Original Article

The effects of anti-depressants on depression symptom scores at 12 months follow-up in patients with cardiometabolic disease: Results from a large primary care cohort

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Abstract

Background: Evidence on the long-term usefulness of anti-depressants in managing depression in cardiometabolic disease is limited. **Aim:** We examined the effects of anti-depressant prescribing on depressive symptoms at 12 months follow-up in patients with cardiometabolic disease and a positive depression screening result at baseline. **Design and Setting:** We retrospectively reviewed routine UK primary care data for patients with coronary heart disease, diabetes and previous stroke for the year 2008–2009. 35,537 patients with one of the three above diseases underwent depression screening using the Hospital Anxiety and Depression Scale (HADS-D). Of 7080 patients with a positive screening result (HADS-D ≥ 8), 3933 (55.5%) patients had a repeat HADS-D recorded at 12 months follow-up. **Methods:** We compared the change in HADS-D at follow-up and remission rate in those who were prescribed anti-depressants (n = 223) against those who were not (n = 3710). **Results:** The mean change in HADS-D from baseline, for the nonprescribed group was similar to the reduction observed in patients who were continuously prescribed (n = 93) with anti-depressants during follow-up. Patients who were prescribed intermittently (n = 72) or only one (n = 58) prescription during follow-up had a lower reduction in HADS-D compared to the nonprescribed group. There was no difference in remission rates between continuously prescribed and the nonprescribed group, but remission was lower in patients prescribed intermittently and single prescription. **Conclusion:** Improvement in depressive symptoms in patients with cardiometabolic disease at 12 months was not any better in patients prescribed with anti-depressants compared to the nonprescribed group. The role of anti-depressants in the management of depression in cardiometabolic disease merits further investigation.

Keywords: Anti-depressants' effectiveness, anti-depressants' efficacy, coronary heart disease, cardiometabolic disease, depression, diabetes, primary care, stroke

Introduction

Depression is up to 2–3 times more common in patients with cardiometabolic diseases such as coronary heart disease (CHD), diabetes and stroke, as compared to its prevalence in the general population.[1-3] Prevalence estimates of depression vary from 15% to 25% in patients with cardiometabolic diseases such as CHD, diabetes and previous stroke.[4-6] Depression, co-morbid with these cardiometabolic diseases, has detrimental effects on mortality, clinical outcomes, treatment adherence and functional outcomes such as the ability to carry out activities of daily living.[5,7-10] Barth *et al.* reported in a meta-analysis of 20 studies that the risk of death in patients with depressive symptoms and CHD was 2 times higher compared to risk of death in patients with CHD and no depressive symptoms (odds ratio [OR], 2.24; 95% confidence interval [CI] 1.37–3.60).[9]

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A review assessing poststroke mortality reported increased odds (OR 1.22, 95% CI 1.02–1.47) for a period of 2–5 years among patients with depressive symptoms based on findings from 13 studies.[11] Another meta-analysis has reported that the prevalence of co-morbid depression with diabetes is associated with a variety of diabetes complications such as diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction.[12] In Scotland, 5.6% of the adult population suffers from diabetes while 8.3% suffer from either CHD or previous stroke.[13] Based on previous findings, the reported prevalence rate of depressive symptoms in this group of patients is 19.9% in Scotland, which is similar to prevalence rates in other countries.[14]

Considering the increased prevalence and associated complications, the American Heart Association Science Advisory recommended routine depression screening for all patients with CHD in 2008.[15] In UK, the National Institute of Health and Clinical Excellence recommends that depression screening in any chronic disease group should be targeted toward high-risk patient groups.[16] The rationale of depression screening in patients with cardiometabolic disease and co-morbid depression is to facilitate early identification and initiation of appropriate treatment. The major drawbacks of the current evidence on use of anti-depressants in treatment of depression with cardiometabolic diseases include little availability of data on effectiveness (anti-depressants leading to complete remission of depressive symptoms) and dearth of evidence on longer follow-up (>6 months). There have been only four trials looking at the remission rates resulting from the use of anti-depressants for depressive symptoms in patients with CHD),[17,18] with three trials investigating outcomes at duration of follow-up <6 months[19-21] and one trial looking at 18 months follow-up.[22] The evidence for patients with depression symptoms in diabetes is similar,[23,24] with four trials examining remission rates[25-28] and one of them looking at follow-up duration of 52 weeks.[28] For patients with poststroke depression,[29] the remission rate was examined for five trials but no data on longer follow-up.

In this paper, we describe how we used a large primary care cohort to examine the effects, if any, of anti-depressant prescribing on depression symptom scores at 12 months follow-up, in patients with chronic disease and a positive depression screening result, at baseline.

Methods

Ethics statement

We received approval from the West of Scotland Research Ethics Committee to undertake this work. The work involved retrospective analysis of a large routinely collected dataset which was completely anonymized and the research team did not have access to patient identifiers, hence individual patient consent was not obtained. NHS Greater Glasgow and Clyde enhanced services data group, which was the authorized "guardian" of this data set, granted the permission to analyze the data.

Study design and participants

The data reported in this paper comes from the West of Scotland, with a population of circa 1.8 million served by two different health boards. The local health boards oversee a program of incentivized depression screening in chronic disease as part of a wider chronic disease management program of "local enhanced services" (LES). These are contractual arrangements at a local health board level, which family practices can opt into and are designed to augment the basic quality outcomes framework (QOF) specification by incentivizing additional indicators that are deemed to be particularly important for a given geographical area. The QOF is part of UK wide, pay for performance, General medical services contract for primary care physicians.[30] General practices in the health boards were paid under the LES scheme to carry out a comprehensive annual health assessment, which included depression screening using the Hospital Anxiety and Depression Score-depressive subscale or HADS-D,[31] for all patients with three common cardiometabolic conditions, CHD, diabetes, and stroke. This included all patients with three cardiometabolic conditions, irrespective of whether they were incident or prevalent cases and their treatment status. The annual health assessment was usually carried out by a practice nurse and lasted approximately 1 h.

We anonymized the routinely collected data returned from the health assessments and used it for this study with permissions from NHS Greater Glasgow and Clyde enhanced the services data group. We restricted our analysis to adults aged from 18 to 90 and health assessments recorded between April 01, 2008 and March 31, 2009. A total of 125,143 patients were listed as having at least one of the three diseases-CHD, diabetes or stroke in the year 2008–2009, and they all underwent a comprehensive health assessment during the observation period in the "DepChron" dataset.[14] Of the total sample, 10,670 (8.5%) patients were under treatment for depression and were thus exempt from screening. The remaining 114,473 (91.5% of total sample size) patients were eligible for depression screening. However, the uptake of depression screening was poor and only undertaken in 35,537 (31.1% of those eligible). We analyzed the health assessment records between April 01, 2009 and March 31, 2010 to look at 12 months follow-up HADS-D, for those who were screened in the 1st year of study and noted to have a positive HADS-D score.

Measurement of variables

The HADS-D gives a total score of 0–21, we used a threshold of ≥8 to define the presence of depressive symptoms, as endorsed by national guidelines.[32] We calculated the change in HADS-D using the respective scores for the 1st year (2008–2009) and for the 2nd year (2009–2010) of health assessments. We analyzed the prescription records for patients who were screened and noted to have depressive symptoms between the dates of first and second assessment, which gave a follow-up duration of approximately 12 months. We excluded amitriptyline from the list of anti-depressants as it is often prescribed for other indications like chronic pain.

We divided patients into four prescription groups based on the pattern of prescribing described in their medical records: Continuous prescription group (anti-depressants prescribed without a break, single prescription group (only one prescription of anti-depressant recorded in the observation period) intermittent group (anti-depressants prescribed with a gap between two prescriptions of anti-depressants longer than 3 months), and no anti-depressant prescriptions.

We used the area based Scottish Index of Multiple Deprivations (SIMD) as a measure of socioeconomic status.[33] The SIMD score was divided into quintiles from 1 to 5 with Q1 representing the most deprived area. Number of co-morbid conditions (range: 1–3) represented a combination of one or more of the three cardiometabolic diseases under investigation: CHD, stroke or diabetes. Smoking status was divided into current nonsmokers and smokers; alcohol status was classified into moderate (<21 units men, <14 units women), hazardous (21–50 units men, 14–35 units women) and harmful (>50 units men, >35 units women) based on their weekly units consumption; this classification was adapted from the latest report of the Scottish Health Survey.[34]

Statistical analysis

We used multiple linear regression with mean and standardized change (one standard deviation), with 95% CIs, in HADS-D in year 2 from baseline (year 1) as the outcome variable; this was used as a proxy measure of efficacy for anti-depressant treatment. The anti-depressant treatment category based on their prescription pattern described above was entered as a predictor variable, and the nonprescribed group was used as the reference category. Age (continuous variable and centered at 60 years), sex (male and female), socioeconomic status (categorized based on SIMD Q 1–5), and number of co-morbid conditions were entered into the models as categorical variables. Baseline HADS-D score was also entered into the regression model as a continuous variable and centered at 11. We visualized the results of the regression with a plot for the mean change in HADS-D against baseline HADS-D for the four different prescription categories.

We calculated the remission rate or the incidence of having no depressive symptoms in year 2 based on an HADS-D score of < 8 for the patients who were screened in year 1 and noted to have depressive symptoms. We used multiple logistic regression with the incidence of having no depressive symptoms in year 2 at 12 months of follow-up as the outcome variable; this was used as a measure of effectiveness for anti-depressant treatment. We used the same predictor variables as described above. We report the OR, 95% CI and *P* values for remission at follow-up for the three groups with different prescribing patterns with nonprescribed group taken as the reference category. Smoking and alcohol status were not included in any of the regression models due to the large number of missing values. Analysis was carried out using the *R* statistical software, version 3.0.2.[35]

Sensitivity analysis

The screened population was a subset of the whole dataset, and the majority of the patients eligible for depression screening did not have HADS-D recorded due to poor uptake of depression screening. We compared the demographic features and distribution of clinical risk factors for screened and the total population. Interaction of baseline HADS-D with the anti-depressant treatment category was tested.

We also repeated the analysis for the subset of patients with HADS-D ≥ 11 at baseline to assess the impact of different anti-depressant prescribing pattern for 12 months follow-up duration (continuous, intermittent, and single prescription) in patients with moderate to severe depression at baseline, adjusting for the confounding factors age, sex, socioeconomic status, and number of co-morbid conditions as described above.

Results

Sample size and characteristics

Of the total sample, 35,537 (32.5%) patients with one of the three chronic cardiometabolic diseases had results of depression screening with HADS-D recorded. *n* = 7080 (19.9%) of the screened population were identified as positives based on HADS-D ≥ 8. 452 patients (6% of positive depression screen at baseline) were started on new anti-depressant treatment (excluding amitriptyline) while 6628 (94%) were not prescribed with anti-depressants. Follow-up HADS-D at 12 months was recorded in 223 (49%) of patients prescribed with anti-depressants and in 3710 (56%) of patients not treated with anti-depressants [Figure 1].

Table 1 provides the details of the demographic characteristics, baseline HADS-D, and health-related behaviors of those patients with recorded HADS-D at 12 months follow-up and compares it with those who did not have HADS-D recorded at follow-up. The table shows that there were no clinically significant differences between the two groups in demographic characteristics and health-related behaviors.

Efficacy of anti-depressants in patients with depression in cardiometabolic disease

Patients who were not prescribed with anti-depressants had the biggest mean change in HADS-D from baseline with a drop of − 2.20 (95% CIs − 2.58–−1.81) over the 12 months follow-up period. There was no difference in HADS-D reduction between the nonprescribed and the continuously treated patients (*n* = 93). The patients who received intermittent (*n* = 72) or single prescription (*n* = 58) also saw a reduction in their HADS-D but the drop was significantly less than compared to the nonprescribed group. These results remained significant after adjusting for age (centered at 60 years), sex, socioeconomic status, number of co-morbid conditions, and baseline HADS-D. The results are summarized in Table 2.

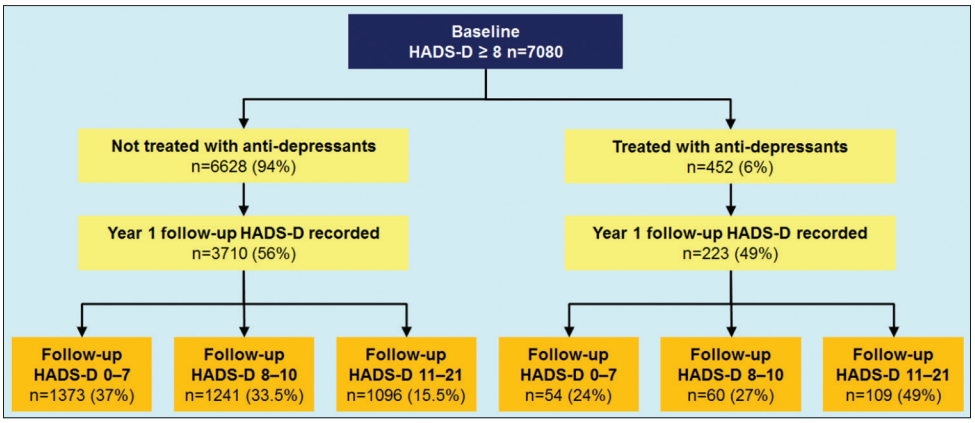

Figure 1: Flow chart of patients in the cohort with cardiometabolic disease and positive depression screening (HADS-D ≥ 8) at baseline. Legend: HADS-D = Hospital Anxiety and Depression Score-depressive subscale

Figure 2 shows the mean drop in HADS-D at 12 months follow-up for the four prescription categories against baseline HADS-D (at the reference level of other predictors), again showing that the drop in HADS-D was greatest for the nonprescribed group. The patients who had continuous anti-depressants prescriptions had a bigger drop in mean HADS-D when compared to the other two prescription categories receiving anti-depressants.

Effectiveness of anti-depressants in patients with depression in cardiometabolic disease

The remission rate at 12 months follow-up based on HADS-D < 8 was 24% among all patients prescribed with anti-depressants as compared to 37% among all patients not prescribed with anti-depressants. There was no difference in the odds of remission between the continuously prescribed and the nonprescribed patients but the odds of remission were lower in patients treated with one prescription or intermittently. These results remained significant after adjusting for age (centered at 60 years), sex, socioeconomic status, number of co-morbid conditions, and baseline HADS-D. These results are summarized in Table 3.

Sensitivity analysis

Interaction of baseline HADS-D with the anti-depressant treatment category was found to be not significant ($P = 0.969$). The sub-group analysis for patients noted to have moderate to severe depression at baseline (HADS-D ≥ 11) ($n = 2925$) were analyzed and a repeat HADS-D at 12 months was recorded for 1417 (48.4%) patients. The mean change in HADS-D from baseline for the nonprescribed group − 2.61 (95% CI − 3.44–−1.79, $P < 0.0001$) was better than the reduction observed in continuously prescribed group 1.09 (0.08–2.10, $P = 0.03$), intermittently prescribed group 1.94 (95% CI 0.71–3.16, $P = 0.002$) and patients who received single prescription 1.69 (95% CI 0.60–2.78, $P = 0.002$). There was no statistical difference between the odds of remission for the nonprescribed group when compared with that of the continuously prescribed group (OR 0.93 95% CI 0.49–1.76, $P = 0.82$) and intermittently prescribed group

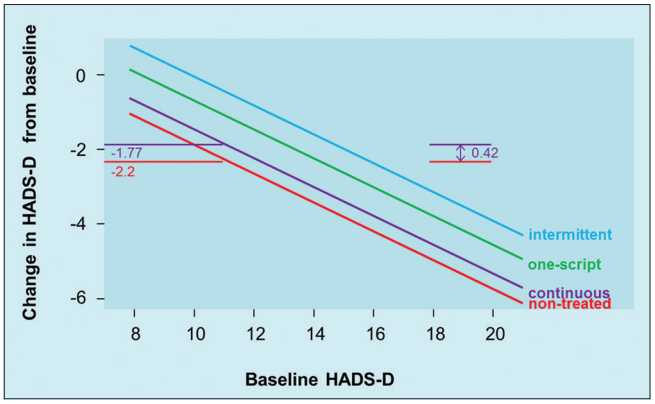

Figure 2: The mean change in HADS-D at 12 months follow-up for four patient groups with different anti-depressants prescribing pattern, in patients with cardiometabolic disease and positive depression screening (HADS-D ≥ 8) at baseline. Legend: HADS-D = Hospital Anxiety and Depression Score-depressive subscale. X-axis = Baseline HADS-D score Y-axis = Mean drop in HADS-D at 12 months follow-up

(OR 0.47 [95% CI 0.18–1.22, $P = 0.12$]) but the remission rate was significantly lower in patients treated with single script (0.21 [95% CI 0.06–0.69, $P = 0.01$]). These results remained significant after adjusting for age, sex, socioeconomic status, number of co-morbid conditions, and baseline HADS-D.

Discussion

Summary of findings

In a large community-based sample of patients with depression and cardiometabolic disease, there was no difference in depressive symptoms at 12 months follow-up, between patients prescribed continuously with anti-depressants and those who were not prescribed anti-depressants. Patients who were prescribed anti-depressants intermittently or issued with only one prescription had significantly worse improvement in depressive symptoms when compared with those who were not prescribed anti-depressants. These findings persisted after adjusting for other possible influencing factors such as age, sex, socioeconomic status, number of co-morbid conditions, and baseline HADS-D and did not change after repeating the

Table 1: Comparison of patients with and without follow-up HADS-D recorded at 12 months (HADS-D ≥8 at baseline)

	Follow-up HADS-D recorded (*n*=3933)	Follow-up HADS-D not recorded (*n*=3147)
Age (years)		
Mean (SD)	67.0 (11.7)	66.8 (13.1)
Median (IQR)	67.0 (59.0, 76.0)	68.0 (58.0, 77.0)
Missing	1	2
Age (years) (%)		
18-44	114 (2.9)	160 (5.1)
45-64	1519 (38.6)	1162 (36.9)
65-75	1140 (29.0)	827 (26.3)
76-90	1158 (29.5)	997 (31.7)
Missing	2	1
Sex (%)		
Female	2249 (57.2)	1651 (52.5)
Male	1681 (42.8)	1491 (47.5)
Missing	3	5
Socioeconomic status quintile (most deprived=1) (%)		
5	414 (10.7)	290 (9.5)
4	333 (8.6)	245 (8.0)
3	407 (10.6)	318 (10.4)
2	729 (18.9)	593 (19.4)
1	1976 (51.2)	1618 (52.8)
Missing	74	83
Number of co-morbid conditions (%)		
Single diagnosis	2826 (71.8)	2269 (72.1)
Two diagnoses	989 (25.1)	792 (25.2)
Three diagnoses	118 (3.0)	86 (2.7)
Missing	0	0
Baseline HADS-D		
Mean (SD)	10.5 (2.6)	10.9 (2.8)
Median (IQR)	10.0 (8.0, 12.0)	10.0 (9.0, 12.0)
Smoking (%)		
Current nonsmoker	1120 (55.4)	782 (50.2)
Smoker	903 (44.6)	777 (49.8)
Missing	1910	1588
Alcohol (units/week) (%)		
Light	3309 (96.6)	2319 (95.5)
Moderate	95 (2.8)	89 (3.7)
Heavy	20 (0.6)	21 (0.9)
Missing	509	718

Number (missing), mean (SD) and median (IQR) are presented for continuous variables and number (%) for a categorical variable. HADS-D: Hospital Anxiety and Depression Scale and depression; SD: Standard deviation; IQR: Interquartile range

analysis for a sub-group of patients with moderate to severe depressive symptoms at baseline.

Strengths and limitations

The study is based on a large community-based sample reflecting real life clinical practice, which is one of the key strengths of this study. However, there are several limitations, as only a subset of the original sample underwent depression screening, and a further subset had repeat HADS-D recorded at 12 months follow-up.

Table 2: Efficacy of anti-depressants in patients with depression in chronic disease

	Mean change (95% CI)	Standardized change (95% CI)	*P*
Change from baseline			
Nonprescribed group	−2.20 (−2.58, −1.81)	−0.84 (−0.99, −0.69)	<0.0001
Treatment category (vs. nonprescribed)			
Single prescription	1.22 (0.49, 1.96)	0.33 (0.13, 0.52)	0.0011
Intermittent prescriptions	1.87 (1.09, 2.64)	0.50 (0.29, 0.70)	<0.0001
Continuous prescriptions	0.42 (−0.21, 1.06)	0.11 (−0.06, 0.28)	0.1919
Sex (vs. male)			
Female	0.14 (−0.09, 0.38)	0.04 (−0.03, 0.10)	0.2379
Age			
5 years increase	−0.06 (−0.11, −0.01)	−0.02 (−0.03, 0.00)	0.0206
Socioeconomic status quintiles (most deprived=1) (vs. 5th quintile)			
4	0.10 (−0.43, 0.63)	0.03 (−0.11, 0.17)	0.7129
3	−0.17 (−0.67, 0.33)	−0.05 (−0.18, 0.09)	0.4953
2	−0.02 (−0.46, 0.43)	0.00 (−0.12, 0.11)	0.9467
1	0.38 (−0.01, 0.78)	0.10 (0.00, 0.21)	0.0576
Comorbidity (vs. one diagnosis)			
Two	0.18 (−0.09, 0.45)	0.05 (−0.03, 0.12)	0.2018
Three	0.23 (−0.47, 0.93)	0.06 (−0.13, 0.25)	0.5220
Baseline HADS-D	−0.39 (−0.43, −0.34)	−0.10 (−0.12, −0.09)	<0.0001

Linear regression model with change in HADS-D (mean and standardized) at 12 months follow-up from baseline for patients with positive HADS-D (≥8) at baseline. Age was centred at 60 years and baseline HADS-D at 11. HADS-D: Hospital Anxiety and Depression Scale and depression; CI: Confidence interval

Table 3: Effectiveness of anti-depressants in patients with depression in chronic disease

	OR (95% CI)	*P*
Treatment category (vs. nonprescribed)		
Single prescription	0.51 (0.30, 0.88)	0.0163
Intermittent prescriptions	0.38 (0.21, 0.69)	0.0016
Continuous prescriptions	0.87 (0.58, 1.32)	0.5152
Sex (vs. male)		
Female	1.04 (0.90, 1.20)	0.6093
Age		
5 years increase	1.03 (0.99, 1.06)	0.1069
Socioeconomic status quintiles (most deprived=1) (vs. 5th quintile)		
4	1.00 (0.73, 1.37)	0.9997
3	1.27 (0.95, 1.72)	0.1115
2	1.18 (0.90, 1.53)	0.2234
1	0.92 (0.73, 1.17)	0.5104
Comorbidity (vs. one diagnosis)		
Two	0.89 (0.75, 1.05)	0.1638
Three	1.05 (0.69, 1.61)	0.8179
Baseline HADS-D	0.79 (0.76, 0.81)	<0.0001

Logistic regression model with remission at 12 months follow-up from baseline for patients with positive HADS-D (≥8) at baseline OR and 95% CI's are presented. Age was centred at 60 years and baseline HADS-D at 11. OR: Odds ratio; HADS-D: Hospital anxiety and depression scale and depression; CI: Confidence interval

Second, there may be significant differences between patients who were prescribed anti-depressants and those who were not, which may not be evident from the information available. For example, it was not known how many of the patients with HADS-D positive at baseline were diagnosed with depression by their general practitioners, which has been previously found to be a marker of depression severity.[36] We did not have complete information on health-related behaviors such as smoking status, alcohol intake, and amount of physical activity; and no information on cardiovascular disease severity or cardiovascular medications. These factors are likely to influence the patient's likelihood of having depressive symptoms and subsequent outcomes. Different groups of anti-depressants may have different results as far as efficacy and effectiveness are concerned; we were unable to undertake analysis at the level of individual anti-depressant group prescribed due to lack of sufficient number of patients receiving anti-depressant treatment. Finally, we also had no information on the use of psychological therapies in our cohort, both for patients who were prescribed and who were not prescribed anti-depressants, which may have influenced the outcome of depressive symptoms at 12 months follow-up.

Comparison with existing literature

The rate of positive screens ranged from 17% to 21% for those with a single condition to 26% for those with multimorbidity.[14] This is consistent with rates of 6–22% which have been reported in other similar studies of depression screening.[37]

In patients with depression with CHD, a meta-analysis based on the 3 trials and 707 patients,[19-21] all using selective serotonin reuptake inhibitors, showed a standardized difference of −0.24 (95% CI −0.38–−0.09) at short-term (<6 months) follow-up favoring anti-depressants against placebo.[17] The reported OR for the short-term remission of depressive symptoms was 1.80 (95% CI 1.18, 2.74) favoring anti-depressants against placebo,[17] again based on the results of the same three trials.[19-21] The only trial investigating long-term follow-up showed that there was no difference in remission rates at 18 months between patients receiving anti-depressants and placebo postmyocardial infarction.[22]

In patients with depression in diabetes, a meta-analysis based on seven trials and 306 patients reported a standardized difference of −0.61 (95% CI −0.94–−0.27) at short-term (<6 months) follow-up favoring anti-depressants against placebo.[23] The reported OR for the short-term remission of depressive symptoms was 2.50 (95% CI 1.20–5.15) favoring anti-depressants against placebo, based on the results of two trials and 68 patients.[23] In the only trial looking at long-term remission (52 weeks) with depression in diabetes, the reported remission rate was 65.8% in patients treated with sertraline against 47.9% in patients receiving placebo.[28]

In the meta-analysis of patients with poststroke depression based on results of five trials and 410 patients, there was no difference in the pooled OR for short-term remission (<6 months) for patients prescribed anti-depressants OR 0.76 (95% CI 0.51–1.12) when compared with control group.[29] The meta-analysis did not report a pooled standardized difference but noted that three out of seven trials reported significant improvement in depressive symptoms in short-term favoring anti-depressants against placebo.[29] Again, there were no studies looking at long-term benefits of anti-depressants in poststroke depression.

This is the first study to our knowledge, which reports the efficacy and effectiveness of anti-depressants from routine clinical practice for treatment of depression with cardiometabolic diseases.

Implications for practice

Improvement in depressive symptoms in patients with the cardiometabolic disease at 12 months was not any better in patients prescribed with anti-depressants when compared with the nonprescribed group. The patients who were prescribed anti-depressants intermittently or with only a single prescription had significantly worse outcomes. These results need to be replicated with other datasets, preferably prospectively and in randomized controlled trials, to further analyze the usefulness of anti-depressants in improving depressive symptoms in patients with the cardiometabolic disease. Further evaluation of the variation in effects, if any of individual subgroups of anti-depressants would also be valuable. Importantly, the role of anti-depressants in the management of depression in chronic disease merits further research and evaluation.

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