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Targeting self-care adherence for glycaemic control in multimorbid type 2 diabetes mellitus with depression using bupropion: a protocol for cross-over randomised controlled trial

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ABSTRACT

Introduction Diabetes and depression are among the 10 biggest health burdens globally. They often coexist and exhibit a strong bidirectional relationship. Depression leads to decreased adherence to self-care activities. This impacts glycaemic control and worsens type 2 diabetes mellitus (T2D). Both conditions have a synergistic effect and lead to greater complications, hospitalisations, healthcare expenditure and a worse quality of life. There is no consensus on managing people with comorbid T2D and depression. Bupropion is an efficacious antidepressant with many properties suitable for T2D with depression, including a favourable metabolic profile, persistent weight loss and improvement in sexual dysfunction. We will assess the efficacy and safety of add-on bupropion compared with standard care in people with T2D and mild depression. This study can give valuable insights into managing the multimorbidity of T2D and depression. This can help mitigate the health, social and economic burden of both these diseases.

Research design and methods This cross-over randomised controlled trial will recruit people with T2D (for 5 years or more) with mild depression. They will be randomised to add-on bupropion and standard care. After 3 months of treatment, there will be a washout period of 1 month (without add-on bupropion while standard treatment will continue). Following this, the two arms will be swapped. Participants will be assessed for glycosylated haemoglobin, adherence to diabetes self-care activities, lipid profile, urine albumin-to-creatinine ratio, autonomic function, sexual function, quality of life and adverse events.

Ethics and dissemination The Institutional Ethics Committee at All India Institute of Medical Sciences, Jodhpur has approved this study (AIIMS/IEC/2022/4172, 19 September 2022). We plan to disseminate the research findings via closed group discussions at the site of study, scientific conferences, peer-reviewed published manuscripts and social media.

Trial registration number CTRI/2022/10/046411.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial focuses on holistic parameters in diabetes including glycaemic control, self-care adherence, sexual function and autonomic function.
⇒ The trial is open-labelled, thereby avoiding the placebo effect commonly noted in trials with antidepressants.
⇒ This detailed protocol can be replicated for other interventions in this common population of multimorbid diabetes and depression.
⇒ The short duration of 3 months may not be enough to capture the complete effect of increased self-care adherence on glycaemic parameters.
⇒ This is a single-centre study with limited participants.

INTRODUCTION

Diabetes and depression are severe chronic illnesses with a very high burden. These are among the 10 biggest contributors to the increase in global disease burden over the past three decades (1990–2019).[1] The increasing health burden due to these two conditions can be better appreciated in table 1.

Diabetes affects over half a billion people across the world. The associated healthcare expenditure is nearly a trillion USD.[2] Alongside, depressive disorders affect over 300 million individuals, corresponding to 4.4% of the population worldwide. It contributes to a disproportionate burden of 7.5% of the total global years lived with disability. Indian figures match global estimates with 4.5% and 7.1%, respectively.[3]

However, these two disease entities are not independent of each other. Depression is more prevalent in people with diabetes, and a clear pattern can be observed. Depression is

Table 1 Increasing global burden due to diabetes and depression

Disease	1990	2019
Diabetes	20th leading cause for DALY	8th leading cause for DALY
	1.1% of all-cause DALY	2.8% of all-cause DALY
Depression	19th leading cause for DALY	13th leading cause for DALY
	1.1% of all-cause DALY	1.8% of all-cause DALY

.DALY, disability-adjusted life-years.

1.8 times more prevalent in previously diagnosed diabetes, 1.27 times more prevalent in undiagnosed diabetes and 1.11 times more prevalent in pre-diabetes.[4] A more recent meta-analysis reports that people with type 2 diabetes (T2D) are 1.76 times more likely to have depression than those without diabetes. This finding is significant across all subgroups but is greater in specialist care settings and low-income and middle-income countries.[5] Women are more likely to be affected, with 34% of women and 23% of men with T2D also suffering from depression.[6]

People with diabetes are more likely to have mild depression than full-blown depression.[7] However, depression may be more persistent and recurrent in them.[8] Depression is a relatively underdiagnosed disease in general. On top of that, it is often not discussed during consultations for diabetes. This could be due to a greater focus on the somatic symptoms of diabetes than the associated psychological symptoms.[9 10]

Diabetes and depression share a strong bidirectional relationship. Depression and diabetes both increase the risk of development of each other.[11] This association is not entirely unexpected. Over three centuries ago, it was hypothesised that prolonged grief could result in diabetes. However, the lack of obviousness meant this idea did not receive the scientific attention it deserved.

Obesity and stress due to the management of diabetes increase the risk of depression in diabetes. The opposite direction of this bidirectional relationship is attributed to a lack of self-care and adverse metabolic effects of antidepressants.[12] Depression can result from improper diet, unsuitable lifestyle activities, inadequate sleep and obesity. Conversely, it can also lead to these conditions. Some antidiabetic medications themselves increase the risk of depression. Depression leads to decreased self-care. This then manifests as inadequate lifestyle modifications and lack of adherence to medication and other healthcare advice, ultimately leading to poor glycaemic control.[12–19]

The pathophysiological mechanisms behind their relationship require further exploration. Both depression and T2D share common pathophysiological processes. Chronic stress, including depression, causes dysregulation of the hypothalamic–pituitary–adrenal axis, overactivity of the sympathetic component of autonomic function, and immune dysregulation. Elevated cortisol and catecholamines lead to insulin resistance and consequent hyperglycaemia. This activates the polyol pathway resulting in oxidative stress and neuronal damage, including hippocampal atrophy. This is followed by the formation of advanced glycation end products associated with depression.[11 20] Thus, there is a cycle of pathophysiological changes.

This comorbid condition of depression and diabetes has a synergistic effect, not just an additive one.[21] These individuals have a much worse quality of life than those with T2D alone without depression.[22] Diabetes with mental health issues get routine biochemical investigations done less frequently, are more likely to develop cardiovascular complications, get hospitalised for complications of diabetes more, have greater mortality (diabetes related, cardiovascular cause related and all cause) and are linked with greater healthcare expenditure.[23–29]

Since commonly used antidepressants do not differ much in efficacy for depression, the choice of an antidepressant drug revolves around the adverse event profile of the drug and the patient profile.[30] The management of this comorbid condition is not a straightforward task. Depression is underdiagnosed and untreated in nearly half of those with diabetes.[9] Pharmacological management, mainly with selective serotonin reuptake inhibitors, has provided mixed results.[31–33] Instead, the usage of antidepressants in general and specifically SSRIs and TCAs has been implicated with a higher risk of developing T2D. Atypical antipsychotics that have recently grown in popularity are also known to predispose to metabolic adverse events, including T2D and weight gain. There is a growing opinion that instead of incriminating classes of antidepressants in general, we should pay attention to the affinity for H1-receptor seen with specific drugs. Bupropion and fluoxetine are among the antidepressants with the lowest affinity for H1-receptor.[34–37] Few trials have reported diverse effects of different antidepressants in diabetes. Thus, they may be better options in the setting of metabolic diseases.

In a systematic review and meta-analysis (SRMA) of 116 studies, antidepressants had varied effects on weight gain. Some increased weight, some were weight-neutral and some decreased. Bupropion was the only antidepressant associated with persistent weight loss and is not limited to the acute phase of treatment.[38] This corroborates using bupropion with naltrexone for weight loss in individuals with weight-related multimorbidities like T2D.[36 39]

Sexual dysfunction often occurs in people with diabetes and is multifactorial in origin.[40 41] To add to our concerns regarding the comorbid population suffering from T2D and depression, antidepressants commonly cause sexual dysfunction. This then leads to premature treatment discontinuation and a worse quality of life. One of the key takeaways from an SRMA investigating sexual dysfunction using antidepressants was that bupropion had a lower risk of sexual dysfunction.[42] A newer review article also lists bupropion as one of the antidepressants with

the least risk of sexual dysfunction.[43] Bupropion is even recommended for antidepressant-related sexual dysfunction and is used for it off-label.[44 45] Instead, bupropion effectively treats females with low sexual dysfunction in a dose-dependent manner, as reported in a recent SRMA.[46] It improves sexual dysfunction in men, too.[47] Moreover, a cost–utility analysis in a specific circumstance found benefits with Bupropion as opposed to other antidepressants like venlafaxine or sertraline.[48]

Bupropion has shown promising results in a single-arm observational study of patients with T2D and depression.[49 50] Inadequate management of depression in diabetes results in poor glycaemic control and consequent diabetic complications.[8]

People with diabetes with depression need increased attention during management. It is crucial that the bidirectional linkage between these two diseases is appreciated and that the vicious cycle is targeted appropriately. We should not consider the two diseases as separate entities requiring separate management. Instead, a holistic model of care involving a multipronged strategy should be employed to control these individuals' unique healthcare needs better.

There is a lack of consensus on managing this public health burden of multimorbidity of diabetes and depression.[51] Moreover, though there is a lack of data on the usage of bupropion in this condition, many factors, including the safety profile of this drug, beg for a study to explore further. Hence, we are planning a crossover randomised controlled trial to assess the efficacy and safety of add-on bupropion in T2D with mild depression. We are evaluating various outcomes, including glycaemic control, self-care adherence, sexual satisfaction, autonomic function, lipid profile, urine albumin-to-creatinine ratio, quality of life and adverse events.

RESEARCH DESIGN AND METHODS

Aims and objectives

Aims

To explore the efficacy and safety of bupropion in glycaemic control, adherence to self-care activities and related parameters in T2D mellitus (T2DM) patients with mild depression.

Objectives

Primary objectives

- To compare the effect of add-on bupropion versus standard of care on glycosylated haemoglobin (HbA1c) in patients with T2DM with mild depression.
- To compare the effect of add-on bupropion versus standard of care on adherence to self-care activities in patients with T2DM with mild depression.

Secondary objectives

- To evaluate the effect on lipid profile parameters of add-on bupropion versus standard of care in patients with T2DM with mild depression.
- To evaluate the effect on the urinary albumin-to-creatinine ratio of add-on bupropion versus standard of care in patients with T2DM with mild depression.
- To evaluate the effect on autonomic function test of add-on bupropion versus standard of care in patients with T2DM with mild depression.
- To evaluate the effect on adverse events of add-on bupropion versus standard of care in patients with T2DM with mild depression.
- To evaluate the effect on the quality of life of add-on bupropion versus standard of care in patients with T2DM with mild depression.
- To evaluate the effect on the sexual satisfaction of add-on bupropion versus standard of care in patients with T2DM with mild depression.

Study design

This is a cross-over open-labelled randomised controlled trial. We are comparing the efficacy and safety of add-on bupropion against standard care in individuals with T2D and mild depression. The study will be performed from October 2022 to June 2024. The study will occur at the All India Institute of Medical Sciences (AIIMS), Jodhpur.

We will screen patients with T2D at the department of endocrinology and metabolism. The following criteria will be used:

Inclusion criteria

- Age of 30–70 years.
- Diagnosis of T2DM as per International Diabetes Federation criteria.
- Duration of T2D for 5 years or more.
- HbA1c between 6.5% and 12%.
- Having a score of 5–9 (mild depression) on the Patient Health Questionnaire-9.

Exclusion criteria

- T1DM.
- History of traumatic brain injury.
- Patients had any comorbid psychiatric disorder other than mild depression or a history of psychiatric illness.
- Treatment with antipsychotic or antidepressant medications, benzodiazepines, dopaminergic medications, monoamine oxidase inhibitors or amantadine within the last 4 weeks before study participation.
- Pregnant and lactating women.
- History of allergy/intolerance to bupropion.
- Patients with any significant neurological disorders or any significant medical or surgical condition.

Eligible patients will be recruited after obtaining informed consent. Participants will be allocated to the two arms using stratified block randomisation. A variable block size of 4 or 6 will be used. According to the computer-generated randomisation sequence, they will be allocated to either add-on bupropion or standard care for 3 months. This allocation will be done using sequentially numbered opaque sealed envelopes. The individuals

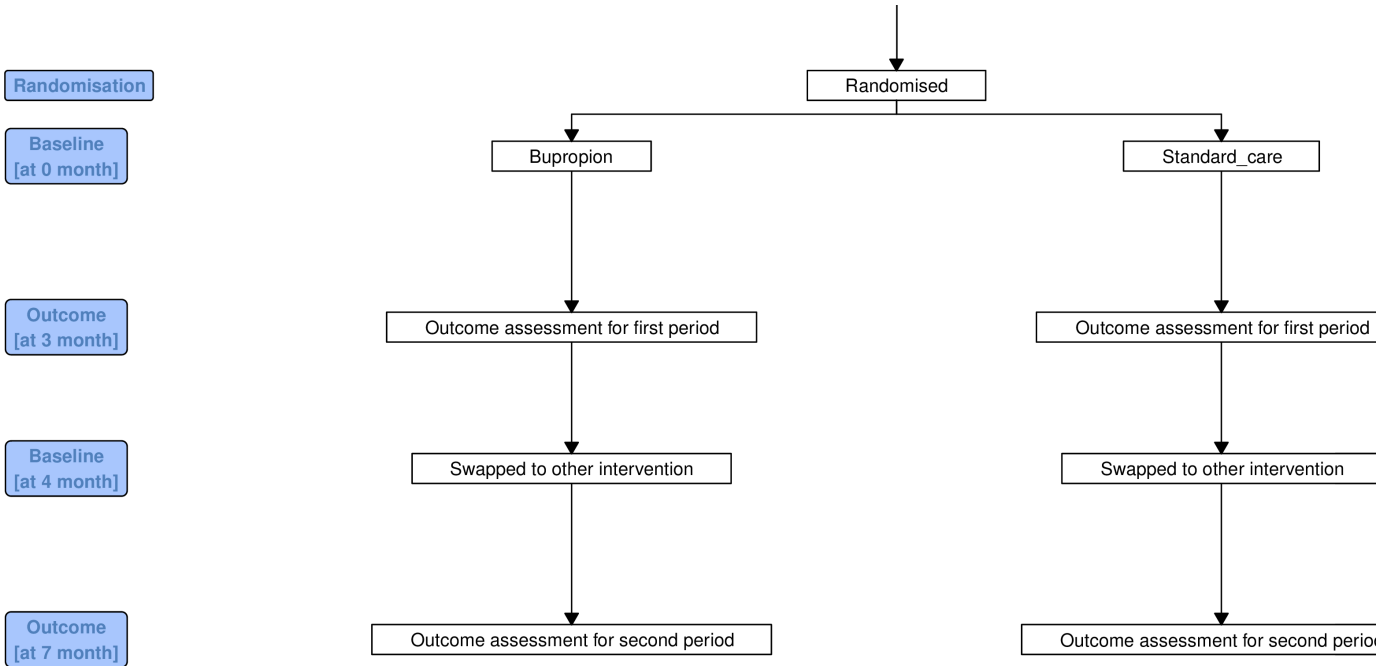

Figure 1 Flow chart explaining study design.

in the intervention arm will receive 150 mg of extended-release bupropion.

They will then be referred to the department of psychiatry. The intervention arm will be prescribed the study drug. Both groups will receive supportive care. The participants will also submit their serum and urine samples at an appropriate time for the investigations discussed under objectives. They will be sent to the physiology department for autonomic function assessment. Autonomic function testing consists of Ewing's battery of tests as deemed feasible.

Standard care consists of treatment for diabetes and mild depression as deemed fit by the treating physicians. Only the intervention of add-on bupropion will undergo randomisation.

Participants will be contacted fortnightly telephonically. Compliance with the study drug and adverse events will be recorded. Participants will be provided support to promote trial retention. They will also be advised to contact the research team at any time throughout the study period if they need to do so. Participants are asked to report any side effects. No further data are collected if a participant decides to quit the trial. After 3 months, participants will be followed up, and all investigations will be repeated. Following a washout period of 1 month, all the investigations will be repeated. Then, the two study arms will be swapped, and investigations will be repeated after 3 months, as depicted in figure 1.

Study tools

The Summary of Diabetes Self-Care Activities Score will assess adherence to self-care activities.[52] Quality of life will be assessed using the revised Diabetes Quality of Life Score.[53] Sexual satisfaction will be measured using a single-item measure.[54] Patient Health Questionnaire-9 will be used to assess depression. At each visit, tests for HbA1c, urine albumin-creatinine ratio, lipid profile and autonomic function test will be done. Safety data and adverse events will be recorded fortnightly, telephonically and during each visit.

We will perform a translation and cross-cultural adaptation of these questionnaires. Following this, we will conduct a field-testing and an instrument review. We will then assess the face and content validity.

Following this guideline,[55] the instruments will be translated from English to Hindi. Two people whose native language is Hindi and who are fluent in English will produce independent translations. One of them is knowledgeable about the content of these instruments while the other is naïve to the intent of these instruments. Thus, the second forward translator is culturally representative of the target population. Both will synthesise their translations into one, considering conceptual equivalence, colloquial language use and clarity. An independent person who feels most comfortable in English and is also fluent in Hindi, will back-translate these synthesised versions to English. The back-translation will be done blindly, with him being unaware of the contents of the original instruments.

Another independent person who is fluent in English and has expertise in the content of the instruments will review. They will compare the original tools with the back-translated versions. They will then give recommendations to the team leader as required. Translation errors will be quantified, comparing it against an adequacy benchmark of 8 errors per 300 words translated. Following this, further cycles of translation and review may be carried out as needed.

A multidisciplinary culture equivalency panel representing bilinguals and monolinguals (Hindi) will be constituted. The final versions will be reviewed by all the panel members and discussed with the team leader. The team leader will take action accordingly, considering adequacy and relevance. We will establish semantic, idiomatic, experiential and conceptual equivalence. The instruments will be field-tested. Per cent agreement between the original and the adapted tool will be assessed and compared against a threshold of 80%. Face and content validity will be established by sending the adapted instruments to experts. All the steps and versions will be recorded in a translation log.

Statistical analysis

We have calculated the sample size based on this study.[49] Assuming an improvement in HbA1c level of 0.6 in two treatment groups with an SD of 1.1 and 0.7 in treatment and control groups and power of 80% with a clinical significance level of 0.05, a sample size of 37 participants has been calculated. With a drop-out rate of about 10 %, 40 participants are required. As it is a cross-over study, 20 participants will be included in each group.

Data will be recorded in a master data file in Google Sheets. Data will be presented as mean±SD or median and IQR depending on the distribution. Data will be checked for normality using the Shapiro-Wilk test. Independent Student's t-test will compare quantitative variables between two groups (Mann-Whitney U test if data do not follow a normal distribution). The χ^2 test will be used to compare categorical variables. Intragroup differences will be evaluated by paired t-test. An intention-to-treat approach will be used for the analyses. A $p<0.05$ will be considered significant.

Ethics and dissemination

We have received approval from the Institutional Ethics Committee at AIIMS Jodhpur. It was approved at a meeting held on 19 September 2022, and the certificate reference number is AIIMS/IEC/2022/4172. We plan to disseminate the research findings via closed group discussions at the site of study, scientific conferences, peer-reviewed published manuscripts and social media. Data generated from this study can be shared on contact with the corresponding author for requests deemed to be reasonable.

Safety monitoring and reporting

Safety data will be obtained by interview and examination at each visit. Open and closed questions will monitor adverse drug events at each visit. Safety data will also be recorded fortnightly telephonically.

All adverse events will be classified as severe and non-serious. A serious adverse event or reaction is any untoward occurrence that at any dose leads to death, threatens life, needs hospitalisation or prolongs hospitalisation, or results in persistent or significant disability or incapacity.

All serious adverse drug events will be reported to the ethics committee within 24 hours and to the Drugs Controller General of India within 7 days. A data safety monitoring board will be constituted, consisting of people not involved in the trial if required.

Confidentiality and ethical considerations

The study commenced only after the approval by the institutional ethics committee at AIIMS Jodhpur. The aims and objectives will be explained to the respondents. The participants will be asked to sign an informed consent form for the study. Participants will be presented with the purpose behind the study, the study design, the expected benefits and risks, and details of contact people. All relevant guidelines will be adhered to.

Confidentiality and respect for personal privacy will be maintained. Participants will have the opportunity to withdraw at any time from the study. Participants' medical records and identities will be treated as confidential documents. They will only be revealed to other doctors/scientists/monitors/auditors of the study if required. The study results may be published in a scientific journal, but participants will not be identified by name.

Patient and public involvement

The authors' clinical experience with participants with diabetes and depression motivated them to undertake this study. Patients or members of the public could not be directly involved in the study due to time concerns during protocol development (as it is an academic dissertation). Nonetheless, we intend to disseminate the findings to the patients and members of the public via medical conferences and social media.

Trial status

We have registered this study at the Clinical Trials Registry of India (CTRI/2022/10/046411). The study began recruiting on 18 October 2022 and is expected to complete the follow-up of patients by June 2024, followed by data analysis.

DISCUSSION

The purpose of this study is to explore the efficacy and safety of bupropion in glycaemic control, adherence to self-care activities and related parameters in patients with T2D with mild depression. Appropriate focus on diabetes and depression is required since these two diseases share a bidirectional relationship. Both contribute to the development and worsening of each other, leading to a vicious cycle of progressive multimorbidity. Poor metabolic control, low rates of blood glucose self-monitoring and diabetes complications all predict an insufficient response to depression treatment.[8]

Strengths

Our study has several strengths. This is the first randomised controlled trial to assess the effect of antidepressants on glycaemic control in T2DM. Moreover, the cross-over

design minimises the interindividual variability between the two study arms. We can assess and compare the two arms with the least confounding, as each individual is their control. Further, multiple departments (endocrinology and metabolism, psychiatry, pharmacology and physiology) are involved in the research, and thus the individual is experiencing collaborative multidisciplinary care.

Limitations

There are a few limitations to our study. We may need more than 3 months to capture the benefits of the study drug. Since T2D and depression are both chronic diseases, and we are targeting the former by modulation of the latter, all the effects may not occur within 3 months. However, given that it is an academic trial as a part of a thesis, and given that the cross-over study design makes the follow-up of each participant reach 7 months, we could not increase the follow-up period. Further, recruiting a larger sample size could have helped add adequate power to the secondary outcomes and helped us plan subgroup analyses. Another potential limitation is that we only recruit patients from a tertiary centre's outpatient facility and do not include primary health centres in our study. Finally, depression is a disease that varies with intensity over time and may depend a lot on factors outside the scope of treatment, like personal or professional life incidents.

CONCLUSIONS

This safety and efficacy study will compare add-on bupropion against standard care for treating T2D with mild depression. Improved self-care adherence may lead to better glycaemic controls. The results can guide the management of the multimorbidity of T2D with mild depression.

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Disclaimer The funder did not have any say in the study design or management of the study. None of the investigators have any reported conflict of interest.

Competing interests None declared.

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