Antidepressant Use and Glycemic Control in Diabetic Population: A Meta-analysis

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Abstract

Background: Depression is prevalent in the diabetic population. Primary care physician is busy in treating diabetes and depression among them goes unnoticed. According to the American Diabetic Association, two out of three are not able to achieve glycaemic control. Diabetes and depression both share complex cause-effect relationship. Objectives: To evaluate the effect of antidepressants on glycaemic control among the adult diabetic population suffering from depression. Method: Cochrane database was systematically searched with search strategy and only parallel randomized clinical trial with antidepressant and placebo group were considered. Outcome measures were HbA1c, Fasting blood glucose, weight, body mass index, treatment adherence. Data extraction form were adapted from Cochrane. Two researchers identified studies and extracted data independently. Revman was used for meta-analysis and risk of bias. Level of evidence was generated using Gradepro. Results: Out of 394 studies, six studies fulfilling the eligibility criteria were pooled for analysis. Using mean difference (MD), meta-analysis showed significant evidence of glycaemic control in favor of antidepressant treated diabetic population compared to placebo group (n = 6 studies) (MD = -0.32%; 95% CI = -0.57 to 0.08). Weight, BMI does not show any significant mean difference between two groups. Conclusions and Implications of Key Findings: There is moderate level of evidence that antidepressants improve the glycaemic control in diabetic population suffering from depression. Understanding and treating the mental and psychological determinant with adequate control of depression should be emphasized for the diabetic population.

Keywords: Antidepressant, BMI, depression, diabetes, glycaemic control

Introduction

According to the International Diabetes Federation, diabetes is rapidly becoming a global health emergency. Estimated number of people having diabetes in 2019 is 463 million that will be 578 million by 2030, and 700 million by 2045.¹ Depression is a common illness which is affecting more than 260 million people worldwide irrespective of the age group.² One out of every four patients with type 1 or type 2 diabetes mellitus is found to be having clinical depression.³⁻⁵ The occurrence of diabetes and depression in combination can lead to poor outcome in both conditions and pose a big clinical challenge. Depression in diabetes is both persistent and recurrent. It can affect the quality of life, impairing self-management of diabetes, and enhancing the occurrence of various complications and ultimately affecting the life expectancy of the individual.⁶ Doctors focus on psychological health is reported very low that ultimately affects the treatment part.⁷⁻⁹ It is important to focus upon the confirmed diagnosis of depression, which should be a lead to a treatment plan and continuous monitoring of the patient. Depressed patient may not be able to regularly comply with their treatment regimen, which can result in poor glycaemic control making them prone to various macro and microvascular complications.³⁻⁷⁻⁹ In a general practice setting, two of every three patients are not able to maintain the level of glycaemic control as recommended by the American Diabetes Association (A1c < 7.0%), even with intensive treatment and systematic follow-up.¹⁰ Therefore, the American Diabetes Association in its clinical practice updating recommends that the diagnosis of depression should be integrated into diabetes care and treatment of depression should be an integral part of diabetes care.¹¹ The American Diabetes Association further recommends that the primary care physician should have some understanding of depression in diabetes management.¹² The purpose of the study is to evaluate the effect of antidepressants on glycaemic control among the adult diabetic population suffering from depression.

Access this article online

Quick Response Code: 
Website: www.ijem.in
DOI: 10.4103/ijem.IJEM_258_20

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Submitted: 04-May-2020
Accepted: 03-Jun-2020
Revised: 14-May-2020
Published: 27-Aug-2020

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How to cite this article: Khapre M, Kant R, Sharma D, Sharma A. Antidepressant use and glycemic control in diabetic population: A meta-analysis. Indian J Endocr Metab 2020;24:295-300.
guidelines invites the use of complementary treatments including depression treatment and stress reduction that supports good glycaemic control.\cite{11} Limited Randomized controlled trials (RCTs) with small sample size are available to support the efficacy of antidepressants in glycaemic control.\cite{10,12-16}\ The result of which remains inconclusive due to small sample size. Therefore, in the present study we want to pool the data and give recommendations on the importance of identifying and treating diabetic population suffering from depression with antidepressants and its effect on glycaemic control.

**Objectives**
The main aim of this systematic review and meta-analysis is to evaluate the effect of antidepressants on glycaemic value among the adult diabetic population screened positive or diagnosed with some form of depression.

**Methodology**
This review adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 guidelines.\cite{17} (Additional file 1).

**Data source and search strategy**
To identify eligible studies on the effect of antidepressants on glycaemic value among the adult diabetic population diagnosed with clinical depression, we implemented a comprehensive computerized search of Cochrane library, till Dec 30, 2019, using variant Medical Subject Headings (MeSH) and free-text (Text) terms. The detailed search strategy is presented in an additional box file (Additional file 2). As only RCTs were decided to be included we searched only Cochrane as Pubmed and Embase databases are already included in Cochrane or it will lead to unnecessary duplications.

We defined the participants, intervention, comparator, outcome(s), and type of study “PICO (T)”. The PICO (T) statement provides the framework for the identification and selection of studies for inclusion.

**Inclusion and exclusion criteria**

**Participants**
Adults (aged ≥18 years) with diabetes and screened positive or diagnosed with some form of depression, already on an anti-diabetic drug since last 6 months. Positive test on any validated screening tool for assessing the depression or diagnosis done using DSM IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria or as confirmed by psychiatrist or psychologist was considered to be case of depression for this study.

**Intervention**
Antidepressant medications like Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors and Tricyclic antidepressants.

**Comparator**
Placebo (no active drug).

**Outcome**
- Primary outcome: Effect on glycaemic value (HbA1c)
- Secondary outcome: Effect on Fasting blood glucose (FBG), weight, body mass index (BMI), treatment adherence.

**Types of studies**
This systematic review included only RCTs reported in English. We excluded studies with pre and post-intervention, cross over trials, and cluster randomised trials. We excluded the studies with self-reported depression among diabetic population without any screening/diagnostic tools. We also excluded studies before 2000 with no access to full text and for studies after 2000 we tried to contact the authors twice before exclusion. We excluded studies in combination with psychological intervention.

**Identifying eligible studies**
Titles and abstracts were screened independently by two reviewers (MK and DS) as per eligibility criteria. Initially, studies were screened by title and abstract using Rayyan (http://rayyan.qcri.org), a free web-based software.\cite{18} Full-texts of the identified potentially eligible studies were thoroughly screened and independently assessed by the reviewers. The qualities of the extracted studies were also independently assessed by two reviewers (MK and DS). Discrepancies in data extraction were discussed and resolved. The PRISMA flow chart for the selection of studies is shown in Figure 1.

**Data extraction**
Data from fully eligible studies were extracted into a pre-defined data extraction excel file adapted from Cochrane.\cite{19} We...
extracted the following data on the baseline characteristics of the eligible research reports (author names, year of publication, country, city, and study setting), study methodology (design, time period, sampling strategy, and diagnostic methodology for depression), and study population (type of diabetes). For each outcome of interest (Number of participants allocated to each intervention arm, Missing participants, Summary data for each intervention group).

The outcome measure was entered in terms of mean and Standard deviation (SD). In studies where change score is mentioned from baseline to end of the study in both the groups, then change score was considered for meta-analysis. In studies with only end results mentioned, only final value was considered for analysis in terms of mean (SD). For treatment adherence proportion was entered. All the data were double-checked.

Of any missing statistics then an attempt was made to collect from the author or calculate using Revman calculator tool. If data is still missing then it was reported in narrative form.

**Evaluation of the risk of bias and data analysis**

The use of intention-to-treat analysis in a study was considered as a confirmation that the number of randomized participants was the same as the number of analyzed participants. Studies without this characteristic were considered not to meet this criterion.

Cochrane risk of bias assessment tool was used to evaluate each study rated from high risk to low risk. Quality of evidence for each outcome across the studies is done by Grade pro DT. Any disagreements were recorded and resolved by involvement of an additional reviewer (RK and AS).

Meta-analysis was performed using the fixed-effects model and effect measures were calculated as the mean difference (MD) between two groups as all outcome variables were measured in similar scales across studies. An α value = 0.05 was considered statistically significant. Statistical heterogeneity of treatment effect across studies was assessed using the inconsistency I^2 test, in which values less than 40% and 30–60% were considered to be indicative of might not be important and moderate heterogeneity, respectively. Subgroup analysis was done for studies with type 2 diabetes only if heterogeneity is found to higher than 40%. All analyses were conducted with the software Review Manager, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK).

![Table 1: Characteristics of the included studies](image_url)

| Study       | Study Population | Depression screening criteria                | Study drug | Follow up period |
|-------------|------------------|---------------------------------------------|------------|-----------------|
| Lustman 2000 | Type 1 and 2     | Major depression score >14 by BDI          | Fluoxetine | 8 weeks         |
| Paile 2003   | Type 2           | Mild to moderate depression by MADRS       | Fluoxetine | 10 weeks        |
| Lustman 2006 | Type 1 and 2     | 14 or more by BDI1 and 15 or more by HDRS  | Fluoxetine | 52 weeks or till depression returns |
| Paile 2007   | Type 2           | Mild depression DSM IV                      | Paroxetine | 6 months        |
| Echeverry 2009 | Type 1 and 2 but | CDIS^2 and severity by HAM-D^3 survey       | Sertraline | 6 months        |
| Nicolau 2013 | Type 2           | BD1 test score >16                          | Citalopram | 6 months        |

^1BDI: Beck Depression Inventory, ^2MADRS: Montgomery Asberg depression rating scale, ^3HAM-D or HDRS: Hamilton Depression rating scale, ^4DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4^th Edition, ^5CDIS: Computerized diagnostic interview study

![Figure 2: Forest plot showing HbA1c comparison in antidepressant and placebo group of depressed diabetic population](image_url)
RESULTS

A total of 394 articles were searched from the Cochrane database. A total of 385 articles were selected after removing duplicates. Thirty-eight articles were assessed for full-text eligibility of which 6 were finally selected for meta-analysis. Detail flow chart is given in Figure 2. Characteristics of included studies are given in Table 1. Out of six studies, three studies exclusively included only type 2 diabetic patient and one included 99% of type 2 diabetic populations. Studies defined depression by various screening/diagnostic tools including varying severity of depression. Three studies examined fluoxetine versus placebo, one study studied paroxetine, sertraline, and citalopram each. Study duration ranged from 8 weeks to 52 weeks.

Forest plot showing HbA1c comparison in antidepressant and placebo group of diabetic population suffering from depression is shown in Figure 1. The confidence interval (CI) of all the six studies were overlapping, heterogeneity by I² was 32%. The pooled estimate shows that Mean difference (MD) of HbA1c is 0.32% lower (-0.57 to -0.08) in the antidepressant group compared to placebo. Subgroup analysis of studies with mainly type 2 diabetic population further lowers the heterogeneity to 16%. MD was further lowered to 0.42% in the antidepressant group compared to placebo. Risk of bias was low in all the studies. We cannot generate a funnel plot due to small number of studies.

No significant mean difference of weight was found in pooled estimates of three studies.[13,15,16] Only two studies Nicolau and Paile studied BMI among two groups. There was substantial heterogeneity where Nicolau et al.[16] reported a decrease in BMI by 3.7 kg/m² with very wide CI (-7 to -0.4) while Paile-Hyvarinen et al. (2003)[15] not demonstrated any significant MD in between two groups. None of the included studies reported treatment adherence at the end of the study period.

Table 2 demonstrates a summary of finding table of included studies. Pooled estimate of six studies calculated MD for HbA1c is 0.32% lower (0.57 lower to 0.08 lower) with a moderate level of evidence.

DISCUSSION

Depression is prevalent in diabetes population due to demanding lifestyle changes. However mild depression usually goes unnoticed and primary care physician is busy in managing diabetes by anti-diabetic drugs only. The key finding of present meta-analysis shows that HbA1c is 0.32% lower in the group treated with antidepressant compared to those treated with placebo. The level of evidence was moderate. This is similar to the finding of metaanalysis published in 2012 on five trial with 238 participants demonstrated improved glycaemic control in the short term mean difference (MD) for glycosylated hemoglobin A1c (HbA1c) -0.4%; (95% CI -0.6 to -0.1; P = 0.002).[23]

This study included psychological and pharmacological intervention while the present study includes solely antidepressant drugs without any other intervention. A large retrospective study by Brieler et al. also supported the fact that depressed patients receiving Anti Depressant Medications (ADM) were twice as likely as those not receiving ADM to achieve good glycaemic control.[24]

Subgroup analysis of studies with type 2 diabetes only shows a greater improvement of HbA1c level by 0.15% (0.32% and 0.47%) compared to pooled data of all studies. Pharmacotherapy for depression in type 2 diabetes is associated with better glycaemic control. Observed improvements in HbA1c may occur through antidepressant effects on mood or via direct drug effects, or both. Depression increases the diabetes risk by behavioral mechanisms, psycho-neurohormonal mechanisms, or both.[25] Remission of depression might then lead to improved adherence to antihyperglycemic medication and increased health behaviors. Meta-analysis has not shown a significant effect for non-pharmacologic treatment of depression on HbA1c.[25] Silva and colleagues[26] review evidence that SSRIs have been shown to reduce hypothalamic-pituitary-adrenal axis hyperactivity that may be evidence for a direct ADM contribution to glycaemic control interventions resulting in increased physical activity improve depression and glycaemic control.

Fasting blood glucose was considered in only one study (Paile 2003) that showed significant improvement in both the group may be due to Hawthorne effect.[15] However, FBS may incidentally vary a lot and may also be affected by duration of fasting so HbA1c is a better parameter to assess control over past 8–12 weeks. The difference in pooled estimated means of weight (3 trials) in antidepressant and placebo group was not found to be

| Outcomes | Anticipated absolute effects* (95% CI) | No of participants (studies) | The certainty of the evidence (GRADE) |
|----------|--------------------------------------|-----------------------------|--------------------------------------|
| HbA1c    | Risk with placebo: The mean HbA1c was 8.4% MD is 0.32% lower (0.57 lower to 0.08 lower) | 399 (6 RCTs) | ★★★★ MODERATE† |
|          | Risk with antidepressant: The mean HbA1c was 9.7% MD is 0.42% lower (0.62 lower to 0.22 lower) | 157 (3 RCTs) | ★★★★ LOW ‡,§ |
| weight   | Risk with placebo: The mean weight was 194 pound MD is 0.07 pound higher (1.79 lower to 1.93 higher)  | 53 (2 RCTs) | ★★★★ VERY LOW ‡,§ |
| BMI      | Risk with placebo: The mean BMI was 32 kg/m² MD 0.12 kg/m² lower (0.82 lower to 0.58 higher) |  |  |

*wide CI, †studies were heterogeneous, ‡only two studies included
significant. Only two trials reported BMI but heterogeneity is more than 50% to pool study estimates together. Heterogeneity may be due to different study duration that is 10 weeks to 6 months or effect of a different class of antidepressant on weight. Meta-analysis study by Serretti and Laura (2009) showed that the effect of antidepressants on weight varies. The effect also depends on the individual characteristics and becomes more evident in long term to a variable degree across compounds.[27] None of the studies had studied other confounders like treatment and lifestyle adherence.

**Strength and limitations**

Though the risk of bias in all included studies was low, the result was based on studies with small sample sizes with wide CI. We limited our search for Cochrane (includes both PubMed and embase) database. RCTs related to antidepressant and diabetes are limited and effect of treatment adherence in not being considered in any of the included studies. None of the above studies includes long term follow up more than 6 months so we could only confirm short term effect of antidepressant therapy on glycaemic control in diabetics suffering from depression. Publication bias cannot be ascertained.

**Conclusion**

There is a moderate level of evidence that antidepressants treatment among depressed diabetic population leads to improved glycemic control. There is no significant difference in pooled FBG, weight, and BMI measured at the end of study in antidepressant and placebo group. Our results support the emphasis on early recognition and prompt pharmacological treatment and control of depression in diabetes population to achieve better glycemic control.

**Author contribution**

Study conception/design: MK, DS, RK, data collection: MK, DS data analysis, and interpretation: MK, Drafting Manuscript: MK, Revising manuscript: MK, AS, Approval of final version of the manuscript for publication: MK, DS, RK, AS, responsibility for accuracy and integrity of all aspects of research involvement in drafting or revising the manuscript: MK, DS, RK, AS, acquisition of funding: NA

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. International Diabetes Federation. IDF Diabetes Atlas 9th edition 2019 [Internet]. [cited 2020 Mar 16]. Available from: https://www.diabetesatlas.org/en/.
2. WHO. Depression [Internet]. [cited 2020 Mar 16]. Available from: https://www.who.int/westernpacific/health-topics/depression.
3. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: A randomized double-blind placebo-controlled trial. Diabetes Care 2000;23:618-23.
4. Lustman PJ, Clouse RE, Nix BD, Freedland KE, Rubin EH, McGill JB, et al. Sertraline for prevention of depression recurrence in diabetes mellitus: A randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 2006;63:521-9.
5. Andreoullakis E, Hyphantis T, Kandyli D, Iacovides A. Depression in diabetes mellitus: A comprehensive review. Hippokratia 2012;16:205-14.
6. Holt RIG, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep 2014;14:491.
7. Arambewela MH, Somasundaram NP, Jayasekara HBPR, Kumbukkage MP. Prevalence of depression and associated factors among patients with type 2 diabetes attending the diabetic clinic at a Tertiary care hospital in Sri Lanka: A descriptive study. Psychiatry J 2019;2019:e7468363.
8. Hermanns N, Caputo S, Dziga G, Khunti K, Meneghini LF, Snook F. Screening, evaluation and management of depression in people with diabetes in primary care. Prim Care Diabetes 2013;7:1-10.
9. Petrak F, Röhrig B, Ismaïl K. Depression and diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dunger K, Grossman A, et al. Editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000.
10. Lustman PJ, Clouse RE. Depression in diabetic patients: The relationship between mood and glycemic control. J Diabetes Complications 2005;19:113-22.
11. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2015;38(Supplement 1):S1-2.
12. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, et al. Effects of nortriptyline on depression and glycemic control in diabetes: Results of a double-blind, placebo-controlled trial. Psychosom Med 1997;59:241-50.
13. Echeverry D, Duran P, Bonds C, Lee M, Davidson MB. Effect of pharmacological treatment of depression on A1C and quality of life in low-income hispanics and African Americans with diabetes: A randomized, double-blind, placebo-controlled trial. Diabetes Care 2009;32:2156-60.
14. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomised placebo controlled 6-month trial. BMC Fam Pract 2007;8:34.
15. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: A single-blind randomised placebo controlled trial. BMC Fam Pract 2003;4:7.
16. Nicolau J, Rivera R, Frances C, Chacartegui B, Masmiquel L. Treatment of depression in type 2 diabetic patients: Effects on depressive symptoms, quality of life and metabolic control. Diabetes Res Clin Pract 2013;101:148-52.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan — a web and mobile app for systematic reviews. Sys Rev 2016;5:210.
19. Effective Practice and Organisation of Care (EPOC). Data Collection Form. EPOC Resources for Review Authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2013.
20. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:4898.
21. Grade working group. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). [Internet]. Available from gradepro.org. [Last accessed on 2020 Mar 10].
22. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman, and other grade working group. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. [Internet]. 2013. Available from: https://gdt-gradeupro.org/app/handbook/handbook.html#h.2d2pq9je57e. [Last accessed on 2020 Mar 13].
23. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus: an abridged Cochrane review. Diabetic Medicine. 2014;31:773-86.
24. Brieler JA, Lustman PJ, Scherrer JF, Salas J, Schneider FD. Antidepressant medication use and glycaemic control in co-morbid
25. Rubin RR, Ma Y, Peyrot M, Marrero DG, Price DW, Barrett-Connor E, et al. Antidepressant medicine use and risk of developing diabetes during the diabetes prevention program and diabetes prevention program outcomes study. Diabetes Care 2010;33:2549-51.

26. Silva N, Atlantis E, Ismail K. A review of the association between depression and insulin resistance: Pitfalls of secondary analyses or a promising new approach to prevention of type 2 diabetes? Curr Psychiatry Rep 2012;14:8-14.

27. Serretti A, Mandelli L. Antidepressants and body weight: A comprehensive review and meta-analysis. J Clin Psychiatry 2010;71:1259-72.
| Section/topic       | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE             | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                              | 1                 |
| ABSTRACT          | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2                 |
| INTRODUCTION      | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                     | 3                 |
| METHODS           | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                 | 4                 |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                             | NA                |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                   | 4                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                           | 4                 |
| Search            | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                      | Additional file 2  |
| Study selection   | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                        | 4,5               |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                      | 5                 |
| Data items        | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                              | 5                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.       | 5                 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                     | 5                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.                                                            | 5                 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                   | 5                 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                 | 6                 |
| RESULTS           | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                 | 7,8               |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                    | 7,9               |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                          | 9,10              |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9,10              |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                           | 9,10              |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                  | 9,10              |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                              | 10                |
| DISCUSSION        | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                               | 7,13              |
| Summary of evidence | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                       | 13                |
| Limitations       | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                           | 12                |
| FUNDING           | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                   | 13                |
Additional file 2
Search methods for identification of studies

Electronic searches (Cochrane)

#17 (diabet*):ti, ab, kw (Word variations have been searched)
#18 MeSH descriptor: [Diabetes Mellitus] explode all trees
#19 (“antidepress*”):ti, ab, kw OR (“norepinephrine”):ti, ab, kw OR (“Fluoxetine*”):ti, ab, kw OR (“olanzapine”):ti, ab, kw OR (“serotonin”):ti, ab, kw (Word variations have been searched)
#20 (“dopamine”):ti, ab, kw OR (“nortryptiline”)(Word variations have been searched)
#21 #19 or #20
#22 #17 or #18
#23 #21 and #22
#24 (“glycaemic”):ti, ab, kw OR (“HbA1c”):ti, ab, kw (Word variations have been searched)
#25 MeSH descriptor: [Glycemic Index] explode all trees
#26 #24 or #25
#27 #23 and #26