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Effect of a Collaborative Care Model on Anxiety Symptoms Among Patients with Depression and Diabetes in India: The INDEPENDENT Randomized Clinical Trial

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Author statement

I certify that all authors have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere.

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Abstract

Objective: We assessed the impact of a collaborative care intervention on anxiety symptoms among participants in India with comorbid depression, poorly controlled diabetes, and moderate to severe anxiety symptoms.

Method: We analyzed data from a randomized controlled trial conducted at four diabetes clinics in India. Participants received either collaborative care or usual care. We included only participants who scored ⩾10 on the Generalized Anxiety Disorder-7 (GAD-7) at baseline. We estimated the effect of the intervention on clinically significant reduction in anxiety symptoms; we considered several potential baseline moderators and mediation by anti-depressant use.

Results: One hundred and seventy-two participants scored 10 or above on the GAD-7 at baseline. Collaborative care participants were more likely than control participants to achieve a clinically significant reduction in anxiety symptoms at 6 and 12 months (65.7% vs. 41.4% at 12 months, $p = 0.002$); these differences were not sustained at 18 or 24 months. There was little evidence of moderation by participant characteristics at baseline, and effects were not mediated by anti-depressant use.

Conclusions: Collaborative care for the treatment of depression and type 2 diabetes can lead to clinically significant reductions in anxiety symptoms among patients with anxiety. Effects were notable during the active intervention period but not over the year post-intervention.

Keywords

Anxiety; depression; diabetes; collaborative care; integrated care; India

INTRODUCTION

Diabetes is among the leading causes of death and disability worldwide. The International Diabetes Federation estimates that 463 million adults were living with diabetes in 2019, of whom 79% were living in low- or middle-income countries (LMICs).[1] The global cost of diabetes for 2015 was estimated to be US$1.31 trillion or 1.8% of the global gross domestic product (GDP).[2] India, in particular, faces a massive and growing burden of diabetes; globally, one in six people living with diabetes are in India.[3] Type 2 diabetes (T2DM) is associated with an increased prevalence of mental health conditions, in particular depression and anxiety.[4, 5] Among people with T2DM, both anxiety and depression are associated with poorer diabetes outcomes, including increased risk of microvascular complications and cardiovascular events, poorer quality of life, increased costs and health care services

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utilization, and increased mortality.[6–9] Moreover, depression and anxiety commonly co-occur, complicating the treatment of either disorder.[10]

A robust literature supports the bidirectional relationship between diabetes and depression,[11, 12] but there has been much less research about the relationship between diabetes and anxiety. This is surprising because anxiety disorders are one of the leading causes of disability worldwide, with estimates of global prevalence ranging from 3.3% to 7.3%.[13, 14] Several mechanisms have been proposed to explain the relationship between diabetes and anxiety. Chronic anxiety might cause or exacerbate T2DM through activation of the hypothalamic-pituitary-adrenal (HPA) axis, which triggers release of counter-regulatory hormones such as glucagon, epinephrine, and cortisol—leading to increased glucose levels in the blood.[15] Psychological hypotheses suggest that the emotional impact of a diabetes diagnosis, compounded with the burden of daily diabetes management, can also lead to anxiety. People with anxiety may be more likely to engage in poor health behaviors, including overeating, which can contribute to or exacerbate T2DM.[16] Given that an estimated 34% of people receiving care for diabetes in India also have at least mild anxiety symptoms (GAD-7 ≥ 5),[17] it is possible to examine the relationship between these comorbidities and the potential for integrated treatment for diabetes and anxiety in this context.

The treatment of comorbid depression and anxiety among people with diabetes is often fragmented and relies on referrals to off-site mental health specialists which can fail because of logistical challenges (e.g., costs, transportation, need for time off from work or for childcare) or because of the stigma associated with seeking mental health treatment. Patients are more likely to follow through with mental health referrals when services are offered within the primary care practice.[18] Collaborative care is an evidence-based multi-component model that integrates treatment for common mental disorders into primary care and other medical settings.[19] Collaborative care is based on a broader conceptual model for the longitudinal care of chronic conditions and includes a team approach to treatment of a defined population, monitoring of outcomes and response to treatment, and structured communication among team members.[20] Several clinical trials have demonstrated the efficacy of collaborative care for improving anxiety outcomes.[21–23]

The INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) trial demonstrated the effectiveness of collaborative care in improving depression and diabetes outcomes among individuals with poorly-controlled diabetes and depression in diabetes clinics in India.[24, 25] We conducted a secondary analysis of the INDEPENDENT trial to 1) assess the impact of the 12-month INDEPENDENT intervention on anxiety symptoms among study participants with comorbid depression and poorly controlled diabetes with anxiety symptoms; 2) examine whether impact(s) of the intervention on anxiety symptoms were sustained 12 months after the end of the intervention; and 3) explore factors associated with the response of anxiety symptoms to the intervention.

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METHODS

Study design and participants

The INDEPENDENT study was a randomized controlled trial conducted at diabetes clinics in four Indian cities: a public hospital outpatient clinic in Delhi and three private diabetes clinics in Bangalore, Chennai, and Visakhapatnam. The study protocol was approved by the Indian and US coordinating centers (Institutional Ethics Committee of Madras Diabetes Research Foundation and Emory University Institutional Review Board, respectively), ethics committees at each clinic site, as well as the Health Minister Screening Committee of the International Health Division of the Indian Council of Medical Research.

Patients at the participating diabetes clinics were eligible to participate in the INDEPENDENT trial if they met the following criteria: (1) age ≥ 35 years; (2) physician-confirmed diabetes; (3) moderate to severe depressive symptoms, defined as Patient Health Questionnaire-9 (PHQ-9) score ≥10 (range 0-27);[26] and (4) one or more poorly controlled cardiometabolic indicators (HbA1c ≥ 8.0%; SBP ≥ 140 mm Hg, or LDL-c ≥ 130 mg/dl). Patients with bipolar or psychotic disorders (based on bipolar and schizophrenia modules of the Mini-International Neuropsychiatric Interview [MINI]), cognitive impairment, alcohol or substance use disorders, type 1 diabetes, kidney failure, or cardiovascular events in the last 12 months (i.e., myocardial infarction, unstable angina, or stroke), or who were pregnant or breast-feeding were excluded. Patients were screened and enrolled into the trial from March 2015 to May 2016.

Randomization and masking

Baseline assessments were conducted with consented participants by a blinded outcomes assessor. Blinded study staff then assigned participants to receive the collaborative care intervention or usual care using a password-protected web-based system that randomized patients in randomly generated blocks of 4, 6, 8, or 10, stratified by site. Participants and their physicians were not blinded to treatment randomization, though outcomes assessors and analysts remained blinded to treatment assignment for the duration of the study. A total of 404 participants were randomized to receive either collaborative care or usual care.

Intervention

The intervention was delivered by a team at each site, which included a care coordinator and two consulting physicians (a psychiatrist and a diabetologist/endocrinologist). Most care coordinators had backgrounds in allied health fields (primarily nutrition counseling) but no previous experience or training in mental health; the exceptions were psychologist care coordinators, who were not trained in health psychology.

As a part of this intervention, care coordinators received training in a brief evidence-based behavioral treatment for depression (behavioral activation) and how to support diabetes self-management. Care coordinators had regular contact (at least monthly in clinic or by phone) with intervention participants, assessing severity of depression symptoms, blood glucose and blood pressure at every visit. At these visits, care coordinators provided counseling to support patients to achieve individualized treatment goals.

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Two intervention components supported diabetes physicians in their clinical decision making. First, a decision support tool provided evidence-based clinical prompts from built-in algorithms based on prevailing treatment guidelines. In addition, the collaborative care team members at each site met every two weeks to systematically review the caseload of patients and recommend treatment changes for patients who were not improving as expected or who were not consistently engaged in care.

For participants randomized to the usual care arm, their diabetes physician was notified of their clinically significant depressive symptoms. These participants continued to receive their usual diabetes care from their physicians, including whatever depression care or referrals their clinics typically provided.

Data collection and follow-up

All participants attended a baseline visit prior to randomization as well as research follow-up visits at 6-, 12-, 18- and 24-months.

As the focus of the current study is on clinically-significant anxiety, only those INDEPENDENT trial participants who scored ⩾10 on the Generalized Anxiety Disorder (GAD-7) clinical rating scale[27] at baseline were included in the following analyses.

Outcome

Our outcome of interest was clinically significant reduction in anxiety symptoms, as measured using the GAD-7, which was administered at baseline and all follow-up study visits. The GAD-7 is a valid and reliable instrument, and its psychometric properties in India are comparable to western settings.[28] The total score from the seven items ranges from 0 to 21, with higher scores indicating more severe symptoms of anxiety, and scores of 10 or above suggesting at least moderate anxiety symptoms. We parameterized a clinically significant reduction as both: (1) moving from above to below the cutoff of 10 and (2) changing by six or more points from baseline to the index measurement.[29]

Statistical analysis

We descriptively analyzed characteristics of participants with clinically significant anxiety at baseline, stratified by treatment assignment. We assessed missing data patterns and used a bootstrap expectation-maximization procedure for tenfold multiple imputation.[30] Unless noted, all results are derived from these imputed data sets. Final estimates were pooled using Rubin's rules.[31]

For the primary analysis, we used a longitudinal regression model to estimate the effect of the intervention on the outcome of interest over time. Risk differences (RDs) between the intervention and usual care groups at 6, 12, 18, and 24 months were estimated using Gaussian generalized estimating equations (GEE) with identity link (i.e., linear probability models). The model accounted for correlation within patients over time,[32] and included site (categorical), treatment group (binary), time (dummy variables for each time point), and treatment × time interactions as covariates.

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We additionally conducted moderation analyses to identify heterogeneity in intervention effects across participant characteristics at baseline. The baseline moderators assessed were: age group (35-49, 50-64, ⩾ 65 years), sex (men, women), marital status (not married, married), educational attainment (none/unsure, primary/secondary, or post-secondary), household income per month (<10,000 Indian Rupees [INR, approximately USD$150 in 2015], 10,001-20,000 INR, >20,000 INR), HbA1c (<8.0%, ⩾ 8.0%), PHQ-9 depressive symptom score (moderate [10-14], at least moderately severe [15-27]), and GAD-7 anxiety symptom score (moderate [10-14], severe [15-21]). Each of the eight moderation analyses replicated the primary analysis with the addition of a moderator variable and its interactions with treatment, time, and treatment × time. The magnitude and statistical significance ($p < 0.05$) of the treatment × time × moderator interactions were assessed at each timepoint.

Finally, we conducted a causal mediation analysis to estimate the indirect effect of the intervention on anxiety symptom reduction via increased anti-depressant medication use. Linear mixed effects models were used to estimate associations between the intervention and anti-depressant use, and between anti-depressant use and anxiety symptom reduction, adjusting for treatment arm, including random subject-specific intercepts. Causal mediation analysis was run using 1,000 simulations on all ten imputed datasets.[33]

As a sensitivity analysis, we repeated the primary and moderation models using continuous GAD-7 scores as the outcome.

All analyses were performed in version 4.0.5 of R.[34]

Role of the Funding Source

The National Institute of Mental Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

Of 404 patients randomized, 172 participants (43%) – 82 in the intervention arm and 90 in the control arm – scored 10 or above on the GAD-7 at baseline (Table 1). See Supplemental Figure 1 for the CONSORT diagram. Participant demographic and clinic characteristics were similar between groups. The mean (standard deviation [SD]) age of participants was 52.3 (8.4) years, 119 (69.2%) were women, 145 (84.3%) were married, 31 (18%) had more than a secondary education, and 69 (40.1%) had monthly household incomes over 20,000 INR (approximately USD$300 in 2015). 78 (45.4%) had at least moderately severe depressive symptoms, and 77 (44.8%) had severe anxiety symptoms. Mean HbA1c was 9.6% (2.0%).

A statistically significantly higher proportion of collaborative care than control participants achieved clinically significant reduction in anxiety symptoms at 6 and 12 months (at 6 months, 48.4% vs. 30.0%, RD 17% [SE 7%]; at 12 months, 65.7% vs. 41.4%, RD 23% [SE 7%]) (Table 2). There were no statistically significant differences in anxiety symptom reduction between treatment arms at 18 or 24 months (24 months: 85.6% vs. 86.7% %,

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RD −2% [SE 5%]). A statistically significantly higher proportion of collaborative care than control participants were also using anti-depressant medications at 6 and 12 months (at 6 months, 26.7% vs. 8.5%; at 12 months, 32.3% vs. 11.6%); these differences were not sustained at 18 or 24 months.

There were no statistically significant differences in intervention effects on anxiety reduction at any time point by sex, marital status, education, income, baseline hemoglobin A1C, baseline depressive symptom severity, or baseline anxiety symptom severity (Table 3). Statistically significant differences were only observed by age group at 24 months (Supplemental Figure 2). Compared to younger participants, older participants were more likely to have clinically significant reduction in anxiety symptoms at that time point (aged 50-64 years, RD 29% [SE 12%]; aged ⩾ 65 years , RD 50% [SE 17%]).

Table 4 presents parameters from the mediation models estimating direct and indirect effects of the intervention on anxiety symptom reduction via anti-depressant use. While participants in the treatment group had increased use of anti-depressants relative to control participants at 6 months (RD 0.18 [SE 0.06]) and 12 months (RD 0.20 [SE 0.05]), that difference was not observed at 18 or 24 months. Anti-depressant use was not independently associated with anxiety symptom reduction independent of treatment group assignment (RD 0.05 [SE 0.04]). The average causal mediation effect (ACME) was estimated to be 0.005 (SE 0.005), suggesting no statistically significant mediation by anti-depressant use.

Results from sensitivity analyses using continuous total GAD-7 scores were substantively the same as results from the main analyses (Supplemental Table 1, Supplemental Figure 3).

DISCUSSION

These findings suggest that collaborative care to integrate treatment of depression and poorly controlled type 2 diabetes may also lead to clinically significant reductions in anxiety symptoms among patients with anxiety. The effects on anxiety symptoms were observed during the active intervention, but not over the year post-intervention. We found little evidence of moderation by patient sub-groups. Older participants had greater reductions in anxiety symptoms compared to younger participants at 24 months, though this finding must be interpreted with caution given the small sample sizes in the moderation analyses. Our findings are consistent with previous research demonstrating the effectiveness of collaborative care in the treatment of anxiety.[35] Notably, significant improvements in anxiety symptoms were also observed in the usual care arm, accelerating to match the intervention arm by 24 months; this may suggest that many participants' anxiety symptoms were transient or that participants found other ways to manage their symptoms.

INDEPENDENT intervention components appeared to be helpful in reducing anxiety symptoms even though the intervention was not designed to treat anxiety. The multi-component intervention included evidence-based treatments for depression, including Behavioral Activation (a brief psychological treatment) and medication treatment with SSRIs, which are also first-line treatments for anxiety disorders. Antidepressant use did not appear to be a substantial mechanism of effect, though. Intervention participants were more

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likely to receive antidepressant medications during the intervention period, but only about one third of participants were treated with antidepressant medications at any point during the study, and antidepressant use dropped during the post-intervention period. Therefore, it is much more likely that either psychological or behavioral interventions - or simply the increased attention and support provided to intervention participants - were more likely to have been responsible for the observed effect on anxiety symptoms. The goal setting that is a core component of Behavioral Activation may have helped participants with anxiety gain a sense of control over their health, thus alleviating some symptoms of anxiety. Moreover, the frequent follow up and phone calls by care coordinators between visits to assess adherence and self-care may have mitigated some of the anxiety that patients felt about their diabetes care. Indeed, the diabetes self-management support and education provided by care coordinators itself may also have led to reductions in anxiety. Diabetes education is a patient-centered, evidence-based intervention that draws from principles of motivational interviewing to encourage people with diabetes to make informed decisions about their diabetes care, problem solve to maximize behavior change and play an active role in the health care team with an overarching goal of improving quality of life and diabetes outcomes.

Because culture has a profound relationship with the presentation, diagnosis, and treatment of depression and other common mental disorders,[36] the INDEPENDENT intervention was tailored for the Indian context. In our formative qualitative research with patients, family members, and healthcare workers prior to the study, we found that people with diabetes can feel isolated and distressed when having to eat separately prepared meals (particularly at social gatherings), and that a poor understanding of diabetes or being publicly labeled as having diabetes contributes to poor mental health.[37] In reviewing the content and structure of the INDEPENDENT care model, these stakeholders liked the counseling, activation, and coping mechanisms provided by the intervention. Suggested adaptations included engaging families and counseling patients on how to overcome individual barriers to exercise. Additional cultural adaptations occurred during the implementation of the study. For example, team psychiatrists supported care coordinators in utilizing interventions that were most acceptable to patients, and treatment and recommendations often included meditation or brief deep breathing exercises. Research suggests that mindfulness-based interventions, including deep breathing exercises can improve depression, anxiety and diabetes-related distress. Deep breathing exercises, in particular, have been shown to improve glycemic control and blood pressure among people with T2DM.[39] A process evaluation of the intervention identified that additional cultural tailoring of behavioral intervention components occurred differentially across sites during implementation of the intervention,[38] thus making it difficult to evaluate the impact of adapted components on intervention outcomes.

Strengths of the current study include the rigor of the trial design, use of validated measures for evaluation of anxiety symptoms, the high rate of patient follow-up over the trial period, and our use of multiple imputation to account for missing data. Several limitations of the study must also be acknowledged. First, while the findings suggest that anxiety symptoms among patients with diabetes can improve with collaborative care treatment, the study was designed and powered to assess effects on depression and was

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not designed to test this specific hypothesis. As described above, it is likely that the treatments for depression provided by these collaborative care teams were also effective anxiety treatments. An alternative explanation, however, is that elevated GAD-7 scores in this sample of patients with complex co-morbidity reflected distress, and not a discrete anxiety disorder. The observed improvement over time (86% overall at 24 months) may be explained by the waning of intervention effects, or may reflect the natural course of anxiety in this complex population, the reduction of distress with improvement in diabetes disease control or reduction in depression symptoms, or even unexpectedly effective management of anxiety symptoms by participants in the control group.[40] Given that participants in the control group also exhibited a steady reduction in GAD-7 symptoms over 24 months, future research might explore whether there are critical windows of time in which to intervene (such as with booster sessions) in order to produce more immediate reductions in anxiety symptoms among patients with anxiety. Second, the trial was conducted in diabetes clinics in urban India, and findings may not generalize to diabetes treatment in primary care settings, or in other LMICs, given cultural and contextual differences. Third, potentially important contributors to anxiety were not evaluated in the trial. Given the evidence that social inequalities contribute to global disparities in mental health,[41] future research should examine how stressors associated with culturally specific structural systems, such as caste and religion, impact mental health.

Our findings have implications for future implementation of collaborative care in settings where patients have high rates of comorbid common mental disorders, particularly in LMICs. India has the highest absolute number of cases of anxiety disorder globally, given its substantial population size of 1.2 billion people. The prevalence of anxiety disorders in India has been estimated to be 1.9% and 3.3% for men and women, respectively.[42] Several studies have documented even higher prevalence rates of comorbid depression and anxiety among people with diabetes in India,[43–47] suggesting the need to increase access to effective mental health treatment in this population. This may be particularly important for the management of generalized anxiety disorder, as the diagnostic criteria are psychological symptoms; in cultures where anxiety is predominantly manifest through somatic symptoms, there is a significant risk of under-detection of generalized anxiety disorder.[48] The ability to achieve clinically significant reductions in anxiety symptoms through implementation of a collaborative care model that targets depression suggests the possibility of broadening the base of mental health care in LMICs without requiring additional resources for medical intervention.

In conclusion, this study suggests that a collaborative care intervention to treat depression and poorly controlled diabetes can also lead to clinically significant reduction in anxiety symptoms. These findings extend the literature on the effectiveness of collaborative care for patients with anxiety, depression, and other chronic conditions.

Supplementary Material

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CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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Abbreviations

ACME	average causally mediated effect
GAD-7	Generalized Anxiety Disorder-7
GDP	gross domestic product
GEE	generalized estimating equation
HbA_{1C}	Hemoglobin A_{1C}
HPA	hypothalamic-pituitary-adrenal
INDEPENDENT	INtegrating DEPrEssioN and Diabetes treatment
INR	Indian Rupees
LMIC	low- or middle-income country
PHQ-9	Patient Health Quesitonnaire-9
RD	risk difference
SCL-20	Symptoms Checklist Depression Scale-20
SD	standard deviation
SE	standard error
T2DM	type 2 diabetes

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 2020.
2. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T, et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. The lancet Diabetes & endocrinology. 2017;5(6):423–30. [PubMed: 28456416]
3. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. The Lancet Global health. 2018;6(12):e1352–e62. [PubMed: 30219315]
4. Grigsby AB, Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. Prevalence of anxiety in adults with diabetes: a systematic review. J Psychosom Res. 2002;53(6):1053–60. [PubMed: 12479986]
5. Collins MM, Corcoran P, Perry IJ. Anxiety and depression symptoms in patients with diabetes. Diabetic Medicine. 2009;26(2):153–61. [PubMed: 19236618]
6. Khuwaja AK, Lalani S, Dhanani R, Azam IS, Rafique G, White F. Anxiety and depression among outpatients with type 2 diabetes: A multi-centre study of prevalence and associated factors. Diabetol Metab Syndr. 2010;2:72. [PubMed: 21171976]

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7. Thomas J, Jones G, Scarinci I, Brantley P. A descriptive and comparative study of the prevalence of depressive and anxiety disorders in low-income adults with type 2 diabetes and other chronic illnesses. Diabetes Care. 2003;26(8):2311–7. [PubMed: 12882854]
8. Egede LE, Zheng D, Simpson K. Comorbid Depression is Associated With Increased Health Care Use and Expenditures in Individuals With Diabetes. Diabetes Care. 2002;25(3):464. [PubMed: 11874931]
9. Naicker K, Johnson JA, Skogen JC, Manuel D, Øverland S, Sivertsen B, et al. Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations With Mortality Risk. Diabetes Care. 2017;40(3):352. [PubMed: 28077458]
10. Kircanski K, LeMoult J, Ordaz S, Gotlib IH. Investigating the nature of co-occurring depression and anxiety: Comparing diagnostic and dimensional research approaches. J Affect Disord. 2017;216:123–35. [PubMed: 27554605]
11. Hasan SS, Clavarino AM, Mamun AA, Doi SA, Kairuz T. Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: a meta-analysis of longitudinal studies. Asian journal of psychiatry. 2013;6(6):460–72. [PubMed: 24309855]
12. Zhuang Q-S, Shen L, Ji H-F. Quantitative assessment of the bidirectional relationships between diabetes and depression. Oncotarget. 2017;8(14):23389–400. [PubMed: 28177893]
13. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychological medicine. 2013;43(5):897–910. [PubMed: 22781489]
14. Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A, Ferrari A, et al. The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990–2017. The Lancet Psychiatry. 2020;7(2):148–61. [PubMed: 31879245]
15. Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. American heart journal. 1998;135(5 Pt 1):914–23. [PubMed: 9588425]
16. Surwit RS, Schneider MS, Feinglos MN. Stress and diabetes mellitus. Diabetes Care. 1992;15(10):1413–22. [PubMed: 1425110]
17. Thour A, Nagra R, Gosal A, Sehrawat T, Das S, Gupta Y. Anxiety among patients with diabetes mellitus evaluated using generalized anxiety disorder 7-item scale. Journal of Social Health and Diabetes. 2016;04(02):133–6.
18. Blount A Integrated Primary Care: Organizing the Evidence. Families, Systems, & Health. 2003;21(2):121–33.
19. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. The Cochrane database of systematic reviews. 2012;10:Cd006525. [PubMed: 23076925]
20. Unützer J, Katon W, Callahan CM, Williams JJW, Hunkeler E, Harpole L, et al. Collaborative Care Management of Late-Life Depression in the Primary Care SettingA Randomized Controlled Trial. JAMA. 2002;288(22):2836–45. [PubMed: 12472325]
21. Rollman BL, Belnap BH, Mazumdar S, Houck PR, Zhu F, Gardner W, et al. A randomized trial to improve the quality of treatment for panic and generalized anxiety disorders in primary care. Arch Gen Psychiatry. 2005;62(12):1332–41. [PubMed: 16330721]
22. Craske MG, Stein MB, Sullivan G, Sherbourne C, Bystritsky A, Rose RD, et al. Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. Arch Gen Psychiatry. 2011;68(4):378–88. [PubMed: 21464362]
23. Roy-Byrne P, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. Jama. 2010;303(19):1921–8. [PubMed: 20483968]
24. Kowalski AJ, Poongothai S, Chwastiak L, Hutcheson M, Tandon N, Khadgawat R, et al. The INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) study: Design and methods to address mental healthcare gaps in India. Contemp Clin Trials. 2017;60:113–24. [PubMed: 28642211]
25. Ali MK, Chwastiak L, Poongothai S, Emmert-Fees KMF, Patel SA, Anjana RM, et al. Effect of a Collaborative Care Model on Depressive Symptoms and Glycated Hemoglobin, Blood Pressure, and Serum Cholesterol Among Patients With Depression and Diabetes in India: The INDEPENDENT Randomized Clinical Trial. JAMA. 2020;324(7):651–62. [PubMed: 32809002]

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26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13. [PubMed: 11556941]
27. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Archives of Internal Medicine. 2006;166(10):1092–7. [PubMed: 16717171]
28. De Man J, Absetz P, Sathish T, Desloge A, Haregu T, Oldenburg B, et al. Are the PHQ-9 and GAD-7 Suitable for Use in India? A Psychometric Analysis. Front Psychol. 2021;12:676398-. [PubMed: 34054677]
29. Bischoff T, Anderson SR, Heafner J, Tambling R. Establishment of a Reliable Change Index for the GAD-7. Psychology, Community & Health. 2019;8(1).
30. Honaker J, King G, Blackwell M. Amelia II: A Program for Missing Data. 2011. 2011;45(7):47.
31. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons; 2004.
32. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986;73(1):13–22.
33. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R Package for Causal Mediation Analysis. Journal of Statistical Software; Vol 1, Issue 5 (2014). 2014.
34. R Core Team. R: A language and environment for statistical computing. . Vienna, Austria: R Foundation for Statistical Computing; 2021.
35. Muntingh AD, van der Feltz-Cornelis CM, van Marwijk HW, Spinhoven P, van Balkom AJ. Collaborative care for anxiety disorders in primary care: a systematic review and meta-analysis. BMC family practice. 2016;17:62-. [PubMed: 27250527]
36. Khambaty M, Parikh RM. Cultural aspects of anxiety disorders in India. Dialogues Clin Neurosci. 2017;19(2):117–26. [PubMed: 28867936]
37. Rao D, Lipira L, Kumar S, Mohanraj R, Poongothai S, Tandon N, et al. Input of stakeholders on reducing depressive symptoms and improving diabetes outcomes in India: Formative work for the INDEPENDENT Study. International journal of noncommunicable diseases. 2016;1(2):65–75. [PubMed: 29075675]
38. Johnson LCM, Chwastiak L, Poongothai S, Tandon N, Anjana RM, Aravind S, et al. Adaptations and patient responses to behavioral intervention components in a depression-focused chronic disease care model implemented in India. Translational Behavioral Medicine. 2020;10(1):35–45. [PubMed: 32011720]
39. Noordali F, Cumming J, Thompson JL. Effectiveness of Mindfulness-based interventions on physiological and psychological complications in adults with diabetes: A systematic review. Journal of health psychology. 2015;22(8):965–83. [PubMed: 26721631]
40. Morabia A JUMBO, MRFIT, and the Making of Public Health Epidemiology. Am J Epidemiol 2020 Jun 1;189(6):487–490. [PubMed: 31942923]
41. Yu S Uncovering the hidden impacts of inequality on mental health: a global study. Transl Psychiatry. 2018;8(1):98-. [PubMed: 29777100]
42. Baxter AJ, Charlson FJ, Cheng HG, Shidhaye R, Ferrari AJ, Whiteford HA. Prevalence of mental, neurological, and substance use disorders in China and India: a systematic analysis. The lancet Psychiatry. 2016;3(9):832–41. [PubMed: 27528097]
43. Kanwar N, Sharma RC, Sharma DD, Ramesh, Mokta K, Mokta JK. Prevalence of Psychiatric Comorbidity among Patients of Type 2 Diabetes Mellitus in a Hilly State of North India. Indian J Endocrinol Metab. 2019;23(6):602–8. [PubMed: 32042695]
44. Gururaj G, Varghese M, Benegal V, Rao GN, Pathak K, Singh LK, et al. National Mental Health Survey of India, 2015-16: prevalence, patterns and outcomes. NIMHANS Publication. 2016;129:90–121.
45. Uphoff EP, Newbould L, Walker I, Ashraf N, Chaturvedi S, Kandasamy A, et al. A systematic review and meta-analysis of the prevalence of common mental disorders in people with noncommunicable diseases in Bangladesh, India, and Pakistan. J Glob Health. 2019;9(2):020417-. [PubMed: 31893031]
46. Verma M, Grover S, Tripathy JP, Singh T, Nagaraja SB, Kathirvel S, et al. Co-existing Noncommunicable Diseases and Mental Illnesses Amongst the Elderly in Punjab, India. Eur Endocrinol. 2019;15(2):106–12. [PubMed: 31616502]

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47. Poongothai S, Anjana RM, Pradeepa R, Ganesan A, Umapathy N, Mohan V. Prevalence of depression in relation to glucose intolerance in urban south Indians--the Chennai Urban Rural Epidemiology Study (CURES-76). Diabetes technology & therapeutics. 2010;12(12):989–94. [PubMed: 21128845]

48. Marques L, Robinaugh DJ, LeBlanc NJ, Hinton D. Cross-cultural variations in the prevalence and presentation of anxiety disorders. Expert review of neurotherapeutics. 2011;11(2):313–22. [PubMed: 21306217]

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Table 1:

Baseline characteristics of participants with at least moderate anxiety symptoms in a trial of a collaborative care model for treatment of depression and diabetes in India (n=172)

	Collaborative care group	Usual care group
N	82	90
Age (mean (SD))	52.21 (7.86)	52.38 (8.88)
Female (%)	54 (65.9)	65 (72.2)
Married (%)	65 (79.3)	80 (88.9)
Educational Attainment (%)		
No Education or Unsure	5 (6.1)	9 (10.0)
Primary/Secondary	62 (75.6)	65 (72.2)
Post-Secondary	15 (18.3)	16 (17.8)
Monthly Household Income (%)		
<10000 INR	22 (26.8)	34 (37.8)
10001-20000 INR	23 (28.0)	24 (26.7)
>20000 INR	37 (45.1)	32 (35.6)
PHQ-9 (%)		
Moderate (10-14)	50 (55.6)	44 (53.7)
Moderately-Severe (15-19)	36 (40.0)	34 (41.5)
Severe (19+)	4 (4.4)	4 (4.9)
GAD-7 (%)		
Moderate (10-14)	49 (54.4)	46 (56.1)
Severe (15+)	41 (45.6)	36 (43.9)
HbA_{1C} (mean (SD))	9.85 (2.05)	9.37 (1.89)

Abbreviations: SD, standard deviation. INR, Indian Rupees. SCL-20, Symptoms Checklist Depression Scale. GAD-7, Generalized Anxiety Disorder-7. HbA_{1C}, Hemoglobin A_{1C}.

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Table 2:

Clinically significant reduction in anxiety symptoms and use of antidepressant medications, stratified by time and treatment group, in a trial of a collaborative care model for treatment of depression and diabetes in India (n=172)

		Proportion (SE) with clinically significant reduction in anxiety symptoms			***Proportion (SE) on antidepressant medications***		
Time	**N**	**Collaborative care group**	**Usual care group**	**p**	**Collaborative care group**	**Usual care group**	**P**
0m	172	0% (1.0%)	0% (0.1%)	0.46	3.8% (2.1%)	3.2% (1.9%)	0.82
6m	162	48.4% (5.3%)	30.0% (4.6%)	0.019	26.7% (5.0%)	8.5% (3.1%)	0.003
12m	167	65.7% (5.1%)	41.4% (5.0%)	0.002	32.3% (5.2%)	11.6% (3.5%)	0.002
18m	165	79.6% (4.5%)	65.7% (4.8%)	0.06	20.4% (4.5%)	12.7% (3.7%)	0.23
24m	167	85.6% (4.1%)	86.7% (3.6%)	0.68	11.1% (3.6%)	10.3% (3.3)	0.95

Abbreviations: SE, standard error.

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Table 3:

Primary and moderation model estimates of risk difference in anxiety symptom reduction among patients with at least moderate anxiety symptoms a trial of a collaborative care model for treatment of depression and diabetes in India (n=172)

	6 months			12 months			18 months			24 months		
	RD	***SE***	***p***	***RD***	***SE***	***p***	***RD***	***SE***	***p***	***RD***	***SE***	***p***
Primary Analysis [1]												
Control	--	--	--	--	--	--	--	--	--	--	--	--
Intervention	**0.17**	**0.07**	**0.02**	**0.23**	**0.07**	**0.002**	0.13	0.07	0.06	−0.02	0.05	0.68
Moderators [2]												
Age												
35-49	--	--	--	--	--	--	--	--	--	--	--	--
50-64	0.08	0.16	0.61	−0.11	0.16	0.48	0.26	0.16	0.10	**0.29**	**0.12**	**0.02**
65+	−0.35	0.29	0.23	0.07	0.25	0.79	0.39	0.22	0.08	**0.50**	**0.17**	**0.004**
Sex												
Male	--	--	--	--	--	--	--	--	--	--	--	--
Female	−0.01	0.17	0.96	−0.04	0.16	0.81	0.16	0.14	0.25	−0.01	0.12	0.95
Marital Status												
Unmarried	--	--	--	--	--	--	--	--	--	--	--	--
Married	0.00	0.19	0.99	0.09	0.21	0.65	−0.19	0.20	0.35	−0.01	0.14	0.94
Education												
No Education/Unsure	--	--	--	--	--	--	--	--	--	--	--	--
Primary/Secondary	−0.11	0.28	0.71	0.06	0.26	0.82	−0.21	0.18	0.22	−0.20	0.25	0.42
Post-Secondary	−0.06	0.32	0.84	−0.27	0.30	0.37	−0.23	0.22	0.30	−0.08	0.26	0.77
Monthly Household Income												
<10,000 INR	--	--	--	--	--	--	--	--	--	--	--	--
10,001-20,000 INR	−0.13	0.19	0.51	−0.08	0.20	0.67	−0.01	0.18	0.97	−0.13	0.14	0.34
>20,000 INR	0.09	0.18	0.62	−0.17	0.18	0.34	0.03	0.17	0.86	−0.04	0.13	0.73
HbA_{1C}												
<8%	--	--	--	--	--	--	--	--	--	--	--	--
≥8%	−0.15	0.19	0.43	−0.12	0.18	0.49	−0.29	0.16	0.08	−0.06	0.11	0.61
PHQ-9												
Moderate	--	--	--	--	--	--	--	--	--	--	--	--
Moderately Severe or Severe	0.12	0.15	0.43	0.18	0.15	0.22	0.19	0.14	0.17	0.10	0.11	0.36
GAD-7												
Moderate	--	--	--	--	--	--	--	--	--	--	--	--

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	6 months			12 months			18 months			24 months		
	RD	***SE***	***p***	***RD***	***SE***	***p***	***RD***	***SE***	***p***	***RD***	***SE***	***p***
Severe	0.24	0.15	0.11	0.15	0.15	0.30	0.07	0.13	0.58	−0.12	0.11	0.26

Abbreviations: RD, risk difference. SE, standard error. INR, Indian Rupees. A1C, HbA_{1C}, Hemoglobin A_{1C}. SCL-20, Symptoms Checklist Depression Scale.

Footnotes:

[1] Treatment × time interaction effect

[2] Treatment × time × moderator interaction effect.

Bold text indicates statistically significant estimate ($p < 0.05$).

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Table 4:

Mediation of intervention effects on anxiety symptom reduction by antidepressant use among patients with at least moderate anxiety symptoms in a trial of a collaborative care model for treatment of depression and diabetes in India (n=172)

	RD	SE	p
Intervention → anti-depressant use			
6 months	**0.18**	**0.06**	**<0.001**
12 months	**0.20**	**0.05**	**<0.001**
18 months	0.07	0.05	0.20
24 months	0.00	0.05	0.95
Anti-depressant use → anxiety symptom reduction	0.05	0.04	0.10
Average causal mediation effect	0.005	0.005	0.32
Direct effect	**0.108**	**0.03**	**0.002**
Total effect	**0.113**	**0.03**	**<0.001**
% Mediated	4.0%	5.5%	0.47

Abbreviations: RD, risk difference. SE, standard error.

Footnotes: **Bold text** indicates statistically significant estimate ($p < 0.05$).