta-analysis suggests that numerous interventions are required to maintain adherence to long-term treatment in conditions such as diabetes.

Diabetes Control

Diabetic control was measured using HbAc1 levels in all 10 RCTs to indicate if there was any change in the levels between baseline and following the interventions. The primary aim of all these studies was to determine the effectiveness of care interventions on adherence measured in outcomes of depression and diabetes control.

A total of 6 out of 10 studies showed an improvement in HbA1c levels. Bogner *et al.* [28] found patients randomized to their integrated care intervention showed higher rates of adherence to diabetic medication. Glycaemic control was also improved supporting a link between adherence and improvement in diabetic control. Similarly, Cummings *et al.* [29] found that patients in their intervention groups experience an average decrease of 1.0% in HbAc1. This finding is consistent with a prior study conducted in the same year by Lauffenburger *et al.* [27] which also concluded that glycaemic control was improved with high-intensity interventions compared to usual care. Sharif *et al.* [30] and Weinger *et al.* [33] found that HbA1c mean variation was significant in intervention groups with Sharif *et al.* [30] stating that the change in blood glucose changes was significant but had uncertainty regarding intervening factors that could have accounted for this large change such as patients knowing their blood glucose levels before the interventions due to ethical reasons. Comparably, Huang *et al.* [26] showed that participants displayed statistically significant improvements in HbA1c 90 days after interventions which shows the potential for long-term improvements as well as short-term.

Conversely, 4 out of the 10 chosen studies showed no improvements in diabetic control following interventions. Piette *et al.* [31] stated that although there was no improvement in haemoglobin A1c values, they were initially reasonably good at the beginning and were therefore unaffected by the intervention. This was identical to findings from Williams *et al.* [35] as they found that patients had good glycaemic control at baseline so there was limited power to detect small clinical changes in HbA1c levels, hence no improvement was observed in both studies. Newby *et al.* [34] and Ell *et al.* [36] also showed no differences in HbA1c levels with levels increasing in the intervention group compared to usual care. However, both of these studies measured HbA1c through patient self-reporting. This could be a factor in why there were no visible improvements.

Depression Control

Eight out of 10 studies showed an improvement in depressive symptoms following the intervention. Bogner *et al.* [28] identified that compared to patients who are not depressed, depressed patients who have diabetes are more likely to be non-adherent to medication regimens, including their antidepressants and diabetic medications. Cummings *et al.*

[29] postulated a hypothesis that patients with T2DM are twice as likely to have depressive symptoms and that the relationship between the two could be bidirectional. Shariff *et al.* [30] and Newby *et al.* [34] and agreed, stating that proactive detection and treatment of depression is essential to reduce the burden of depression in people with T2DM and that depression interferes with metabolic control of diabetes leading to weak control of blood glucose levels. All of these studies showed improvement in depression symptoms with intervention. Two of the studies [26, 28] showed a decrease in depression scores and improvement in QoL© immediately after the intervention, and with Huang *et al.* [26] improvements were seen 90 days later in follow-up routine appointments. Newby *et al.* [34] and Williams *et al.* [35] had similar results whereby patients were seen to have less severe depression and greater progress in overall functioning than in usual care measures with a comparison from baseline to after intervention showing substantial developments. On the contrary, Weinger *et al.* [33] showed no improvements in depression outcomes. Since this difference has not been found elsewhere it can be assumed that this is possibly due to other factors and not solely based on intervention measures not being effective.

Adherence

Adherence is the main factor identified to have an impact on clinical outcomes in all chronic diseases [37]. All the studies evaluated whether intervention on depression had an impact on adherence to medication and overall improvement in clinical outcomes. Weinger *et al.* [33] identified that an important reason for poor glycaemic control is the patient's difficulty in following treatment and self-management recommendations. This is directly linked to adherence, as adherence is the patient's commitment to their treatment and if they find this difficult then it will lower disease control in those patients. Lauffenburger *et al.* [27] implied that effectively targeting adherence to the patients most likely to benefit, has the potential to improve efficacy in treatment but it has not been widely assessed.

Newby *et al.* [34] suggested that depression could be a major factor in lower adherence and Ell *et al.* [36] looked at enhancing adherence by integrating depression and diabetes care as they projected that providing care for both diseases will aim to improve adherence overall for diabetes with comorbid depression. Bogner *et al.* [28] agreed as they explored an adherence-based approach as they stated that even though pharmacological treatment is highly efficacious, many patients do not adhere to the treatment and this is a high risk especially in patients with comorbid diabetes and depression. They hypothesized that integrating the care of the two with interventions would enhance adherence.

Cummings *et al.* [29] suggested that depression symptoms are a risk factor for poor adherence, and their results showed that there were significant reductions in depressive symptoms and consequent improvement in medication adherence. Similarly, Huang *et al.* [26] found that their intervention group facilitated an increase in adherence rates as significant improvement in the psychological state helped strengthen diabetes by improving glycaemic control. Sharif *et al.* [30] discussed how CBT interventions were effective for treating depression but they have been poorly utilized in depression associated with physical illness. However, it has proven effective in diabetic patients and has been proven to improve adherence measured in depression outcomes which were evident in results observed in this study.

Interestingly, Piette *et al.* [31] observed depression symptoms improving greatly, however, this was not reflected in the patient's medication adherence as there were no important differences found. Medication adherence was measured using the Morisky© medication adherence scale. This raises the question of whether improvement in depression symptoms has an impact on medication adherence. However, this could be linked to the no change in glycaemic control also. Correspondingly, Williams *et al.* [35] expected effective treatment for depression could benefit adherence to self-care regimens which therefore would improve diabetic control in patients. They found that patients reported almost perfect adherence to medication however, lower adherence rates were reported for glucose testing and foot inspections. This could be explained by looking at the measure for these self-care behaviors which showed ceiling effects, meaning that the participants already had high scores for the medication adherence so there was little room for improvement.

Intervention

Cognitive behavior therapy is a form of psychological treatment that has been proven effective for depression. It helps change the way of individual thinking and behavior [38]. Out of the 10 studies, 6 used CBT as a form of intervention to assess its effectiveness in improving adherence and consequently clinical outcomes. Cummings *et al.* [29] stated that an integrated care model involving delivering CBT plus lifestyle counseling to patients with T2D is feasible in primary care practice and has the promise to be highly effective. Newby *et al.* [34] performed a study on online CBT (iCBT). They stated that it is as efficacious as face-to-face CBT and can be delivered at a fraction of the cost and clinical time. CBT has been shown to help patients feel better when participating in enjoyable activities when they can discuss their mental well-being as it can help the patient be their therapist and use self-management skills to improve adherence and control depressive symptoms [29]. The rest of the studies looked at educational interventions as opposed to psychological measures. They looked at using counseling and collaborative care with physicians offering education and tailored guidance to participants. Bogner *et al.* [28] looked at addressing patient-subjective factors that could affect adherence and ensured they addressed them during the intervention.

Piette *et al.* [31] found that telephone-delivered CBT was

more likely to increase depression remission at 58% compared to 39% in usual care.

The risk of bias summary table **(Figure 4)**, shows 4 studies having a relatively high risk of bias [26, 31, 35, 36]. This is mirrored in discrepancies in the results, for example, Piette *et al.* [31] and Williams *et al.* [35] were the only 2 studies to have no improvement or worsening of glycaemic control, and both had SMD of <0.01. Interestingly, the study with the highest risks of bias, Weinger *et al.* [33] was the only study not to show improvements in depression outcomes.

Huang *et al.* [26] projected that motivation enhancement therapy combined with CBT would improve HbA1c and depressive symptoms in patients from baseline to follow-up. The interventions included enhancing patients' motivation to improve their self-care and introduced stress-coping strategies to help patients cope with hyperglycemia and other symptoms of their conditions. This study found that these interventions significantly helped to improve diabetes and depression control.

Lauffenburger *et al.* [27] looked at delivering intensive insulin adherence interventions in patients with type 2 diabetes which included regular phone consultations and a weekly text message program that focused on reminding patients on taking their medication and essentially improve medication adherence. They found that high-intensity intervention improved glycaemic control compared to low intensity.

Limitations

This analysis had limitations. Firstly, using combined results from different RCTs, showed differences in measured outcomes, specifically for the depression outcome as different psychometric measures were used to measure depression in participants. This could have been the main cause of the high heterogeneity.

Another limitation is the use of different interventions in each of the studies. Some studies looked at collaborative care whilst others looked at psychotherapy and although this was an aim of this study to assess; the methods to each of these interventions were different e.g., some studies had nurses conduct counseling and educational sessions whilst others had doctors and pharmacists. In addition to that, the number of sessions differed between all the studies. This could have created a bias in the results.

This study included only 10 RCTs with a total of 5759 patients with all except for Lauffenburger *et al.* [27] having small sample sizes and mainly being conducted in the USA which means that results are not representative of the population as a whole, limiting generalisability. Many studies found for this analysis were not accessible without payment, for which no funding was available.

Four of the studies included results for both Type 1 and type 2 diabetes which could have taken the focus out away from the type 2 diabetes sub-group. Also, some of the studies used self-reporting as a form of measuring depression symptoms and HbA1c % which is demonstrated in the table of bias as a category **(Figures 2 and 3)** which could have introduced detection bias.

Finally, sub-group analysis was not conducted for short-term effects compared to long-term; only long-term effects were analyzed. This may have identified differences in how interventions work by time and their estimated time of response.

Conclusion

In this study, the aim was to investigate whether intervention strategies in the form of psychological (CBT) and educational programs had an impact on the clinical outcomes of depression and diabetes compared to usual care concerning adherence determined by improvements in both outcomes. The consensus for diabetes outcome showed 6 out of 10 studies that had an improvement in HbA1c values in the intervention group compared to usual care. Four of the studies showed either no improvement with values being indistinguishable or an increase in HbA1c value in the intervention group. Depression outcomes showed 8 out of the 9 studies showing a significant improvement in depression outcomes in the intervention group compared to the usual group with only 1 study showing no improvement.

These findings indicate that intervention with psychological and educational measures has a positive impact on depression outcome and is therefore reflected in the improved diabetic HbA1c control which shows a link between the two and adherence measured in diabetic control highlights an improvement.

Recommendations from this study include the investigation of cost-effectiveness to examine the costs and clinical outcomes of depression and diabetes by comparing the intervention to usual care and estimating the cost. Also, consistent CBT or educational measures need to be investigated over a longer period to investigate the long-term effects compared to the short-term effects this intervention will have. In addition to this, it is recommended that the implementation of depression screening in all diabetic patients be carried out regularly, to manage early depressive symptoms if any, and try preventative measures before resulting in treatment which can be difficult and result in adherence issues from patients.

In conclusion, adherence follows a complex process and is not a singular occurrence, therefore adherence support should be integrated into all health consultations in diabetic patients with or without comorbid depression.

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