Citalopram May Ease Depression in Heart Disease

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TUCSON, ARIZ. — A randomized, multicenter Canadian trial testing interpersonal psychotherapy and citalopram in 284 depressed patients with stable coronary artery disease produced mixed results, investigators reported at the annual meeting of the Academy of Psychosomatic Medicine.

Citalopram (Celexa) was significantly more effective than placebo, reducing Hamilton Depression Rating scale (HAM-D) scores by an additional 3.3 points on average, according to Dr. François Lespérance, principal investigator of the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial.

Adding interpersonal psychotherapy (IPT) to 12 weekly clinical management sessions was a disappointment, however. Short-term therapy turned out to be no more effective in relieving depression than clinical management alone.

The Canadian Institutes of Health Research gave the CREATE trial a $1,342,996 (Canadian) grant. Starting in 2002, the study enrolled patients in Montreal, Kingston, Ottawa, and Toronto. Faced with slow enrollment, it added sites in Halifax and Calgary.

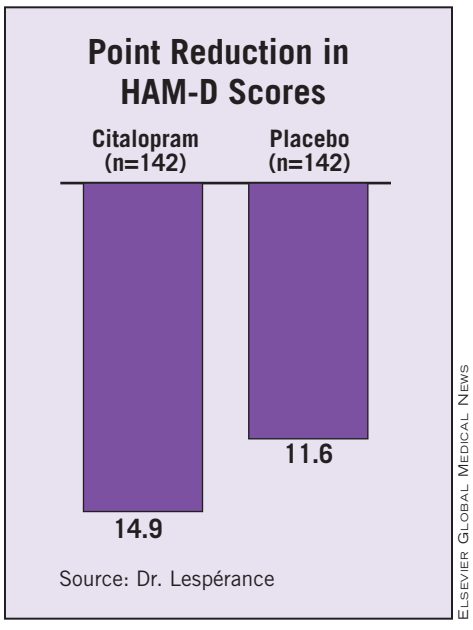
To maximize resources, the investigators randomized patients twice under a 2-by-2 factorial trial design. The participants comprised four cohorts: IPT/clinical management and citalopram (67 patients), IPT/clinical management and placebo (75 patients), clinical management alone and citalopram (75 patients), and clinical management alone and placebo (67 patients).

Consequently, the analyses were based on 142 patients exposed to IPT/clinical management vs. 142 patients exposed to clinical management alone and 142 patients treated with citalopram vs. 142 treated with placebo.

The presentation did not address the combined effect of IPT and citalopram in patients given both therapies.

Dr. Nancy Frasure-Smith, a coinvestigator, said the investigators neither expected nor saw any synergy between IPT and citalopram.

Dr. Frasure-Smith, a professor of psychiatry at McGill University in Montreal and senior research associate at the Montreal Heart Institute, emphasized that the trial used broad inclusion criteria. She cited growing evidence that depression is a risk factor for heart disease, but said little is known about treating depression in coronary disease patients because most depression treatment trials exclude patients with comorbidities.



In addition to having stable coronary artery disease, patients entered the CREATE trial having a current major depressive episode lasting at least 4 weeks based on the Structured Clinical Interview for Depression (SCID) and a baseline score of 19 or more on the 24-item Hamilton Depression Rating scale (HAM-D).

In the medication arms described by Dr. Lespérance, chief of psychiatry at the Centre Hospitalier de l'Université de Montréal, citalopram or placebo was titrated up from 10 mg per day during the first week to 20 mg per day for the next 5 weeks. If a patient's HAM-D score did not fall to 8 or less by week 6, the dose was increased to 40 mg per day for the duration of the study. Dr. Lespérance said the average dose was 33 mg per day by the end of the trial.

The advantage of citalopram over placebo was evident by the sixth week, he said. By the end of the trial, HAM-D scores fell by 14.9 points with citalopram and 11.6 points with placebo. Similar effects were

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reported on the Beck Depression Inventory and the Inventory for Depressive Symptomatology.

Although side effects typical of selective serotonin reuptake inhibitors (SSRIs) were reported, Dr. Lespérance said cardiovascular side effects were rare and small with no difference between groups. CREATE gave "no evidence that we should be concerned about cardiac safety," he said. As for evidence that SSRIs might be cardioprotective, he cautioned that the data are inconclusive.

The investigators conducted a biomarker analysis that found treatment with citalopram was associated with enhanced production of nitric oxide. Dr. Louis T. van Zyl, a coinvestigator from Queens University in Kingston (Ont.), said the clinical implications are unclear. He added, however, that increasing nitric oxide might reduce cardiovascular risk.

All of the patients received 15-20 minutes of clinical management each week. During these sessions, therapists reviewed patient progress and side effects, according to Dr. J. Robert Swenson, a coinvestigator from the University of Ottawa Heart Institute.

Weekly IPT sessions were limited to 45 minutes duration and 12 weeks in all, he said. Patients assigned to IPT had to choose one issue to focus upon in short-term therapy, which typically followed clinical management.

Dr. Swenson said patients who received clinical management without IPT did slightly better halfway through the trial. No significant difference was found at 12 weeks, as he reported about half the patients in both groups responded to treatment, and a third went into remission.

Therapists who were experienced in IPT or specially trained for the trial delivered both the clinical management and IPT sessions.

This use of the IPT therapists for clinical management generated extensive discussion at the meeting. Despite assurances by the investigators that the clinical management sessions were closely monitored, some audience members questioned whether the clinical management–alone arm received more therapy than a nurse practitioner would deliver as usual care to similar patients who were outside of the trial. ■

Does Treatment Reduce Deaths?

CREATE was the third large clinical trial to investigate treatment of major depressive disorder in heart disease patients.

In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), investigators did not find the selective serotonin reuptake inhibitor sertraline (Zoloft) to be significantly better than placebo in reducing depressive symptoms for the population overall, but it was safe and more effective for recurrent depression in patients with a recent myocardial infarction or unstable angina (JAMA 2002;288:701-9).

In the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, investigators compared 6 months of cognitive-behavioral therapy supplemented as needed with sertraline with usual care in 2,481 patients who were depressed when enrolled 1 month after an acute myocardial infarction. Changes on the Hamilton Depression Scale were statistically significant, but therapy had no impact on the primary outcomes of the study: death or recurrent myocardial infarction (JAMA 2003;289:3106-16).

The direct effect that lowering cholesterol or relieving depression has on heart disease may never be known, said Dr. Nancy Frasure-Smith, a CREATE investigator, in a plenary lecture before release of the CREATE results at the Academy of Psychosomatic Medicine meeting. Statins and antidepressants have pleiotropic effects, she said; they can affect multiple systems or metabolic processes. With respect to antidepressants, she cited human and animal studies showing impacts on platelet activation, endothelial function, C-reactive protein levels, and inflammation.

"If any of these treatments improves prognosis in coronary artery disease patients, we'll know [it] should be widely used because it helps improve survival," she said. "But because of the pleiotropic effects of most available depressant treatments, we will not know what the impact is because of a change in depression itself." Depression should be treated in its own right, she advised, reminding cardiologists about "the compliance issue:" Depressed patients are less likely to adhere to treatment of their coronary artery disease.