

Psychopharmacology for the Clinician Psychopharmacologie pratique

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Selective serotonin reuptake inhibitors (SSRIs) and depression after myocardial infarction (MI)

Major depression (MD) often occurs after MI and has been shown to be an independent predictor of poor cardiovascular (CV) outcome. In spite of this, there are only 2 published double-blind randomized placebo-controlled studies of the safety and efficacy of SSRIs in patients with MD after MI.

In the SADHART study (Glassman et al, *JAMA* 2002;288:701-9), patients admitted to hospital for recent MI or unstable angina who had MD were randomly allocated either sertraline or placebo for 24 weeks. Sertraline, which was administered to 186 patients, was assessed to be safe from a CV point of view. There were no statistically significant differences between placebo and sertraline in the occurrence of CV events (MI, angina, congestive heart failure, stroke and death) or for left ventricular ejection fraction, heart rate, electrocardiogram changes or premature ventricular complexes. Strik et al (*Psychosom Med* 2000;62:783-9) assessed the safety of fluoxetine in a double-blind randomized placebo-controlled trial. They found that 25 weeks of fluoxetine treatment in 27 patients with MD after MI was safe compared with placebo. Although suggestive of the safety of certain SSRIs after MI, an obvious limitation of these 2 studies is the small number of patients who received the drug in question. Thus, drug-drug interactions between SSRIs and cardiac medications cannot be ruled out. For example, certain anti-arrhythmics were an exclusion criterion in the SADHART study. Furthermore, the SSRIs were not administered early after MI, which precludes comment on their safety during this medically critical period, and severely medically ill patients were excluded from these studies. Long-term

deleterious CV effects of SSRIs are possible. For example, some SSRIs have been shown to increase low-density lipoprotein levels (Lara et al, *J Clin Psychiatry* 2003;64:1455-9), the main conventional CV risk factor. Long-term treatment with SSRIs and, particularly, paroxetine can induce marked weight gain, which is another conventional CV risk factor.

The efficacy of SSRIs in patients with MD after MI has not been clearly shown. In the SADHART study, sertraline induced a non-statistically significant mean reduction of 8.4 points on the Hamilton Rating Scale for Depression (HAM-D) compared with a 7.6-point mean reduction with placebo. The high placebo response is not surprising and may have been compounded by the high percentage of patients with post-MI MD that remits spontaneously. The apparently lower efficacy than that usually observed in MD clinical trials with physically healthy patients may have been the result of the short duration of depressive episodes after MI in a significant number of subjects. A limitation of the study was the heterogeneity of the sample, with a mix of patients with MD who were depressed before admission to hospital and those who developed MD after admission. Regarding only patients with a previous history of MD, the decrease in mean HAM-D score was statistically significant with a mean decrease of 9.8 and 7.6 in the sertraline and placebo groups, respectively. Even in this subgroup, however, compared with physically healthy patients included in MD clinical trials, the observed decrease in mean HAM-D scores in the treatment group after MI would only be considered moderate. In the study by Strik et al, the difference of 2.7 HAM-D points at week 25 between the fluoxetine and the placebo groups was not statistically significant.

In the SADHART study, the incidence of severe CV events was smaller in the sertraline group (14.5%) than in the placebo group (22.4%), but no statistically significant differences were found between the groups in terms of overall CV events. As stated by the authors, this study did not have the statistical power to detect a reduction in CV events. It is also possible that cardiac drugs such as statins affect the biologic CV risk factors associated with MD, thereby masking an additional biologic effect that SSRIs may have on CV outcome. Lesperance et al (*Am J Psychiatry* 2004;161:271-7) have shown that, in patients not taking statins after acute coronary syndrome, depressed patients had markedly higher levels of C-reactive protein (CRP), which is a well-recognized CV risk factor, than nondepressed patients. In contrast, in patients taking statins, CRP levels of depressed patients did not differ from those of nondepressed patients.

After 6 months of treatment and follow-up, sertraline and probably other SSRIs appear to be safe and moderately efficacious in the treatment of depression after MI. However, the limitations of the available studies preclude the blanket prescribing of SSRIs for MD in this patient population. At this point, it is not possible to determine whether SSRIs improve CV outcome, and further investigations are needed.

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Competing interests: Dr. Le Mellédo has organized symposia and given talks sponsored by Lundbeck, Wyeth, Pfizer, Eli Lilly, GlaxoSmithKline and Merck Frosst. He has been an investigator in clinical trials sponsored by the aforementioned companies as well as Roche, Servier, Novartis, Hoechst, Bristol-Myers Squibb and Janssen Ortho. None declared for Dr. Perez.

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.