Elevated Depression Symptoms, Antidepressant Medicine Use, and Risk of Developing Diabetes During the Diabetes Prevention Program

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OBJECTIVE — To assess the association between elevated depression symptoms or antidepressant medicine use on entry to the Diabetes Prevention Program (DPP) and during the study and the risk of developing diabetes during the study.

RESEARCH DESIGN AND METHODS — DPP participants (n = 3,187) in three treatment arms (intensive lifestyle [ILS], metformin [MET], and placebo [PLB]) completed the Beck Depression Inventory (BDI) and reported their use of antidepressant medication at randomization and throughout the study (average duration in study 3.2 years).

RESULTS — When other factors associated with the risk of developing diabetes were controlled, elevated BDI scores at baseline or during the study were not associated with diabetes risk in any arm. Baseline antidepressant use was associated with diabetes risk in the PLB (hazard ratio 2.25 [95% CI 1.38–3.66]) and ILS (3.48 [1.93–6.28]) arms. Continuous antidepressant use during the study (compared with no use) was also associated with diabetes risk in the same arms (PLB 2.60 [1.37–4.94]; ILS 3.39 [1.61–7.13]), as was intermittent antidepressant use during the study in the ILS arm (2.07 [1.18–3.62]). Among MET arm participants, antidepressant use was not associated with developing diabetes.

CONCLUSIONS — A strong and statistically significant association between antidepressant use and diabetes risk in the PLB and ILS arms was not accounted for by measured confounders or mediators. If future research finds that antidepressant use independently predicts diabetes risk, efforts to minimize the negative effects of antidepressant agents on glycemic control should be pursued.

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Abbreviations: BDI, Beck Depression Inventory; DPP, Diabetes Prevention Program; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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The concurrence of depression and diabetes is a serious problem. Among people with diabetes, whose risk of depression is 50–100% greater than the general population (1), depression is associated with higher complication (2) and mortality (3) rates and higher health care costs (4). In 1674, Thomas Willis speculated that diabetes was caused by "long sorrow and other depressions" (5). Findings consistent with Willis' hypothesis, as it applies to type 2 diabetes, were reported recently in a meta-analysis (6), but not all studies included in the meta-analysis reported positive findings. Some studies lacked sufficient statistical power or objective determination of baseline diabetes status. Even studies with positive findings suggested that they applied only to individuals with high levels of depression symptoms or to certain demographic groups.

To our knowledge, no studies have considered the effects of elevated depression symptoms on diabetes risk in a large sample of individuals at high risk for developing diabetes because they have impaired glucose regulation or obesity. In addition, very few studies have identified an independent increment in the risk of developing diabetes associated with use of antidepressant medication (7), despite evidence suggesting that such medications may have an impact on glucose tolerance. Tricyclics appear to contribute to weight gain (8) and to increase blood glucose levels in patients with diabetes (9). Selective serotonin reuptake inhibitors (SSRIs) and related agents appear to be associated with less weight gain and perhaps improve insulin sensitivity (10).

Data from the Diabetes Prevention Program (DPP) offer an opportunity to better understand the natural history of elevated depression symptoms, antidepressant medication, and type 2 diabetes in a large racially/ethnically diverse cohort of overweight individuals with elevated fasting glucose and impaired glucose tolerance. The protocol included objective measures of glucose tolerance

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and potential mediators of the effect of depression symptoms or antidepressant medication on diabetes risk, including weight, weight change, physical activity, and insulin secretion and resistance.

We reported earlier that on entry to the DPP 10.3% of participants had symptoms consistent with at least mild depression, and 5.7% reported taking antidepressants, with 0.9% reporting both elevated symptoms and antidepressant use (11). Depression symptoms were higher among women and those having less education; antidepressant use was more common among women, those having more education, and those of white race/ethnicity. During the study, the proportion of participants taking antidepressants increased (to 8.7% at year 3), while the proportion with elevated depression symptoms declined (to 8.4% at year 3), with no significant differences among DPP treatment arms.

The current study was designed to determine *1*) whether depression symptoms or antidepressant medicine use were associated with progression to type 2 diabetes in the DPP cohort, 2) if these associations varied by DPP treatment arm, and 3) whether these associations were mediated by potential diabetes risk factors.

RESEARCH DESIGN AND METHODS

The DPP involved individuals at high risk for developing type 2 diabetes and was conducted at 27 centers. DPP methods (12,13) and results (14) are described in detail elsewhere. The protocol is available at http://www.bsc.gwu.edu/dpp. At each DPP center, an institutional review board approved the protocol and all participants gave written informed consent.

This analysis is based on the 3,187 of 3,234 enrolled DPP participants who completed the Beck Depression Inventory (BDI) at baseline. Participants were aged ≥25 years, had a BMI of ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans), and had a plasma glucose concentration of 95–125 mg/dl (5.3–6.9 mmol/l) in the fasting state (≤125 mg/dl in American Indians) and 140–199 mg/dl (7.8–11.0 mmol/l) 2 h after a 75-g oral glucose load. Individuals were excluded from the study if they were taking antidepressant medication that might contribute to weight loss (bupropion or an SSRI at more than the lowest usual dose [i.e., >20 mg of fluoxetine or the equivalent]) (15), if they had conditions that could seriously reduce their ability to participate in the DPP (including major psychiatric disorders), or if they could not successfully complete the 3-week run-in period during which participants took placebo medicines and recorded eating and activity. Recruitment was designed to randomize approximately half the participants from racial/ethnic minority groups.

Interventions

Eligible participants were randomly assigned to one of three interventions: standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily (MET arm), standard lifestyle recommendations plus a placebo pill twice daily (PLB arm), or an intensive lifestyle modification program (ILS arm). Goals for ILS participants were to achieve and maintain a reduction of ≥7% of initial body weight through a calorie-controlled, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for ≥150 min per week (16).

Outcomes

As part of a comprehensive protocol, DPP participants completed the BDI (17) and a measure of leisure activity (18) before randomization and subsequently at each annual visit. Participants brought all prescription medicines, including antidepressants, to each quarterly clinic visit, and all were recorded.

Diabetes was diagnosed according to the 1997 American Diabetes Association criteria (19) based on an annual oral glucose tolerance test or a semiannual fasting plasma glucose test. A confirmation test was performed, usually within 6 weeks (12). Fasting insulin was measured at annual visits with the oral glucose tolerance test. Detailed measurement methods for glucose and insulin have been previously published (20).

We report follow-up through July 2001, after which the primary results were announced and the interventions unmasked. This was 4 months longer than the results reported previously (14), resulting in a total mean follow-up of 3.2 years per participant.

We identified participants with BDI scores ≥11 as having elevated depression symptoms; others have chosen scores ranging from 10 to 16 (21–23) generally as a function of the importance placed on depression recognition. We chose a symptom threshold toward the low end of the severity range because we believed few severely depressed participants would pass the screening process for eligibility in the DPP. We identified participants who had elevated BDI scores at baseline and those who ever had elevated BDI scores during the DPP. We used this measure of depression symptoms (rather than the absolute BDI score) because we were interested in assessing the association between possible depression (i.e., elevated symptoms) and diabetes risk.

Analysis

At baseline, categorical variables are reported as percentages and continuous variables as means ± SD. χ^2 tests were used to compare baseline differences in categorical variables. To test for baseline differences among groups on continuous variables, the Wilcoxon's rank-sum test (24) was used for those with nonnormal distributions; otherwise, the Student's *t* test was used. During DPP, antidepressant use was reported quarterly and depression symptoms annually. Mixed-effects modeling (25) was used to compare the difference in continuous variables such as weight by antidepressant use or depression symptoms, and least-square means with SEs were reported. For categorical variables such as sex, repeated-measures modeling with general estimation equation (26) was used to compare differences by antidepressant use or elevated depression symptoms.

Cox proportional hazard models (27) were used to evaluate whether elevated depression symptoms or taking antidepressants were associated with developing diabetes. Having elevated depression symptoms during the DPP was defined as a time-dependent covariate: ever having BDI score ≥11 up to each time point evaluated. Antidepressant use during DPP was also defined as a time-dependent categorical variable up to each time point evaluated with three levels: never used, used intermittently (at least once but not always), and used continuously (at all visits). Time-dependent covariate analyses (28) were used to model the above covariates and diabetes risk with adjustment for race/ethnicity and factors associated with an increased risk of developing diabetes (age, sex, education, fasting plasma glucose at baseline, weight at baseline, and weight change during the study).

The life-table method (29) was used to estimate cumulative diabetes incidence rates at 3 years. These rates and the Greenwood estimate (30) of the SE were

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used to calculate the number of individuals needed to treat with an antidepressant associated with one case of diabetes and its 95% CI. All analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS — At baseline (Table 1), 10.3% of DPP participants had BDI scores indicating at least mild depression (≥11), and 5.7% were taking antidepressants. During the DPP (Table 1), intermittent antidepressant use was reported for 7.2% of total person-years and continuous antidepressant use for 3.2% of total person-years.

At baseline the median BDI score for all three treatment arms was 3 (interquartile range 1–7). At follow-up the median BDI score was 2 (0–5) for the ILS arm and 2 (0–6) for the MET and PLB arms. Elevated BDI scores at baseline and during the study were associated with *1*) female sex, *2*) race/ethnicity other than non-Hispanic white, *3*) less education, and *4*) higher BMI, higher fasting insulin levels, and lower levels of physical activity. Elevated BDI scores were not related to age at baseline, but during the DPP older participants (aged ≥60 years) were less likely to have elevated BDI scores than younger participants.

Antidepressant use on entry to the study and use during the study (Table 1) was associated with female sex, non-Hispanic white race/ethnicity, and (on entry to the study only) more education. In contrast to elevated depression symptoms, antidepressant use was not associated with fasting insulin levels or physical activity level on entry to the DPP. Antidepressant use was associated with BMI on entry to and during the study and with lower levels of physical activity during the study. Antidepressant use at baseline was not related to age, but during the DPP older participants (aged ≥60 years) were less likely to take these agents than younger participants.

At baseline, 7.4% of women, but only 2.0% (21 of 1,029) of men, took antidepressants. The associations between antidepressant use and age, race/ethnicity, and education were similar for male and female participants, but when analyzed separately these associations were no longer significant among men, possibly due to lack of statistical power. Higher BMI at randomization was significantly associated with antidepressant use at baseline and during the study for women only.

When other factors associated with an increased risk of developing diabetes (age, sex, fasting glucose, baseline weight, and weight change during the study) as well as race/ethnicity were controlled, neither elevated BDI scores at baseline nor during the study were significantly associated with diabetes risk in any treatment arm (see lines labeled HRa in Table 2). Leisure activity was not controlled because it was not associated with diabetes risk. (Absolute BDI scores at baseline were significantly associated with diabetes risk in the ILS arm only [$P = 0.04$].)

Baseline antidepressant use, on the other hand, was strongly associated with diabetes risk for participants in the PLB (hazard ratio 2.25 [95% CI 1.38–3.66]) and ILS (3.48 [1.93–6.28]) arms. Continuous antidepressant use during the study (compared with no use) was also significantly associated with diabetes risk in the same arms (PLB hazard ratio 2.60 [95% CI 1.37–4.94]; ILS 3.39 [1.61–7.13]), as was intermittent antidepressant use during the study in the ILS arm (hazard ratio 2.07 [95% CI 1.18–3.62]). In the PLB arm, the association between intermittent antidepressant uses during the study and diabetes risk approached significance (1.50 [0.97–2.33]). In the MET arm, antidepressant use was not associated with diabetes risk. There was a significant difference between the ILS and MET arms in the association between antidepressant medication and diabetes risk.

We further analyzed baseline antidepressant use, comparing only participants who were taking SSRIs, selective serotonin and norepinepherine reuptake inhibitors, or serotonin modulators with those who did not take any antidepressant, since these agents were considered less likely to increase the risk of diabetes. The results for this subgroup, which included 78% of all those taking antidepressants at baseline, were similar to those for all antidepressant users; taking SSRIs or related agents at baseline was significantly associated with the risk of developing diabetes during the DPP in the PLB and ILS arms but not in the MET arm. For this reason, our analysis of the association between antidepressant use during the DPP and diabetes risk included all antidepressants.

Our findings suggest that antidepressant use might have increased diabetes risk in the PLB and ILS arms. Under this assumption, we calculated that treating 5.4 PLB participants (95% CI 3.1–24.8) or 5.2 ILS participants (3.2–15.5) with antidepressants would have caused one additional case of diabetes 3 years later (31). We did not perform this calculation for the MET arm, in which it would not be meaningful because there was no association between antidepressant use and diabetes risk.

CONCLUSIONS

Elevated depression scores were not associated with diabetes risk

Elevated BDI scores (≥11, consistent with mild depression) at baseline and during the study were not associated with diabetes risk during the DPP, despite the fact that elevated depression symptoms were associated with several risk factors for diabetes (BMI, fasting glucose, and lower levels of physical activity). Absolute BDI scores were weakly associated with diabetes risk in the ILS arm only. These findings differ from the conclusions of a meta-analysis that suggested that elevated depressive symptoms are associated with the risk of developing type 2 diabetes (6). DPP participants were selected because their risk for developing diabetes was high and rates of developing diabetes in the DPP were 5- to 10-fold higher than those in earlier studies included in the meta-analysis, where subjects did not have impaired glucose regulation at baseline. In addition, the DPP cohort was relatively free of depression. At baseline, only 2.7% of participants had BDI scores indicating even moderate levels of depression (>16). Perhaps in a population at high risk of developing diabetes, generally mild depression symptoms were not potent enough to significantly affect overall diabetes rates. In some studies, increased diabetes risk was seen only in those with more severe depression symptoms (6).

Antidepressant medication was associated with diabetes risk

The present study of individuals at very high risk for developing diabetes, with excellent ascertainment of diabetes onset and exposure to antidepressant medication, found an increased risk of diabetes associated with antidepressant medication. Two recent studies also assessed antidepressant-related diabetes risk. One study (7) found no increased risk of diabetes among subjects taking antidepressant medication, but the study did not include a definitive determination of diabetes. The other study (32) compared the risk of developing diabetes for patients taking different antidepressants and re-

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Table 1—*Depression symptoms and antidepressant use at baseline and during the DPP*

Characteristic	At baseline			During DPP			
	n	BDI ≥11 [*n*(%)]	Antidepressant medicine use [*n*(%)]	Total person-years	BDI ≥11 [person-years (% of total person-years)]	Intermittent use [person-years (% of total person-years)]	Continuous use [person-years (% of total person-years)]
Total participants	3,187	328 (10.3)	181 (5.7)	8,637.1	1,302.1 (15.1)	622.0 (7.2)	272.4 (3.2)
Age (years)					*		
25–44	983	115 (11.7)	47 (4.8)	2,628.2	460.3 (17.5)	223.4 (8.5)	53.7 (2.0)
45–59	1,567	160 (10.2)	102 (6.5)	4,267.2	639.6 (15.0)	318.6 (7.5)	151.7 (3.6)
≥60	637	53 (8.3)	32 (5.0)	1,741.7	202.1 (11.6)	80.0 (4.6)	66.9 (3.8)
Sex		‡	‡		‡	‡	
Female	2,158	255 (11.8)	160 (7.4)	5,854.1	1,011.2 (17.3)	520.0 (8.9)	240.4 (4.1)
Male	1,029	73 (7.1)	21 (2.0)	2,783.0	290.9 (10.5)	102.0 (3.7)	32.0 (1.1)
Race/ethnicity		‡	‡		‡	‡	
White	1,746	132 (7.6)	144 (8.2)	4,736.0	578.6 (12.2)	436.2 (9.2)	238.0 (5.0)
African American	636	81 (12.7)	11 (1.7)	1,690.0	299.0 (17.7)	66.8 (4.0)	9.2 (0.5)
Hispanic	498	67 (13.5)	18 (3.6)	1,343.8	244.3 (18.2)	75.4 (5.6)	21.0 (1.6)
American Indian	165	33 (20.0)	6 (3.6)	460.4	125.4 (27.2)	32.4 (7.0)	1.3 (0.3)
Asian	142	15 (10.6)	2 (1.4)	406.8	54.8 (13.5)	11.1 (2.7)	3.0 (0.7)
Education in years		‡	*		‡	*	
≤12	822	122 (14.8)	33 (4.0)	2,249.2	453.2 (20.1)	137.8 (6.1)	54.5 (2.4)
13–16	1,534	152 (9.9)	91 (5.9)	4,176.7	615.2 (14.7)	302.7 (7.2)	129.8 (3.1)
≥17	831	54 (6.5)	57 (6.9)	2,211.2	233.7 (10.6)	181.5 (8.2)	88.1 (4.0)

	BDI ≥11 (means ± SD)		Antidepressant use (means ± SD)		BDI ≥11 (least-square means ± SE)		Antidepressant use (least-square means ± SE)		
	No	Yes	No	Yes	No	Yes	Never exposed	Intermittent use	Continuous use
Weight (kg)	94.1 ± 20.1	95.6 ± 21.3	94.0 ± 20.2	97.8 ± 20.9*	93.2 ± 0.4	93.8 ± 0.4*	93.3 ± 0.4	93.1 ± 0.4	94.7 ± 0.6*
BMI (kg/m^2)	33.8 ± 6.6	35.5 ± 7.0‡	33.9 ± 6.7	35.8 ± 7.1†	33.6 ± 0.1	33.9 ± 0.1*	33.6 ± 0.1	33.6 ± 0.1	34.2 ± 0.2†
Fasting glucose (mg/dl)	106.5 ± 8.2	106.6 ± 8.9	106.6 ± 8.3	105.3 ± 8.2*	105.7 ± 0.1	106.2 ± 0.3	105.8 ± 0.1	105.8 ± 0.4	105.6 ± 0.6
Fasting insulin (μU/ml)	26.6 ± 15.2	28.5 ± 14.9*	26.8 ± 15.3	26.5 ± 13.9	25.0 ± 0.2	27.4 ± 0.5‡	25.3 ± 0.2	26.7 ± 0.7	25.1 ± 0.9
Leisure activity (MET-hours)	16.6 ± 26.1	14.5 ± 25.0‡	16.5 ± 26.2	14.4 ± 22.4	18.6 ± 0.3	15.8 ± 0.7†	18.4 ± 0.3	15.7 ± 1.0	15.0 ± 1.4*

Significance levels of differences in depression symptoms or antidepressant use are noted as follows: *$P < 0.05$; ‡$P < 0.0001$; †$P < 0.001$. Thus † noted for sex in column "BDI ≥11" (at baseline) indicates that the proportion of those with elevated baseline BDI scores differed by sex with $P < 0.001$. During DPP, variables age, sex, race/ethnicity, and education remain the same. Variables weight, BMI, fasting glucose, fasting insulin, and leisure activity are measured repeatedly during the study, and repeated-model–based means are reported.

Table 2—*Prediction of diabetes by depression symptoms and antidepressant drug exposure*

	At baseline				During follow-up			
	BDI <11	BDI ≥11	No medications	Taking medications	BDI always <11	BDI ever ≥11	No medications	Intermittent medications	Continuous medications
PLB arm									
Pyr	2,451.6	300.4	2,624.9	127.1	2,316.7	435.3	2,460.0	218.8	73.2
Cases	270	30	277	23	245	55	259	28	13
IR	11.0	10.0	10.6	18.1	10.6	12.6	10.5	12.8	17.8
HRu	1	0.90 (0.61–1.32)	1	1.80 (1.15–2.82)	1	1.11 (0.82–1.50)	1	1.17 (0.78–1.76)	1.80 (1.00–3.25)
HRa	1	0.84 (0.56–1.26)	1	2.25 (1.38–3.66)	1	0.99 (0.72–1.37)	1	1.50 (0.97–2.33)	2.60 (1.37–4.94)
MET arm									
Pyr	2,584.9	289.0	2,675.7	198.2	2,441.0	432.9	2,549.2	224.4	100.3
Cases	199	25	213	11	187	37	200	19	5
IR	7.7	8.7	8.0	5.5	7.7	8.5	7.8	8.5	5.0
HRu	1	1.14 (0.74–1.75)	1	0.69 (0.37–1.27)	1	1.00 (0.69–1.43)	1	0.96 (0.59–1.57)	0.68 (0.28–1.68)
HRa	1	1.07 (0.68–1.68)	1	0.72 (0.38–1.36)	1	0.91 (0.62–1.33)	1	0.99 (0.59–1.65)	0.71 (0.28–1.78)
ILS arm									
Pyr	2,711.2	299.9	2,863.5	147.6	2,577.2	433.9	2,733.4	178.7	99.0
Cases	130	21	134	17	120	31	123	19	9
IR	4.8	7.0	4.7	11.5	4.7	7.1	4.5	10.6	9.1
HRu	1	1.49 (0.93–2.39)	1	2.68 (1.59–4.52)	1	1.35 (0.90–2.02)	1	1.91 (1.15–3.19)	2.51 (1.29–4.89)
HRa	1	1.15 (0.69–1.93)	1	3.48 (1.93–6.28)	1	0.87 (0.56–1.39)	1	2.07 (1.18–3.62)	3.39 (1.61–7.13)

Data are hazard ratio (95% CI), unless otherwise indicated. Cases, incident cases of diabetes developing during follow-up. Pyr, person-years of follow-up. HRa, hazard ratio (from Cox proportional hazard model) with 95% CI, adjusted for age, sex, race/ethnicity, education, fasting plasma glucose, weight, and weight change. HRu, hazard ratio (from Cox proportional hazard model) with 95% CI, unadjusted for covariates. IR, incidence rate (cases/100 person-years of follow-up). In addition, depression symptom and antidepressant drug use are adjusted for each other.

ported that the risk associated with taking SSRIs in addition to tricyclic antidepressants (TCAs) was greater than the risk associated with taking TCAs alone. Since that study did not include those not taking antidepressants, the authors could not assess the diabetes-related risk associated with taking any antidepressant.

Among psychotropic agents, only second-generation atypical antipsychotic agents have been associated with increased diabetes risk (33). Weight gain, a known risk factor for diabetes, is a recognized side effect of TCA use, and TCA-associated hyperglycemia has been reported in patients who already have diabetes (9). SSRIs or related agents, taken by 78% of DPP participants who took antidepressants, are generally considered to have less effect on weight, with some reports that in people with type 2 diabetes they can actually contribute to lowering weight (34) and improving insulin sensitivity (10). In contrast, SSRI use in the DPP was associated with weight gain during the study. Use of antidepressants was still associated with diabetes risk in the PLB and ILS arms when weight gain was controlled.

Explaining the association between antidepressant use and diabetes risk

The association between antidepressant use and diabetes risk remained significant when likely mediators (e.g., fasting glucose, weight, and weight gain) of this association were controlled. Thus, we are unable to say how use of antidepressants increases diabetes risk, if it does at all. Antidepressant use could simply be a marker for the actual cause(s) of increased diabetes risk, which may be more severe, chronic, or recurrent depression. Perhaps antidepressant users were more severely depressed in the past or had a history of chronic or recurrent depression. If so, the lingering effects of past depression, or the current effects of that depression, even with its symptoms controlled by medication, could explain the association between antidepressant use and diabetes risk. This argument depends on the presence of past moderate or severe depression (or a history of chronic or recurrent depression) and on an effect of depression that operates after symptoms have resolved (since these participants did not have elevated depression symptoms) or on an unidentified continuing effect of depression not detected by our questionnaire.

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Antidepressant use was not associated with diabetes risk in the MET arm

Antidepressant use was not associated with diabetes risk in the MET arm. Although there is no obvious explanation for this finding, it is similar to our previous report that metformin treatment not only reduced the incidence of diabetes but also obliterated the predictive effect of BMI (14).

Strengths and limitations

Strengths of the current study include the large, racially and ethnically diverse population; the definitive assessment of glucose tolerance and diabetes; and the fact that data were collected about antidepressant medication and depression symptoms. We were also able to pinpoint the diagnosis of diabetes, a considerable advance over studies that rely on clinical records that may not accurately capture when diabetes actually developed.

The absence of data on specific antidepressants is a limitation, but use of the most commonly used class of agents (SSRIs) was associated with diabetes risk in the PLB and ILS study arms, just as was the use of any antidepressant. Excluding participants from the DPP if they were taking bupropion, or SSRIs, in greater than low doses might limit the generalizabilty of our findings, but antidepressant medication and dosage were not limited during the study, where we still found an association between antidepressant use and diabetes risk.

We did not confirm that all patients using antidepressants were taking them for depression. Some SSRIs and related agents are used to treat other disorders (35), but patients with these disorders probably represent a small proportion of those taking SSRIs. TCAs are sometimes prescribed for relief of neuropathic symptoms in patients with diabetes, but DPP participants did not have diabetes at the outset of the study. The antidepressant bupropion is also indicated for smoking cessation, but only 6% of DPP participants reported taking this agent.

Our categorical classification of antidepressant use, based on patient self-report, precludes an examination of the association between incremental antidepressant dosage and diabetes risk. We also could not determine whether chronicity of depressive symptoms or the number of past episodes of depression were related to diabetes risk in this cohort or modulated the noted association with antidepressant use.

Implications

Research implications. The finding of an association between antidepressant use and diabetes risk requires replication. Ideally, future studies will examine the diabetes risk associated with different classes of antidepressant medication and even specific agents. Such studies will require large populations (e.g., prescription databases to obtain the necessary sample sizes). If the association between antidepressant use and diabetes risk is replicated, studies are needed to determine whether use of these agents is a causal risk factor for developing diabetes or a marker of depression severity. Studies should seek to clarify the metabolic effects of various antidepressants to determine how each agent affects diabetes risk. Comparing the diabetes risk associated with antidepressant use to the risk associated with psychological treatment could also be illuminating.

Clinical implications. If antidepressants prove to be an independent diabetes risk factor, clinicians will need to consider this when prescribing depression treatment in patients at high risk for diabetes. One possibility is to consider psychological treatment to avoid potential iatrogenic effects of antidepressants (although limited resources may often make this infeasible). In one study of depressed patients with diabetes who had high A1C levels, cognitive behavioral therapy counseling was associated with improved glycemic control (36). This suggests a potential benefit for patients at high risk for developing diabetes.

Public health implications. According to recent estimates, there are >40 million people in the U.S. with pre-diabetes (IGT or impaired fasting glucose [37]), and this number is rising rapidly. More than 10% of DPP participants were taking antidepressants when the study ended in 2001. Antidepressant use in the U.S. has continued to rise, so probably at least 4 million people in the U.S. who have pre-diabetes are taking antidepressants. If future research confirms an etiologic role for antidepressants in diabetes, efforts to minimize the potentially negative effects of these agents on glycemic control should be pursued.

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