Antidepressant Medicine Use and Risk of Developing Diabetes During the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study

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Objective: To assess the association between antidepressant medicine use and risk of developing diabetes during the Diabetes Prevention Program (DPP) and Diabetes Prevention Program Outcomes Study (DPPOS).

Methods: DPP/DPPOS were assessed for diabetes (every six months), and antidepressant use (every 3 months in DPP, every 6 months in DPPOS) for a median 10.0-year follow-up.

Results: Controlled for factors associated with diabetes risk, continuous antidepressant use (compared with no use) was associated with diabetes risk in the placebo (PLB) (adjusted hazard ratio, HRa= 2.34 [95% CI: 1.32-4.15]) and lifestyle (ILS) arms (HRa= 2.48 [95% CI: 1.45-4.22]), but not in the metformin (MET) arm (HRa= 0.55 [95% CI: 0.25-1.19]).

Conclusions: Continuous antidepressant use was significantly associated with diabetes risk in the PLB and ILS arms. Measured confounders and mediators did not account for this association, which could represent a drug effect or reflect differences between antidepressant users and non-users not assessed in this study.

Our earlier report from the Diabetes Prevention Program (DPP) (1) was the first to examine ADM-related diabetes risk in an overweight population with elevated fasting glucose and impaired glucose tolerance. We found that when other factors associated with diabetes risk (age, sex, education, fasting plasma glucose at baseline, weight at baseline and weight change during the study, depression symptoms at baseline and during the study) were controlled, baseline ADM use and continuous ADM use during the study (compared to no use) were associated with significantly increased diabetes risk; in the ILS arm intermittent ADM use during the study was also associated with increased diabetes risk. Among metformin arm participants, ADM use was not associated with developing diabetes.

The present study extends the duration of follow-up in our previous report by including seven years of the Diabetes Prevention Program Outcomes Study (DPPOS), providing a median 10.0-year (inter-quartile range [IQR] 9.0-10.5) follow-up since randomization to the DPP.

METHODS

Participants. Participants (N = 3234) at high risk for developing type 2 diabetes were randomized to the DPP between 1996 and 1999. Characteristics of the study population are reported elsewhere (1).

In July 2001 masked DPP treatment was discontinued, after it was established that lifestyle intervention reduced incidence of diabetes by 58% and metformin by 31% compared to placebo (2).

All 3150 surviving DPP participants who had not withdrawn consent were eligible for the DPPOS, and 2665 enrolled. Institutional review boards approved all DPP and DPPOS protocols and informed consent procedures. Participants signed written consent forms after discussion of all aspects of the studies with study staff (3).
Measures. DPP/DPPOS participants brought all prescription medicines, including ADM, to clinic visits, where study staff identified all ADM by generic name, brand name, or both.

Diabetes was diagnosed based on an annual oral glucose-tolerance test or a semiannual fasting plasma glucose test. A confirmation test was required, usually within 6 weeks (1). Fasting insulin was measured at annual visits with the OGTT (2).

Statistical Analysis. ADM use was reported quarterly during the DPP and every six months during the DPPOS. Cox proportional hazard models (1) were used to evaluate whether taking ADM were associated with developing diabetes.

ADM use was 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). A significant interaction between ADM use and treatment groups was detected and we modeled the association separately for each treatment group.

Time dependent covariate analyses (1) were used to model the above covariates and diabetes risk with adjustment for factors associated with an increased risk of developing diabetes (race/ethnicity, age, sex, education, fasting plasma glucose at baseline, weight at baseline and weight change during the study). These risks are reported as adjusted hazard ratios (HRa).

We now present data over a median of 10 years since randomization, including the time period of the first phase of the DPP that was reported previously (1). Therefore these analyses are not independent of the previous paper and should be considered an extension, not a replication, of those findings.

All analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS

When other factors associated with an increased risk of developing diabetes were controlled, continuous ADM use during the DPP/DPPOS (compared to no use) was strongly associated with diabetes risk (Figure 1) for participants in the PLB (HRa= 2.34 [95% CI: 1.32-4.15] and ILS (HRa= 2.48 [95% CI: 1.45-4.22]) arms. In the PLB arm the association between intermittent ADM use and diabetes trended toward statistical significance (HRa=1.34 [95% CI: 0.99-1.81]). In the MET arm, ADM use was not associated with diabetes risk ((HRa= 0.55 [95% CI: 0.25-1.19]). There was a significant difference between the ILS and MET arms in the association between ADM and diabetes risk. Results did not change when we excluded participants taking ADM that are more likely to cause weight gain (tricyclic and tetracyclic agents).

DISCUSSION

The current findings extend those of our earlier report (1), although over the longer follow-up in this study that includes the DPPOS, we did not find an association with intermittent ADM use and diabetes risk in the ILS arm. These findings are similar to a previous report that long-term use of ADM increased the risk of developing diabetes (4). Other studies (5, 6), have also reported increased ADM-related diabetes risk.

The association between ADM use and diabetes risk remained significant when likely mediators of this association were controlled. This association could represent a medication effect, or it could reflect differences between ADM users and non-ADM not assessed in the study. ADM use was not associated with diabetes risk in the MET arm. Although there is no obvious explanation for this latter finding, one study found that metformin induces the release of 5-HT through neuronal and non-neuronal mechanisms, and thus increases insulin secretion (7). Metformin also appears to
ameliorate inflammation (8), and inflammatory markers appear to be associated with depression (9).

**Strengths and Limitations.** Strengths of the current study include the large, racially and ethnically diverse population, the definitive assessment of glucose tolerance and diabetes, repeated collection of data on both ADM and depression symptoms, and repeated assessment of metabolic diabetes risk factors. We were also able to more accurately determine the onset of diabetes, a considerable advance over studies that rely on clinical records that may not accurately capture when diabetes actually developed.

Potential DPP participants were excluded if they were taking bupropion or any ADM in greater than the lowest therapeutic dose, so the study sample was not representative of the general population. The absolute number of diabetes cases in the continuous ADM group was quite small (N=18 PLB, N=15 ILS). During the DPP/DPPOS we did not collect data on ADM dosage, so we could not examine the association between dosage and diabetes risk.

**Implications.** Further study of ADM-related diabetes risk has substantial public health implications. The possible benefits of metformin in depression treatment should also be studied.

**Author Contributions.** RRR wrote manuscript, reviewed/edited manuscript, contributed to discussion. YM researched data, reviewed/edited manuscript. MP reviewed/edited manuscript, contributed to discussion. DGM reviewed/edited manuscript, contributed to discussion. DWP reviewed/edited manuscript, contributed to discussion. EBC reviewed/edited manuscript, contributed to discussion. WCK reviewed/edited manuscript, contributed to discussion.

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Parts of this study were presented in poster form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, June 25-29, 2010.
**Figure legend:** for each treatment group, from left to right, the three bars represent: no exposure, intermittent exposure and continuous exposure. The error bars represent 95% confidence intervals for the point estimates.

**REFERENCES**


