

## Letters to the Editor

### Dosing of Selective Serotonin Reuptake Inhibitors

**Sir:** I am writing to address an inaccuracy written about the dosing and administration of selective serotonin reuptake inhibitor (SSRI) medications in the article by Marken and Munro published in the December 2000 issue of the *Companion*.<sup>1</sup> Contrary to the contention by Drs. Marken and Munro that sertraline is more effective at the high end of the dosage range, the evidence suggests that sertraline is effective at its minimum effective dosage of 50 mg across the range of indicated mood and anxiety disorders and that, for patients not achieving optimal response, dose titration occurs among all SSRI agents.

In the section on Dosing and Administration, there is only 1 paragraph on the “dose-response” relationship and 1 reference to support its only point for this section: “Recent data and widespread clinical observation suggest that sertraline, unlike the other SSRIs, is more effective at the higher end of its dose range than at its recommended starting dose of 50 mg/day.”<sup>1(p205)</sup> Unfortunately, the single study cited to support this contention<sup>2</sup> has severe limitations, including its retrospective nature, its small sample of 59 patients limited to 1 site, and its utilization of retrospective chart interpretation to indicate depression.

Fortunately, there is a significant literature related to sertraline and SSRI dosing to which we can refer. Prospective dose-finding studies in major depression, panic disorder, and obsessive-compulsive disorder (OCD); double-blind comparator studies; and well-designed retrospective studies all demonstrate with remarkable consistency that sertraline is effective at 50 mg. In cases in which a greater response is necessary, sertraline, as do all other SSRI agents, has a dosing range within which patients can be titrated. Widespread clinical experience and multiple studies demonstrate that all SSRI agents have similar rates of titration in the general population. Some of these studies are summarized as follows:

1. Fixed-dose studies for sertraline across its indications of major depression, panic disorder, OCD, and posttraumatic stress disorder confirm that 50 mg is the minimum effective dose and provide no evidence for a dose-response relationship in the dosing range of 50 to 200 mg.<sup>3-5</sup> In other words, all sertraline doses studied in this range were considered effective with no evidence for greater response rates at higher doses. This finding has recently been reconfirmed in another prospective randomized controlled study by Schweizer et al.,<sup>6</sup> which demonstrates that patients who are randomly assigned to 50 mg or 150 mg of sertraline after not responding at 50 mg in 3 weeks do respond to both doses over the next 6 weeks with no difference in outcome. This study clearly demonstrates that many patients do respond at 50 mg without required titration.

2. In contrast, other SSRI agents have different minimum effective doses depending on their clinical indication. For example, paroxetine has a minimum effective dose of 20 mg

for depression, but for panic disorder, it is 40 mg.<sup>7,8</sup> In another example, the prescribed information for citalopram recommends that for patients with depression (its only approved indication), citalopram “should be administered at an initial dose of 20 mg/day, generally with an increase to 40 mg/day.”<sup>9</sup> In this regard, citalopram is the only SSRI whose approved label carries a recommendation to titrate dosages for most patients beyond its starting dose for the treatment of depression.

3. A recent well-designed comparative, flexible-dose, 12-week study of SSRIs in anxious depression<sup>10</sup> demonstrates equivalent efficacy in response rates among the studied agents. According to Fava et al.,<sup>10</sup> there were no differences in percentages of patients who were titrated, and final mean doses for fluoxetine, sertraline, and paroxetine were 44 mg, 104 mg, and 36 mg, respectively.

4. IMS data, which represent current practitioner prescribing across the United States, indicate that the mean sertraline dose in the month of March 2001 was 86 mg, demonstrating that the majority of patients are being treated with doses between 50 and 100 mg.<sup>11</sup>

Finally, it is worthwhile to mention that for many clinical trials on which efficacy of SSRI agents was established, patients who enroll often have severe and recurrent disorders. When given the flexibility to do so, investigators in clinical trials increase a medication’s dosage to the maximum tolerated level to achieve maximal response in patients. The evidence suggests that many patients will benefit from dose increases of SSRI agents beyond the recommended starting dose, if a satisfactory response is not achieved in the 4- to 6-week period after initiation.<sup>12</sup>

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### Dr. Marken Replies

**Sir:** My colleagues and I thank Dr. Chung for his views; he makes several important points about our article.<sup>1</sup> I would like to point out that some of his data, although interesting, reflect dosing in diseases not covered directly in our article. My colleagues and I do appreciate the update of data that was unavailable when we wrote this article.<sup>2,3</sup>

The data with respect to optimal sertraline dosing are mixed. There are a number of additional studies suggesting that sertraline is more effective at higher doses. For example, Reimherr et al.<sup>4</sup> published the results of a double-blind study comparing the efficacy of sertraline with that of amitriptyline or placebo. Titration was permitted, but not forced, and the mean daily dose of sertraline was 145 mg at the end of the study. Cohn et al.<sup>5</sup> also conducted a double-blind comparison trial of sertraline (starting dose = 50, 100, or 200 mg/day) and amitriptyline in which titration was allowed but not forced. In addition, dose could be decreased at any time at the investigator's discretion. At the end of 8 weeks, the mean daily dose of sertraline was 116 mg. Gregor et al.<sup>6</sup> published an analysis of how selective serotonin reuptake inhibitors were prescribed to outpatients in an urban hospital. For sertraline, the mean starting dose was 57 mg/day, and after 9 weeks, the mean daily dose was 110 ± 65 mg. Thus, data derived from both controlled and naturalistic studies have suggested that sertraline may be more effective at higher doses.

There are also additional studies suggesting that all recommended doses of sertraline are equally effective.<sup>7,8</sup> In the study by Fabre et al.,<sup>7</sup> however, the design of the trial may have favored a flat dose-response profile. In particular, the high dropout rate for patients in the 200-mg-dose group (a result of initi-

ating patients at that dose) most likely undercut efficacy data derived from last observation carried forward.

My colleagues and I concur with the widely held perspective that results from clinical trials often are not replicated in clinical practice—the efficacy-effectiveness gap—and that subjects in clinical trials do not reflect the needs of the population as a whole. In fact, many patients in practice can be either underdosed because they are not titrated when they have only a partial response or are too aggressively dosed when they are titrated too quickly instead of waiting for a lower dose to be effective. We also support the dosing strategies of the Agency for Health Care Policy and Research published in 1993, as referred to by Dr. Chung.<sup>9</sup>

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