

## Sertraline Does Not Improve Well-Being in Patients with Advanced Cancer Who Do Not Have Depression

Stockler MR, O'Connell R, Nowak AK, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer but without major depression: a placebo-controlled double-blind randomised trial. *Lancet Oncol* 2007;8:603–12.

### Study Overview

**Objective.** To determine the effects of sertraline on symptoms of depression and anxiety, quality of life, and mortality in patients with advanced cancer but without major depression.

**Design.** Randomized, double-blind, placebo-controlled trial.

**Setting and participants.** Patients were recruited from several oncology clinics in Australia between July 2001 and February 2006 and were included if they had advanced cancer, defined as the presence of metastatic disease and receipt of palliative therapy; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; a life expectancy of  $\geq 3$  months; serum creatinine  $< 200 \mu\text{mol/L}$ ; bilirubin  $< 30 \mu\text{mol/L}$ ; the ability to provide informed consent and complete quality of life questionnaires; and baseline scores of  $\geq 4$  out of 10 on scales for depression, anxiety, or fatigue from the Patient Disease and Treatment Assessment Form. Patients were excluded if they had major depression, delirium, a contraindication for treatment with selective serotonin reuptake inhibitors (SSRIs), a past history of schizophrenia or bipolar disease, or recent treatment with an antidepressant.

**Intervention.** Participants were randomized to sertraline 50 mg once daily or matching placebo.

**Main outcome measures.** The primary outcome was depression, as assessed by the Centre for Epidemiologic Studies Depression scale. Secondary outcomes included anxiety, as measured by the Hospital Anxiety and Depression Scale; fatigue, as measured by the Functional Assessment of Cancer Therapy General and Fatigue scales; and somatic and psychological distress, as measured by the Somatic and Psychological Health Report screening tool. Quality of life was assessed using the Utility-Based Questionnaire–Cancer instrument. Scores for all surveys were linearly transformed to a scale ranging from 0 to 100. Study assessments were performed at baseline and then at weeks 4, 8, 12, 16, 26, 39, and 52. Comparison of treatment groups were based on scores at 4 and 8 weeks.

**Main results.** 189 patients were enrolled, with 95 patients randomized to sertraline and 94 patients randomized to placebo. Based on recommendations of the data and safety monitoring board (DSMB), the study was terminated early due to a lack of any effect in the sertraline group along with a possibility of increased mortality seen in participants allocated to sertraline. At 8 weeks, there were no statistically significant differences between the groups on any of the measures for depression, anxiety, fatigue, overall well-being, physical well-being, emotional well-being, or ECOG performance status. At the first interim analysis (median time, 15 weeks), there was an increased risk of mortality in sertraline-treated patients as compared with placebo-treated patients (adjusted hazard ratio, 1.62 [95% confidence interval, 1.06–2.41];  $P = 0.02$ ). However, at the conclusion of the trial, there was a nonsignificant increased risk of mortality in the sertraline group compared with the placebo group (hazard ratio, 1.27 [95% confidence interval, 0.87–1.84];  $P = 0.20$ ).

**Conclusion.** In patients with advanced cancer but without major depression, sertraline does not improve symptoms of depression, anxiety, or well-being. Sertraline should only be prescribed for cancer patients diagnosed with major depression.

### Commentary

Major depression is common in patients with advanced cancer, and randomized controlled trials have demonstrated that SSRIs are effective for improving symptoms of depression in this patient population [1,2]. This is of particular significance given that depression is associated with increased mortality in cancer patients [3]. Many cancer patients suffer from psychologic or emotional stresses, including anxiety or fatigue, and although SSRIs are clearly indicated for major depression, these medications have been used “off-label” to treat numerous psychologic complaints other than depression. Indeed, some trials have suggested that SSRIs might improve overall quality of life in cancer patients without clinical depression [4]. However, prior studies have been limited by small sample sizes.

This trial by Stockler et al was designed to evaluate the

use of SSRIs in advanced cancer patients without major depression. The study was well-designed and demonstrated that sertraline had no effect on any of the psychologic or emotional outcome scales. Of note, there was a statistically significant increased risk of death at the first interim analysis, which prompted the DSMB to stop patient recruitment and collect additional follow-up data. On a subsequent analysis, there was a nonsignificant increase in mortality. As with any interim analysis, this finding could be related to chance; however, in the context of a lack of any benefit seen with sertraline, it only supports the need for caution when using SSRIs in patients without clinical indications.

### Applications for Clinical Practice

Prescribing sertraline to patients with advanced cancer but without major depression is unlikely to improve overall well-being, anxiety, or quality of life. Sertraline is effective for cancer patients with depression, and clinicians should

carefully assess for signs and symptoms of major depression in all cancer patients.

—Review by Harvey J. Murff, MD, MPH

### References

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