COMMENT ON VIMALANANDA ET AL.

Depressive Symptoms, Antidepressant Use, and the Incidence of Diabetes in the Black Women's Health Study. Diabetes Care 2014;37:2211–2217

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Vimalananda et al. (1) report antidepressant use, regardless of severity of depressive symptoms, to be associated with an increased risk of diabetes. The authors note that "this may represent a direct effect of the medications" (1). We would like to suggest a different interpretation of their results, because in light of previous studies, the antidepressants use–diabetes association might not be causal (3–5).

Type 2 diabetes is characterized by impaired β-cell function and insulin resistance leading to high levels of circulating glucose. The disease develops gradually such that elevated fasting glucose and impaired glucose tolerance are typically seen years before the onset of manifest disease. This is known as the prediabetes phase. After the onset of disease, many patients are not aware of their condition as the initial symptoms in manifest diabetes can be fairly mild. It has been estimated that as many as one-third of diabetes is undiagnosed.

If antidepressant use "causes" diabetes, an association would be apparent with prediabetes and undiagnosed in addition to diagnosed diabetes. Vimalananda et al. used a questionnaire survey to ascertain diabetes and therefore were only able to examine the association between antidepressants and self-reported physician-diagnosed diabetes (1). In the Whitehall II study of 5,978 U.K. adults, prediabetes and undiagnosed

diabetes were assessed repeatedly by clinical examinations to supplement data on self-reported diagnosed diabetes (2). In agreement with Vimalananda et al., antidepressant use was associated with an increased incidence of self-reported physician-diagnosed diabetes, with an odds ratio of 3.1 (2). However, antidepressant use was not associated with undiagnosed diabetes at any follow-up examination, nor was it associated with higher fasting or 2-h glucose levels or increasing glucose levels over time. The mean difference in glucose changes over 10 years between participants reporting antidepressant use compared with those not on antidepressant treatment was 0.0 mmol/L (95% CI −1.1 to 1.1) ($P = 0.98$).

These are not chance findings because they were subsequently replicated in another cohort, the U.S. National Health and Nutrition Examination Survey (NHANES, $N = 3,183$). In that study, antidepressant use was associated with 1.8-fold greater odds of diagnosed diabetes but not with undiagnosed diabetes (3). Furthermore, in treatment trials and studies measuring metabolic traits before and after drug therapy, use of antidepressants has not been shown to increase the risk of type 2 diabetes (4,5).

If antidepressant use is unlikely to cause diabetes, what explains the observed association between its use

and diagnosed diabetes? Detection bias is one possible explanation. Antidepressant use may be associated with an increased likelihood of being diagnosed with diabetes because patients treated for one disorder also are more likely to be screened for and diagnosed with another disorder due to their more frequent contact with health care givers.

More research is needed on the off-target effects of antidepressants. However, at this stage we urge caution in suggesting a causal link between antidepressant use and diabetes because the available evidence does not show antidepressant use to be associated with pathophysiological changes characterizing prediabetes or diabetes.

References

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