Archives of Psychiatry and Psychotherapy, 2019; 2: 41–47

DOI: 10.12740/APP/103602

Two birds with one stone: How depression and distress in diabetes respond to antidepressants

Harshil Yogesh Chauhan, Keshava Kota Pai

Summary

Aim of the study: As with other chronic diseases, depression is more prevalent among the patients with type 2 diabetes mellitus. Depression and diabetes-related distress adversely affect diabetes-related outcomes. This study aims at identifying comprehensive effects of antidepressant treatment in patients with type 2 diabetes mellitus and co-morbid depression.

Material and methods: 124 subjects with type 2 diabetes mellitus were screened for depression using the Patient Health Questionnaire – 9 (PHQ-9). 34 subjects with PHQ score > 10 were recruited to the study and rated on Beck's Depression Inventory (BDI), the Montgomery Asberg Depression Rating Scale (MADRS) and the Diabetes Distress Scale (DDS). Subjects' glycemic parameters – Fasting Blood Sugar (FBS), Post-Prandial Blood Sugar (PPBS) and Glycated Hemoglobin (HbA1C) were recorded. All subjects were treated with either escitalopram or mirtazapine for a period of 8 weeks. Post-intervention changes in BDI, MADRS, DDS and glycemic parameters were noted.

Results: Antidepressant treatment has led to a significant improvement in depressive symptoms (reduction in BDI: 19.13 ± 8.06; reduction in MADRS: 17.16 ± 5.3) and diabetes-related distress (reduction in DDS: 17.81 ± 8.93). Significant improvements were also noticed in glycemic parameters: FBS (p= 0.015) and HbA1C (p=0.004).

Discussion: Distress in diabetes leads to poor self-care and higher HbA1C, while depression predicts poorer glycemic control, more complications and higher health-care costs. Improvement in depression and distress in diabetes yields much greater benefits.

Conclusions: Antidepressant treatment with escitalopram or mirtazapine can effectively treat depression and reduce diabetes-related distress in patients with type 2 diabetes mellitus. Beneficial effects are noted on glycemic parameters as well.

depression, type 2 diabetes mellitus, diabetes distress, antidepressant

INTRODUCTION

According to WHO estimates, 422 million adults in the world were living with diabetes in 2014 and about half of them were residents of South-East Asia and Western Pacific regions [1]. As per International Diabetes Federation, India had around 73 million cases of diabetes in 2017,

Harshil Yogesh Chauhan[1], Keshava Kota Pai[2]: [1]Gujarat Cancer Society Medical College, Hospital and Research Center, Ahmedabad; [2]Kasturba Medical College Hospital, Mangalore; India
Correspondence address: harshells4u@gmail.com

second only to China [2]. Diabetes is a chronic medical illness and as seen with other chronic medical illnesses, depression is found to be its common comorbidity [3]. Research has yielded too compelling evidence to overlook the bidirectional association between diabetes and depression [4]. Some possible shared mechanisms include activated innate immunity and inflammation, HPA axis dysregulation, insulin resistance and disturbances of circadian rhythm [5]. As regards the diabetes-depression relationship, diabetes poses a 24% increased risk of developing depression [6].

What calls for even more attention is that once set in, depression hampers the course of diabetes in many ways. Patients with diabetes and co-morbid depression have poorer self-management, poorer adherence to medications [7], along with worse glycemic control [8]. Depression also carries higher risk of subsequent micro – and macro-vascular complications in patients with type 2 diabetes [9]. Other adversities include accelerated cognitive decline [10], impaired quality of life [11] and almost 50-75% increased health care expenditure [12]. Having depression also carries higher mortality risk in patients with diabetes mellitus [13].

Benefits of recognizing and managing depression in patients with diabetes mellitus may go well beyond just improvements in depressive symptoms and have multi-fold implications [14]. Unfortunately, there exists a huge gap between patients with diabetes who are depressed and the ones who actually receive the diagnosis of depression [15]. Frequently under-recognized, screening for depression in diabetes becomes the first and pivotal step in this direction.

Research has examined various treatment modalities like antidepressant medications, cognitive behavioral therapy (CBT), supportive psychotherapy, etc. for treatment of depression in diabetes mellitus. While these approaches are useful in treating depression, studies of their effect on glycemic parameters have yielded mixed results [14]. Most of the research has emerged from North-American or European countries, with very limited information from other regions of the world [16]. Indian studies of depression in diabetes have mainly focused on epidemiological findings. It is surprising that in India, which is argued to be the diabetic capital of the world, research evidence on treatment of depression in diabetes has been scarce.

The aim of this study was to examine the effects of antidepressants on depression, distress, self-care behaviours and glycemic control in type 2 diabetes mellitus. We examined antidepressants from two different classes – escitalopram and mirtazapine. Findings on self-care behaviours will be published later. Considered as the first choice antidepressant treatment by some authors [16, 17], selective Serotonin Reuptake Inhibitors (SSRI) have been found efficacious in the management of depression in diabetes. So far, studies evaluating mirtazapine in patients with diabetes mellitus have been very scarce.

METHODOLOGY

The study had an open label follow-up design. It was approved by a scientific and ethical committee of the institute. It was carried out in an outpatient department as well as an outreach clinic of the tertiary care teaching hospital in the urban area of Southern India. The sample size included in our study was 34.

Males and females aged 35-65 years attending a medical outpatient department or an outreach medical clinic, diagnosed with type 2 diabetes mellitus as per American Diabetes Association criteria [18], were approached for the study and duly briefed on the study and its purpose. Inclusion criteria were diagnosis of type 2 diabetes mellitus for at least 3 years and Patient Health Questionnaire – 9 (PHQ-9) score of > 10 [19]. A written informed consent was collected from all participants upon their approval. Sociodemographic details of the participants were recorded. Exclusion criteria were: 1) diagnosis of depression prior to onset of type 2 diabetes mellitus, 2) antidepressant treatment or any other alternative form of therapy for depression at baseline, 3) complications of diabetes mellitus or other serious medical comorbidities such as ischaemic heart diseases, cerebrovascular accidents, thyroid disorders etc., and 4) history of alcohol use disorder, bipolar disorder or psychotic disorder, or other major psychiatric comorbidity.

The PHQ-9 was used as a screening questionnaire for the study subjects. The other

scales which were used in the study were the Montgomery-Asberg Depression Rating Scale (MADRS) [20], Beck's Depression Inventory (BDI) [21] and the Diabetes Distress Scale (DDS) [22]. Primary outcome measures for this study were changes in these scales and glycemic parameters – fasting blood sugar (FBS), post-prandial blood sugar (PPBS) and glycated hemoglobin (HbA1C) – following treatment.

Enrolled subjects underwent a comprehensive psychiatric evaluation on the first appointment. They were rated on the MADRS, BDI and DDS. Pre-intervention glycemic parameters such as FBS, PPBS and HbA1C were recorded for all participants. The subjects were put on antidepressant treatment – either escitalopram (5-20 mg) or mirtazapine (7.5-30 mg). Dosing and titration was decided by a treating psychiatrist based on patient response and tolerance. As per Cochrane review [23], SSRIs have robust evidence for efficacy in the treatment of depression comorbid with diabetes mellitus. Hence escitalopram, an SSRI with the least drug-drug interaction, was chosen as one of the two antidepressant agents in our study. Due to SSRIs' unfavourable side effect profile, we chose mirtazapine as the second antidepressant agent, to be prescribed to subjects with concomitant complaints such as gastritis, sexual dysfunction, etc.

Follow-ups were done at two weeks, four weeks and eight weeks in a psychiatric outpatient department. Follow-up interviews consisted in inquiries into subjects' response to treatment and possible side effects. Side effects check list was provided to the study subjects. Change of the antidepressant, if necessary, was allowed only during the first two weeks. In such cases, the second antidepressant was considered for the final analysis. Based on their symptom profile or side effects, some of the participants were also put on benzodiazepines. Final data collection was conducted at 8 weeks, when the subjects were rated on the PHQ-9, BDI, MADRS, DDS and their glycemic parameters were recorded.

We analysed the data in terms of measures such as the mean, median, standard deviation, frequency and percentage. Collected data was also subjected to paired 't' test to compare pre – and post-intervention values of various rating scales and glycemic parameters. The Mann Whitney U test and Kruskal Wallis test were used to assess demographic differences between various outcome measures. The Pearson coefficient was used to analyse correlations between outcome variables. Unpaired 't' test was used to analyse differences between treatment with escitalopram and mirtazapine in the study population. A 'p' value of ≤ 0.05 was considered to be statistically significant.

RESULTS

A total of 124 participants with type 2 diabetes mellitus were screened for the study. Out of 90 participants who were excluded from the study, 83 did not meet inclusion criteria and 7 refused to consent. Remaining 34 participants were included in the study.

Table 1. Socio-demographic details of study population

Demographic variable		Frequency
Age	50 years and below	13 (38.2%)
	51-60 years	13 (38.2%)
	Above 60 years	8 (23.5%)
Gender	Male	12 (35.3%)
	Female	22 (64.7%)
Education	Below 10th grade	23 (67.6%)
	10th grade and above	11 (32.4%)
Occupation	Housewife	15 (44.1%)
	Manual labourer	10 (29.4%)
	Other	9 (26.5%)
Marital status	Married	27 (79.4%)
	Unmarried/ Widow(er)	7 (20.6%)
Socio-economic status	Lower	17 (50%)
	Middle	17 (50%)
Duration of type 2 diabetes	5 years or less	13 (38.2%)
	6-10 years	13 (38.2%)
	More than 10 years	8 (23.5%)

Table 1 depicts socio-demographic characteristics of the study population. 21 subjects (61.7%) were above the age of 50 years. Females represented almost two thirds (22 out of 34) of the study group. Most of the study subjects (27 out

of 34, 79.4%) were married. Average duration of diabetes in our study population was eight years.

All subjects were put on treatment with either escitalopram or mirtazapine. However, the choice of antidepressant was not randomized, and it was treating psychiatrist's discretion. Final doses of antidepressants used depended upon the subject's response to treatment and tolerability. 22 subjects (64.7%) received escitalopram and 12 subjects (35.3%) received mirtazapine. Average doses of escitalopram and mirtazapine were 7.28 mg and 7.5 mg, respectively. 11 subjects (32.3%) required additional benzodiazepines for insomnia or excessive anxiety.

Out of the total of 34 subjects recruited for the study, 2 subjects on mirtazapine were lost to follow-up. 32 subjects completed follow-up period of eight weeks. Out of those 32 subjects, 5 did not agree to undergo glycated haemoglobin (HbA1C) test due to the cost of the test. The remaining 27 were taken into analysis for this parameter.

Table 2. Changes in measures of depression and distress following treatment.

Scale		Mean ± SD (Range)	Mean change ± SD	p value
PHQ-9 (N=32)	Pre	12.6 ± 2.0 (10-19)	-8.1 ± 2.2	<0.0001
	Post	4.5 ± 2.2 (1-12)		
BDI (N=32)	Pre	30.6 ± 9.6 (14-63)	-19.1 ± 8.1	<0.0001
	Post	11.5 ± 6.3 (2-35)		
MADRS (N=32)	Pre	26.6 ± 6.7 (14-48)	-17.2 ± 5.3	<0.0001
	Post	9.4 ± 5.5 (2-27)		
DDS (N=32)	Pre	43.4 ± 10.6 (28-90)	-17.8 ± 8.9	<0.0001
	Post	25.6 ± 5.9 (17-38)		

Shown in table 2 are scores on depression and distress rating scales pre – and post-treatment. For our study, we considered p value of <0.05 to be statistically significant. Antidepressant treatment led to significant improvement in both self-rated and clinician-rated scales for depression (BDI: – 19.1±8.1, p<0.0001 and MADRS: – 17.2±5.3, p<0.0001) at 2 months. We also observed significant improvement in diabetes-related distress (change in DDS: – 17.8±8.9, p<0.0001).

We observed positive trends in all three glycemic parameters at end of the study period. FBS (mean change: – 19.4, p=0.015) and HbA1C (mean change: – 1.2, p=0.004) improved significantly; however, reduction in PPBS did not reach statistical significance (p=0.077).

Analyses using the Mann Whitney and Kruskal Wallis tests showed that the study participants with different demographic characteristics did not differ significantly in terms of outcome variables except that males had significantly higher improvement on BDI scores when compared to females (p=0.044), possibly due to more frequent subjective reporting of depressive symptoms in females [24].

The Pearson correlation coefficient (r) showed that improvement in BDI scores correlated with improvements in MADRS and DDS scores, and vice versa. Similarly, HbA_{1C} improvement correlated with improvements in FBS and PPBS, and vice versa. However, improvement in DDS scores did not correlate with improvements in MADRS.

We also studied differential effects of escitalopram (n=22) and mirtazapine (n=10) on the study population. Using unpaired t test, we found that improvements in PHQ-9, BDI, MADRS, DDS or glycemic parameters did not differ significantly between the escitalopram and mirtazapine groups (mean change in PHQ: escitalopram – 8.27±2.53 vs mirtazapine – 7.70±1.34, p=0.413; mean change in BDI: escitalopram – 17.18±5.30 vs mirtazapine – 23.40±11.34, p=0.126; mean change in MADRS: escitalopram – 17.00±5.42 vs mirtazapine – 17.50±5.30, p=0.809; mean change in DDS: escitalopram – 16.86±6.79 vs mirtazapine – 19.90±12.65, p=0.500; mean change in FBS: escitalopram – 20.14±50.62 vs mirtazapine – 17.80±14.85, p=0.844; mean change in PPBS: escitalopram – 22.55±60.22 vs mirtazapine – 10.60±55.43, p=0.589; mean change in HbA1C: escitalopram: – 1.7±2.40 vs mirtazapine – 0.5±0.65, p=0.069)

Highest reported side effects were nausea/vomiting and decreased appetite, which were re-

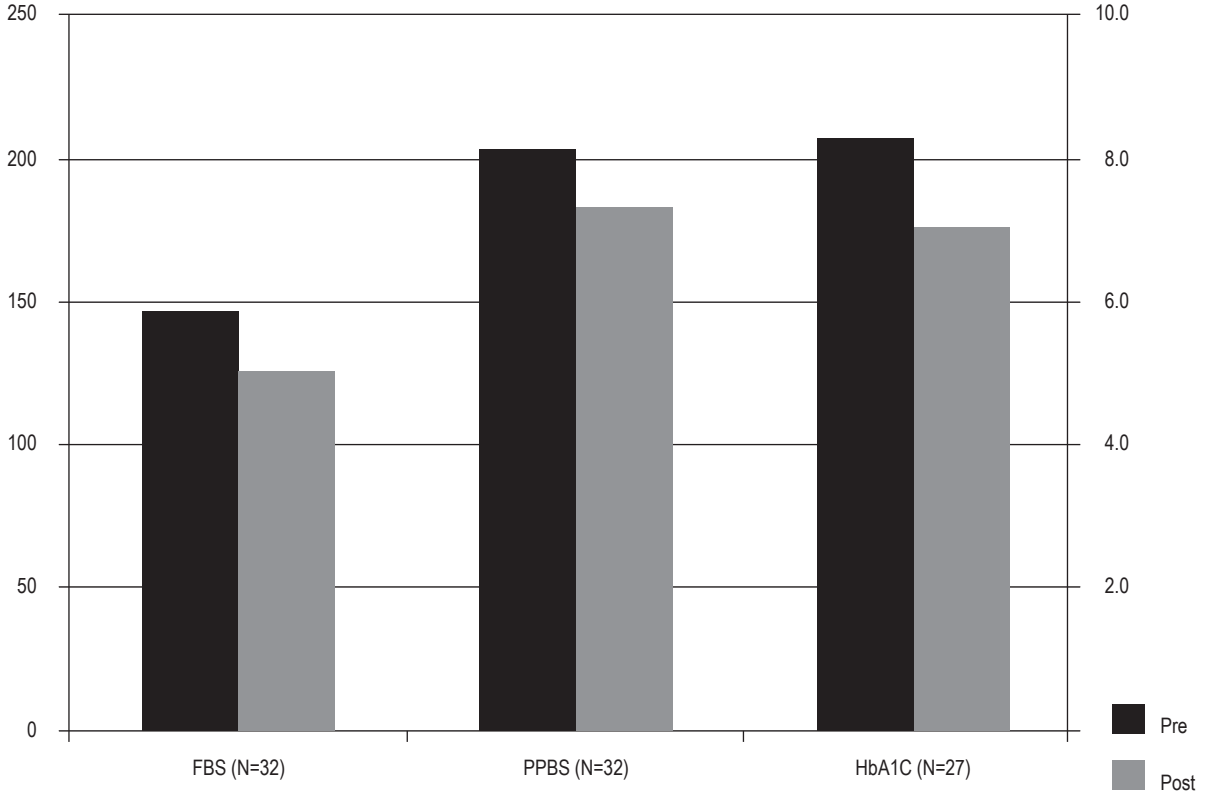

Figure 1. Changes in glycemic parameters following treatment

ported by five patients (14.7%). Other frequently reported side effects were giddiness, dry mouth and drowsiness. Two patients reported weight gain with mirtazapine. Two patients required change of antidepressant from mirtazapine to escitalopram due to excessive sedation. No other serious adverse event, death or suicide was reported during the study.

DISCUSSION

In our study, we were able to recruit 27.4% participants out of the 124 screened patients with type 2 diabetes mellitus. This result emphasizes the magnitude of the problem depression-diabetes dyad poses to clinicians. Previous research has shown that every 10th person fills an antidepressant prescription within 5 years of diagnosis of diabetes mellitus, with the maximum risk present in the first year [25].

This study found that treatment with escitalopram or mirtazapine leads to a significant improvement in both depression and diabetes-related distress. Treatment also resulted in significant benefits in fasting blood glucose and glycated haemoglobin with non-significant reduction in post-prandial blood glucose. In this study, we also assessed self-care behaviours following antidepressant treatment. These findings will be published later. Previous research by Gehlawat and colleagues also reported improvement in depression and glycemic control while using escitalopram for treatment of depression in diabetes mellitus [26]. Other researchers found non-significant reductions in fasting blood glucose and glycated haemoglobin with open-label escitalopram treatment [27]. Overall, SSRIs are found to have beneficial effect on glycemic control [23]. Mirtazapine, indirectly through increased appetite and weight gain, may worsen glycemic control. However, when used in patients with diabetes mellitus, mirtazapine was shown to cause weight gain, but also resulted in non-significant improvements in glycemic parameters [28]. Whether improvement in glycemic control due to improved depression outcomes with mirtazapine overrides worsened glycemic control is still a matter for research. We did not find significant differences between treatment with escitalopram and mirtazapine in depression, distress or glycemic control.

Distress in diabetes is seen as a negative emotional response to the burden of living with a chronic illness and demanding self-care behaviours. It may be considered as a normal anxiety response to the burden of diagnosis, but higher distress could mean poor quality of life [29], increased HbA1C and limited self-care [30]. While depression and diabetes-related distress are partly overlapping constructs, they cannot be used interchangeably [31]. The fact that the presence of depression may act as an amplifier for diabetes-related distress, it is imperative that treatment strategies target both simultaneously. Improvement in diabetes-related distress with antidepressant treatment noted in our study could suggest a simple strategy to overcome distress when depression is existent.

The strength of our study was that it reflected a real-world setting, where the treating psychiatrist had the freedom of choosing type and dose of antidepressant. We approached patients who attended the outpatient department and outreach clinic of a tertiary care hospital for treatment of diabetes mellitus, so there are high chances that we picked set of patients who would not have sought a psychiatrist's help for their depression. We also studied antidepressant effects on multiple facets in diabetes – depression, diabetes-related distress and self-care with glycemic control.

The limitations included an open-label design, lack of control arm or randomization, and a small sample size. Because of a smaller sample size, generalizability of the findings remains uncertain. Chances are that patients with complications of diabetes mellitus who might have been more severely depressed were excluded from the study. We did not compare the two study drugs – escitalopram and mirtazapine. Further, a follow-up period of eight weeks may be too short to comment upon long-term effects of antidepressant therapy in diabetes.

To conclude, antidepressant treatment with escitalopram or mirtazapine improves depression and distress in patients with type 2 diabetes mellitus and leads to positive effect on glycemic control. Further research with a larger sample size and better study design is recommended to investigate the use of mirtazapine in diabetes.

Acknowledgements

We would like to thank our colleagues in the department and the hospital for their valuable support in the study. We are grateful to our patients.

REFERENCES

1. World Health Organization. Global report on diabetes. Geneva: World Health Organization Press; 2016.
2. International Diabetes Federation. IDF Diabetes Atlas, 8th ed. Brussels: International Diabetes Federation; 2017.
3. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011; 13(1):7-23.
4. Pan A, Lucas M, Sun Q, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med. 2010; 170(21):1884-1891.
5. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: The search for shared mechanisms. Lancet Diabetes Endocrinol. 2015; 3(6):461-471.
6. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. Diabetologia. 2010; 53(12):2480-2486.
7. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care. 2004; 27(9):2154-2160.
8. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: A meta-analytic review of the literature. Diabetes Care. 2000; 23(7):934-942.
9. Lin EH, Rutter CM, Katon W, et al. Depression and advanced complications of diabetes: A prospective cohort study. Diabetes Care. 2010; 33(2):264-269.
10. Padilla VL, Rustad JK, Harvey PD, et al. Neurocognitive impairment in patients with comorbid diabetes mellitus and depression. Pers Med Psychiatry. 2017; 1-2:2-10.
11. Schram MT, Baan CA, Pouwer F. Depression and quality of life in patients with diabetes: A systematic review from the european depression in diabetes (EDID) research consortium. Curr Diabetes Rev. 2009; 5(2):112-119.
12. Simon GE, Katon WJ, Lin EH, et al. Diabetes complications and depression as predictors of health service costs. Gen Hosp Psychiatry. 2005; 27(5):344-351.
13. Jeong JH, Um YH, Ko SH, et al. Depression and mortality in people with type 2 diabetes mellitus, 2003 to 2013: A nationwide population-based cohort study. Diabetes Metab J. 2017; 41(4):296-302.
14. Markowitz S, Gonzalez JS, Wilkinson JL, et al. Treating depression in diabetes: Emerging findings. Psychosomatics. 2011; 52(1):1-18.
15. Gary TL, Crum RM, Cooper-Patrick L, et al. Depressive symptoms and metabolic control in african-americans with type 2 diabetes. Diabetes Care. 2000; 23(1):23-29.
16. Petrak F, Baumeister H, Skinner TC, et al. Depression and diabetes: Treatment and health-care delivery. Lancet Diabetes Endocrinol. 2015; 3(6):472-485.

17. Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: A systematic review. Acta Neuropsychiatr. 2017; 29(3):127-139.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33(Suppl 1):S62-S69.
19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9):606-613.
20. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134(4):382-389.
21. Beck AT, Beamesderfer A. Assessment of depression: The depression inventory. Mod Probl Pharmacopsychiatry. 1974; 7:151-169.
22. Polonsky WH, Fisher L, Earles J, et al. Assessing psychosocial distress in diabetes. Diabetes Care. 2005; 28(3):626-631.
23. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. Cochrane Database Syst Rev. 2012; 12:CD008381.
24. Piccinelli M, Wilkinson G: Gender differences in depression: Critical review. Br J Psychiatry. 2000; 177(6):486-492.
25. Cleal B, Panton UH, Willaing I, et al. Incidence of filled antidepressant prescriptions among people with newly diagnosed diabetes and its interaction with occupational status within the working population of Denmark 1996–2010. Prim Care Diabetes. 2018; 12(4):305-311.
26. Gehlawat P, Gupta R, Rajput R, et al. Diabetes with comorbid depression: Role of SSRI in better glycemic control. Asian J Psychiatr. 2013; 6(5):364-368.
27. Amsterdam JD, Shults J, Rutherford N, et al. Safety and efficacy of s-citalopram in patients with co-morbid major depression and diabetes mellitus. Neuropsychobiology. 2006; 54(4):208-214.
28. Song HR, Woo YS, Wang HR, et al. Does mirtazapine interfere with naturalistic diabetes treatment? J Clin Psychopharmacol. 2014; 34(5):588-594.
29. Carper MM, Traeger L, Gonzalez JS, et al. The differential associations of depression and diabetes distress with quality of life domains in type 2 diabetes. J Behav Med. 2014; 37(3):501-510.
30. Fisher L, Polonsky W, Hessler DM, et al. When is diabetes distress clinically meaningful?: Establishing cut points for the diabetes distress scale. Diabetes Care. 2012; 35(2):259-264.
31. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: Time for an appraisal. Lancet Diabetes Endocrinol. 2015; 3(6):450-460.