

## Depression Tied to Faster Atherosclerosis Progression

BY MITCHEL L. ZOLER  
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ORLANDO — Patients who were depressed after coronary artery bypass surgery were significantly more likely to have atherosclerotic-disease progression within their grafted vessels during follow-up, in a post hoc analysis of data collected from more than 1,300 patients.

This suggestive finding should prompt a prospective study to definitely assess whether depression plays a causal role in atherosclerosis, Dr. Ambar Kulshreshtha said while presenting a poster at a conference on cardiovascular disease epidemiology and prevention sponsored by the American Heart Association.

The new analysis used data collected in the Post Coronary Artery Bypass Graft trial, which was designed to test whether treatment with an aggressive lipid-lowering regimen and low-dose warfarin could slow the progression of atherosclerosis within saphenous-vein bypass grafts. The study used patients who had undergone coronary bypass surgery 1-11 years prior to their enrollment. The primary findings of the trial were that aggressive lowering of LDL cholesterol was effective in significantly reducing the progression of atherosclerosis within grafted veins, but low-dose warfarin had no benefit (*N. Engl. J. Med.* 1997;336:153-63).

Almost 98% of the enrolled patients, a

total of 1,319, were evaluated for depression at the time they entered the study using the Centers for Epidemiologic Studies depression (CES-D) scale. Patients were considered to have depression if their score on the CES-D was at least 16. According to the way the CES-D is scaled, a score of 16-27 is considered to represent mild depression, and a score greater than 27 indicates moderate to severe depression.

**Patients with depression at baseline had a 40% increased risk of having substantial atherosclerosis progression in their saphenous vein grafts.**

When they underwent evaluation, 127 of the post-bypass patients scored 16 or greater on the CES-D, and the remaining 1,192 patients had scores of 15 or less.

All patients also had a baseline coronary angiogram when they entered the study, and a follow-up examination at an average of 4.2 years later.

In an analysis that adjusted for several baseline differences, patients who were diagnosed with depression at entry had a 40% increased risk of having substantial atherosclerosis progression in their saphenous vein grafts, compared with patients who were not depressed at baseline, said Dr. Kulshreshtha, a cardiovascular research physician at Beth Israel Deaconess Medical Center in Boston. This difference in the progression of atherosclerosis was statistically significant.

Among the many potential confounders that were used for adjustment in the analysis were gender, race, years since bypass surgery, systolic blood pressure, kidney function, diabetes, body mass index, and physical activity. ■

## Depression Plus Diabetes Affect Mortality Risk in CAD Patients

BY JONATHAN GARDNER  
London Bureau

Having both type 2 diabetes and depression puts patients with coronary artery disease at greater risk of death over a 4.5-year period than does either condition alone.

That finding emerged from a study presented at the American Psychosomatic Society meeting in Budapest, Hungary.

The more severe the depressive symptoms were in those patients with both coronary artery disease and diabetes, the greater their risk of death in the follow-up period.

Having high scores on the Beck Depression Inventory increased the risk of dying during the follow-up period by 20%-30%, compared with patients with similar depression scores but without type 2 diabetes, according to investigators from Duke University, Durham, N.C.

These findings suggest that physicians should screen for and treat depression in patients with diabetes and heart disease.

"There is some sort of synergistic effect between type 2 diabetes and depression that we don't fully understand," lead researcher Anastasia Georgiades, Ph.D., said in a written statement. "In our analysis, we controlled for factors that could influence mortality, such as heart disease severity and age. For whatever reasons, these patients were still at higher risk of dying, and future research will aim to investigate the mechanisms for this association."

The study compared 325 patients with type 2 diabetes and 582 patients without the disease during hospitalization for a coronary angiography. Their depression symptoms were rated using the Beck De-

pression Inventory (BDI). Approximately 25% scored at least 10 on the BDI, indicating depression, Lana Watkins, Ph.D., an investigator in the study, noted in an interview.

During the follow-up period of 4.5 years (median, 3 years), the researchers documented 135 deaths among the study participants. Among the depressed patients, 19% died, compared with 12% of those patients without depression, Dr. Watkins said.

The researchers found statistically significant associations between depressive symptoms and increased mortality and, separately, diabetes and increased mortality. The highest mortality was among patients with both diabetes and elevated BDI scores. The researchers did not publicize hazard ratios, however, because they said those statistics would overestimate the risk and create anxiety among patients.

"Patients with type 2 diabetes typically have an extensive self-care regimen involving special diet, medications, exercise, and numerous appointments with their doctor," Dr. Georgiades said in the statement. "It may be that such patients who are depressed might not be as motivated to carry out all these activities, thereby putting them at higher risk."

Physicians treating patients with heart disease and diabetes need to screen them for depression and treat as needed.

"Regular exercise has been shown to improve depression, too, so that might be an option," Dr. Watkins noted in an interview. "This could potentially improve depression and diabetes, and might be a good first choice for diabetics who would prefer not having to take additional medications." ■

## Try Inhibiting Serotonin to Return Executive Functioning

BY DAMIAN McNAMARA  
Miami Bureau

ORLANDO — Alterations in brain circuitry and chemistry mediated through the dorsolateral prefrontal cortex can cause executive dysfunction in multiple disorders, according to a presentation at a psychopharmacology congress sponsored by the Neuroscience Education Institute.

"Executive dysfunction is there. It hits you in the face if you are dealing with schizophrenia," said Dr. Thomas L. Schwartz. "But in depression you may have to look for it. I was always looking for that in the background—insomnia, fatigue, and executive dysfunction—the key residual symptoms of depression treatment."

Decreased metabolism in the dorsal and medial prefrontal cortex and the anterior cingulate are neurobiologic factors that might

contribute to executive dysfunction in depression, Dr. Schwartz said. A decrease in *N*-acetyl aspartate, a marker or neuronal function, also may play a role. "It's another way to look at the brain, and in depressed folks you can show the brain is not doing what it is supposed to," said Dr. Schwartz, director of the depression and anxiety disorders research program at the State University of New York, Syracuse.

Executive dysfunction is associated with noradrenergic, dopaminergic, and histaminergic projections to the dorsolateral prefrontal cortex. One tactic to get more norepinephrine to flow in that circuitry is to manipulate the serotonin levels, Dr. Schwartz said.

"Too much serotonin can be a bad thing in the frontal lobes. If you inhibit the inhibitor you can get more norepinephrine up there and help return executive functioning," he added.

Pharmacologic agents that might increase norepinephrine, dopamine, and/or histamine and help improve executive function include drugs such as bupropion, atomoxetine (Strattera), and modafinil (Provigil), and drug classes such as stimulants and atypical antipsychotics, Dr. Schwartz said.

"Use of atomoxetine for executive dysfunction in depression makes biological sense and circuitry sense," he said. "But there are no controlled studies [of atomoxetine] in executive dysfunction in depression."

Executive dysfunction also is associated with sleep disorders. "Your brain wants you to have a homeostatic amount of sleep. If you get sleep deprived, no matter what the cause, you function poorly and make errors in omission and commission," Dr. Schwartz said. Again, "there is poor metabolism in the prefrontal cortex." ■

Addition of a sleep aid can have positive effects on next-day functioning. Stimulants, modafinil, or armodafinil can improve attention and concentration during the day, Dr. Schwartz said. "If you can keep people more awake during the day, and they avoid napping, they may not need a sleeping pill at night."

Insomnia is comorbid with depression in around 85% of people (*J. Clin. Psychiatry* 2004;65:27-32). "That is a lot of people," Dr. Schwartz said. Some antidepressant medications can have a direct effect on sleep, he added. For example, bupropion increases REM sleep and sleep latency, but reduces sleep continuity. Trazodone decreases REM sleep time and may cause daytime sedation. In contrast, nefazodone increases REM sleep time and is associated with minimal daytime sedation.

Sleep aids are a treatment option. Examples include zolpidem

(Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). "I don't think one is better than the other, so choose based on half-life," Dr. Schwartz suggested. Sonata has the shorter half-life; Ambien is in the middle; Lunesta has the longest. "Which one can you take at 3 a.m. if you need to work at 9 in the morning? Sonata."

Modafinil is another pharmacologic option in patients with executive dysfunction and other adverse effects of impaired sleep. "This will not save every one of your patients but you can try it," Dr. Schwartz said. "It's the only product that raises histamine that I know of, and histamine going up to the cortex is good for executive function."

Dr. Schwartz said, "Modafinil is a funny drug—doses above 300 mg backfire in certain populations. Lower doses may be better for treatment of executive dysfunction." ■