

Diabetes, Depression Raise Mortality in Women

BY SHERRY BOSCHERT

FROM ARCHIVES OF GENERAL PSYCHIATRY

The combination of type 2 diabetes and depression doubled the overall risk of death and nearly tripled the likelihood of dying of cardiovascular disease within 6 years, an analysis of data on 78,282 women found.

Previous studies have shown an association between depression or diabetes and increased risk of death from any cause or from CVD, but the combined

effects of these diseases on mortality have not been well studied, especially in women. Earlier studies also tended to be smaller and to have shorter follow-up.

An Pan, Ph.D., of the Harvard School of Public Health, Boston, and his associates analyzed data on participants in the prospective Nurses' Health Study who were 54-79 years of age in 2000 and who were followed until 2006. There were 979 deaths from CVD and 4,654

deaths from any cause during that time.

Compared with the 80% of women who developed neither diabetes nor depression, the age-adjusted relative risk of death was 1.71 in the 5% of women with diabetes alone, 1.76 in the 14% with depression alone, and 3.11 in the 1% with both diseases. The relative risk of death from CVD was 1.67 in women with diabetes alone, 1.37 in women with depression alone, and 2.72 in those with

both diabetes and depression (Arch. Gen. Psychiatry 2011;68:42-50).

The increased risks with either diabetes or depression were statistically significant, and the higher risks with both diseases were significant compared with either disease alone, even after adjustment for the effects of age, family history of diabetes and cancer, history of MI, current marital status, ethnicity, body mass index, and other confounders.

Don't Overlook Depression

The study shows that the risks of death in women with diabetes or depression are additive in those who have both diseases, but it doesn't establish a synergistic effect between the two diseases, Dr. Elizabeth Murphy said in an interview.

Given the increasing evidence for a link between diabetes and depression, "this article should provide an important reminder for clinicians to be vigilant about screening and treating depression in patients with diabetes," said Dr. Murphy, who was not involved in the study.

Perhaps more interesting is a previous report by Dr. Pan and his associates that established a bidirectional association between type 2 diabetes and depression, Dr. Murphy added (Arch. Intern. Med. 2010;170:1884-91). That report also drew from the Nurses' Health Study, analyzing data on 65,381 women who had neither diabetes nor depression in 1996. During 10 years of follow-up, 2,844 developed type 2 diabetes, and 7,415 developed clinical depression.

Depressed mood was associated with a 17% increased risk for developing diabetes, and use of antidepressants was associated with a 25% higher risk for diabetes, compared with women with the best depressive symptom scores. Women who developed diabetes were 24%-53% more likely to develop depression, depending on the severity of the diabetes.

DR. MURPHY is chief of endocrinology at San Francisco General Hospital.

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Indication and Important Limitations of Use

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

ONGLYZA has not been studied in combination with insulin.

Important Safety Information

- **Use with Medications Known to Cause Hypoglycemia:** Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug
- **Most common adverse reactions** (regardless of investigator assessment of causality) reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%)
- When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively

Laboratory Tests: There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA.

Drug Interactions: Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).



The highest risks were seen in women with depression combined with more severe diabetes, indicated by a longer duration of diabetes or treatment with oral medication or insulin. Death from CVD was three times more likely in depressed women who had had diabetes for more than 10 years, and four times more likely in depressed women who received insulin therapy for diabetes, compared with women who had neither depression nor diabetes.

The greater likelihood of death or of death from CVD in women with both diabetes and depression deserves greater

attention, especially considering that 20%-25% of people with diabetes are depressed, the investigators suggested. An estimated 24 million U.S. adults have diabetes and 15 million U.S. adults are depressed. Adults with diabetes are twice as likely to be depressed, compared with those without diabetes.

In general, physicians don't do a great job of recognizing major depression, and the United States can claim a relatively high prevalence of untreated mental disorders, they added. Better strategies may be needed to provide adequate psychological management and support for peo-

ple with diabetes. In addition, the coexistence of depression and diabetes should identify women who are at particularly high risk, the investigators concluded.

The mechanisms of the association between increased mortality and depression in women with diabetes are unknown.

The Nurses' Health Study, ongoing since 1976, has followed a large cohort of female nurses every 2 years with questionnaires, and had better than a 94% follow-up rate through 2006. Deaths were identified by the next of kin, postal authorities, or National Death Index. The

investigators obtained medical records and death certificates to determine the cause of death.

The current analysis excluded participants with a history of gestational diabetes, type 1 diabetes, secondary diabetes, or missing data regarding depression or diabetes.

The investigators reported having no conflicts of interest. The study was funded by the National Institutes of Health, the National Alliance for Research on Schizophrenia and Depression, and the Fonds de la Recherche en Santé du Québec. ■



Patients with Renal Impairment: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance [CrCl] \leq 50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

Pregnant and Nursing Women: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Patients: Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

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Please read the adjacent Brief Summary of the Product Information.

*Pioglitazone or rosiglitazone

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Reference: 1. Fingertip Formulary® data as of April 9, 2010. Data on File, April 2010.



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