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).

RESEARCH DESIGN AND METHODS — DPP/DPPOS participants were assessed for diabetes every 6 months and for antidepressant use every 3 months in DPP and 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 (adjusted hazard ratio 2.34 [95% CI 1.32–4.15]) and lifestyle (2.48 [1.45–4.22]) arms, but not in the metformin arm (0.55 [0.25–1.19]).

CONCLUSIONS — Continuous antidepressant use was significantly associated with diabetes risk in the placebo and lifestyle arms. Measured confounders and mediators did not account for this association, which could represent a drug effect or reflect differences not assessed in this study between antidepressant users and nonusers.

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Our earlier report from the Diabetes Prevention Program (DPP) (1) was the first to examine antidepressant medicine (ADM)-related diabetes risk in an overweight population with elevated fasting glucose and impaired glucose tolerance. We found in the placebo and lifestyle arms that when other factors associated with diabetes risk (age, sex, education, fasting plasma glucose at baseline, weight at baseline, weight change during the study, and depression symptoms at baseline and during the study) were controlled, baseline ADM use and continuous ADM use during the study (compared with no use) were associated with significantly increased diabetes risk; in the lifestyle 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 7 years of the Diabetes Prevention Program Outcomes Study (DPPOS) and providing a median 10.0-year (interquartile range 9.0–10.5) follow-up since randomization to the DPP.

RESEARCH DESIGN AND METHODS

— Participants (N = 3,234) 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 with placebo (2).

All 3,150 surviving DPP participants who had not withdrawn consent were eligible for the DPPOS, and 2,665 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).

DPP/DPPOS participants brought all prescription medicines, including ADMs, to clinic visits. Study staff identified all ADMs 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 oral glucose tolerance test (2).

Statistical analysis

ADM use was reported quarterly during the DPP and every 6 months during the DPPOS. Cox proportional hazard models

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The opinions expressed in this study are those of the investigators and do not necessarily reflect the views of the funding agencies.

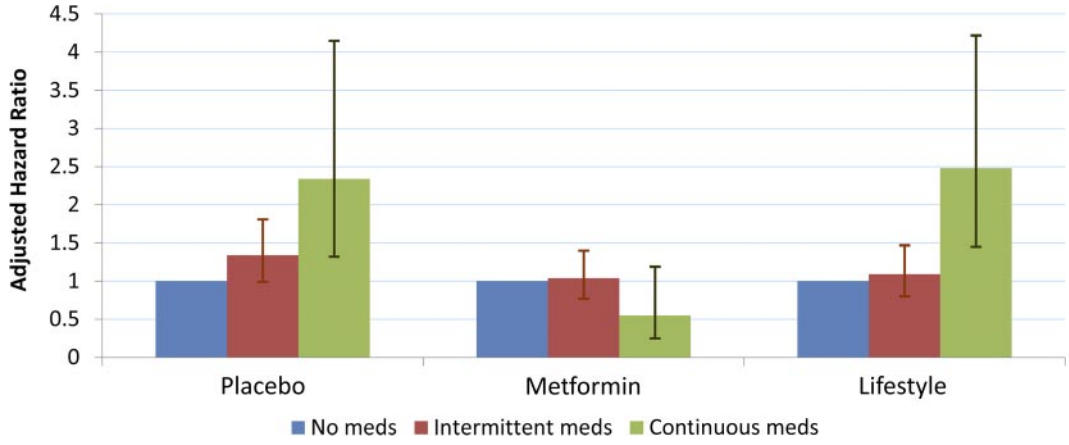

Figure 1—*For each treatment group, from left to right, the three bars represent no exposure, intermittent exposure, and continuous exposure. The error bars represent 95% CIs for the point estimates.*

(1) were used to evaluate whether taking ADMs was 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). At each successive time point, the value of the variable was calculated based on all previous time points, including the current measurement. 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 (HRas).

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 study and should be considered an extension, not a replication, of those findings. All analyses were performed using SAS (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 with no use) was strongly associated with diabetes risk (Fig. 1) for participants in the placebo (HRa 2.34 [95% CI 1.32–4.15] and lifestyle (2.48 [1.45–4.22]) arms. In the placebo arm, the association between intermittent ADM use and diabetes trended toward statistical significance (1.34 [0.99–1.81]). In the metformin arm, ADM use was not associated with diabetes risk (0.55 [0.25–1.19]). There was a significant difference between the lifestyle and metformin arms in the association between ADM and diabetes risk. Results did not change when we excluded participants taking ADMs that are more likely to cause weight gain (tricyclic and tetracyclic agents).

CONCLUSIONS — 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 lifestyle arm. These findings are similar to those in 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 not assessed in the study between ADM and non-ADM users. ADM use was not associated with diabetes risk in the metformin arm. Although there is no obvious explanation for this latter finding, one study found that metformin induces the release of 5-hydroxytryptamine through neuronal and nonneuronal 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 use 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 (placebo $n = 18$, lifestyle $n = 15$). 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.

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