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 [0.25–1.91]).

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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Antidepressant medication and diabetes risk

(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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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.
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No other potential conflicts of interest relevant to this article were reported.

R.R.R. wrote the manuscript, reviewed/edited the manuscript and contributed to the discussion. Y.M. researched data and reviewed/edit ed the manuscript. M.P., D.G.M., D.W.P., E.B.-C., and W.C.K. reviewed/edit ed the manuscript and contributed to the discussion.

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References