

# Letters to the Editor

## Mean Dose After Splitting Sertraline Tablets

**Sir:** Some pharmaceutical companies price all strengths of a particular medication the same. Medications may also be priced so that 1 larger tablet is less expensive than 2 tablets equaling the same dose. Many tablets are scored for breaking or are easy to cut using commercially available tablet cutters.

The Department of Veterans Affairs Medical Centers (VAMCs) and managed care organizations use tablet splitting as a cost-containment measure. For example, a prescription for 10 mg of simvastatin is filled with 20-mg tablets and a pill cutter. Lisinopril, citalopram, metoprolol, and sertraline are medications that are commonly split. If a patient is unable to split tablets, then they are not required to do so.

Concern has been raised regarding the accuracy of the delivered dose of the antidepressant sertraline after splitting the tablets. Since this is one of the medications routinely split, we wanted to determine if tablet splitting caused wide fluctuations in the daily dose.

**Method.** A class 1 electronic scale (Precisa Balance; Viscount Intralabs, Inc., Lawrenceville, Ga.) was placed in an isolated room and was protected on 5 sides from air movement that would alter the weight of the tablets. Five people volunteered for this pilot study. The ages of the people who cut and broke the tablets ranged from 32 to 77 years (mean = 54 years), and 3 people had varying degrees of degenerative changes in their hands (e.g., arthritis). Two of the participants (P.R.M., J.B.G.) work for the VAMC, 1 works at another hospital, and the other 2 are volunteers at the VAMC. No one was paid for splitting the tablets, and all received brief verbal training on use of the tablet cutter. Each volunteer cut sixteen 100-mg sertraline tablets (professional samples, lot number 9JP047E, expires May 1, 2001, and 9JP169F, expires Dec. 1, 2001) using a pill cutter (LGS Health Products, South Euclid, Ohio) and quickly broke 16 scored tablets by hand. The number of tablets was determined by the number of professional samples available at that time. Each tablet was weighed and split, and the pieces were individually weighed. Data were entered in a Microsoft Excel 97 worksheet. The actual weight of each 100-mg tablet allowed us to calculate the amount of active drug in each portion of the split tablets due to equal distribution of sertraline throughout the tablet.

**Results.** When a pill cutter was used, the amount of sertraline in the pieces ranged from 45.3 to 54.9 mg (mean  $\pm$  SD = 49.70  $\pm$  1.98 mg). Breaking tablets by hand gave a range between 43.4 and 56.1 mg (mean  $\pm$  SD = 49.74  $\pm$  2.58 mg). The difference between the total weight of the whole tablets and the split tablets was calculated, since small tablet fragments would sometimes be left over after the splitting process. From the 160 tablets split, only 88.6 mg (0.55%) of sertraline was unaccounted for in the weighing process. More sertraline was lost using a pill cutter versus breaking tablets by hand: 49.3 versus 39.3 mg, respectively. No tablet pieces were destroyed or unusable.

**Discussion.** Sertraline has an elimination half-life of 25 to 26 hours.<sup>1</sup> It is metabolized into the active metabolites desmethylsertraline and *N*-desmethylsertraline, with half-lives between 66 to 80 hours and 62 to 104 hours, respectively.<sup>2</sup> The long half-life of sertraline overlaps the daily doses and acts to minimize potential fluctuations in blood levels due to any variation in the delivered dose. In addition, taking the 2 pieces from 1 tablet on consecutive days would help minimize dosing inconsistencies.

Tablet splitting is effective for reducing pharmaceutical costs and has been used successfully in appropriate patients.<sup>3</sup> Counseling on how to use a tablet cutter may decrease dosage variance. Our pilot study illustrates the mean dose achieved when 5 people split 100-mg sertraline tablets to obtain a 50-mg dose.

*Sertraline tablets were provided by Pfizer, New York, N.Y. The authors acknowledge Jodi L. Fortwengler, B.S.Pharm., and Buck and Evelyn Schuler for their help in splitting tablets.*

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## Lamotrigine in the Treatment of Depersonalization Disorder

**Sir:** It has been proposed that excitatory amino acids such as glutamate might be relevant to the pathophysiology of depersonalization.<sup>1</sup> For example, subanesthetic doses of ketamine, whose effects might be mediated through increased glutamate release, can induce many of the subjective experiences characteristic of depersonalization.<sup>2</sup> Furthermore, pretreatment with lamotrigine, a drug reported to inhibit glutamate release,<sup>3</sup> has been found to attenuate these effects of ketamine.<sup>4,5</sup> We report here on 6 patients with chronic depersonalization disorder in whom treatment with lamotrigine as an add-on therapy brought about a significant clinical improvement.

**Method.** Eleven patients meeting criteria for DSM-IV depersonalization disorder and diagnosed by means of a semistructured interview using the Present State Examination (PSE)<sup>6</sup> were given lamotrigine as an adjunct to their ongoing medication. All patients had continuous (as opposed to intermittent) depersonalization ranging from 2 to 15 years and had proved resistant

Table 1. Summary of Comorbidity, Other Medications, and Outcome Measures Among Responders to Treatment<sup>a</sup>

Case	Age (y)	Sex	Comorbid Conditions	Concurrent Medications (mg/d)	Lamotrigine Dose at Endpoint (mg/d)	PSE Score <sup>b,c</sup>	DES Depersonalization Subscale Score <sup>c</sup>
1	34	M	Bipolar disorder	Lithium, 1000; citalopram, 20	250	4/2	59/32
2	36	F	Panic disorder	Sertraline, 50	250	4/1	90/66
3	32	F	None	None	200	4/2	34/6
4	42	M	Panic disorder with agoraphobia; migraine	Fluoxetine, 40	200	4/2	66/22
5	24	M	Panic disorder; migraine	Paroxetine, 20	250	4/1	55/12
6	29	F	Migraine	Paroxetine, 20	250	4/0	70/7

<sup>a</sup>Abbreviations: DES = Dissociative Experiences Scale, PSE = Present State Examination.

<sup>b</sup>Maximum score = 4.

<sup>c</sup>PSE and DES depersonalization subscale columns show assessment scores before lamotrigine was started and 1 month after the onset of treatment.

to previous pharmacologic treatments. Although 2 patients had a previous history of mood disorders, no affective symptoms were present at the time of diagnosing depersonalization disorder. With 1 exception, all patients were taking selective serotonin reuptake inhibitors (SSRIs) at the time of diagnosis. Lamotrigine was increased gradually over the course of 3 weeks, and its effects were assessed by means of the Dissociative Experiences Scale (DES),<sup>7</sup> its depersonalization subscale (as in Simeon et al.<sup>8</sup>), and a PSE score. These measures were administered at the time of diagnosis and 1 month later (Table 1).

**Results.** Six patients reported subjective beneficial effects ranging from 40% to 80% on a subjective improvement scale. These effects were confirmed by a drop in their PSE score and DES depersonalization subscale score. The other 5 patients in the sample reported no beneficial effect, and their scores on the outcome measures remained unchanged. None of the patients reported side effects. In all cases, improvement occurred on treatment with lamotrigine doses from 200 to 250 mg/day. In regard to comorbidity, the greatest improvement was seen in patients with a history of classic migraine (cases 4, 5, and 6; there were no migraine cases among the nonresponders). An association between depersonalization and migraine has been noted in the literature,<sup>9</sup> and it remains to be seen whether a reported prophylactic effect of lamotrigine on migraine aura might be related to this finding.<sup>10</sup>

**Discussion.** This is the first report, to our knowledge, of a beneficial effect of lamotrigine on depersonalization disorder. Although this was an open trial without control for placebo effects, the chronicity of the condition in all 6 cases, coupled with a poor response to previous pharmacologic treatments, makes the positive therapeutic response to lamotrigine augmentation noteworthy and less likely to be due to suggestion or spontaneous remission. Since lamotrigine has been found to have mood stabilizing effects<sup>11</sup> and might be effective in the treatment of posttraumatic stress disorder<sup>12</sup> and borderline personality disorder,<sup>13</sup> caution is needed at this early stage before ascribing the improvement seen in our patients to a specific anti-depersonalization effect. However, the fact that patients with depersonalization disorder are notoriously resistant to pharmacologic treatment points to a specific effect of lamotrigine in the treatment of depersonalization disorder and clearly indicates the need for placebo-controlled double-blind trials with lamotrigine both as the sole agent and as an add-on therapy with SSRIs.

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## Olanzapine Versus Other Antipsychotics in the Treatment of Schizophrenia

**Sir:** Gómez et al.<sup>1</sup> are to be commended for attempting a large observational study intended to advance the knowledge of the use of atypical antipsychotics under conditions that closely approximate those in the clinic, as opposed to the tightly proscribed circumstances dictated by a clinical study. Paradoxically, the authors undermine their own efforts by standardizing data collection around selected parameters, consequently introducing an ascertainment bias.

The primary finding of the study is that olanzapine is safe and associated with fewer adverse events and extrapyramidal side effects in schizophrenic patients compared with a cohort of schizophrenic patients treated with other neuroleptic therapies. Postmarketing surveillance in significantly larger populations of subjects than could have participated in clinical trials is useful for identifying previously undetected but infrequent adverse events. The authors increased the number of observations in their study beyond what would have been possible in a controlled clinical trial, but failed to identify new safety data. A likely explanation for this is that collection of adverse event information was biased toward the collection of movement disorder events, which are known to be associated with antipsychotics. Therefore, a flaw that has plagued other olanzapine and risperidone comparative studies<sup>2,3</sup> has similarly confounded the findings of this study.

Although the risperidone mean daily dose used in this naturalistic study (5.4 mg) appears reasonable, actual daily risperidone dosages ranged from 1.5 to 30 mg. The average daily doses of risperidone and olanzapine used in the United States for the treatment of schizophrenia are 4.0 and 14.1 mg, respectively (NDTI June 2001, IMS Health, Plymouth Meeting, Pa.). The 10% to 13% difference in adverse events with risperidone compared with olanzapine could, therefore, be totally accounted for by the use of clinically relevant doses of olanzapine and unrealistically high doses of risperidone.

Other events (e.g., diabetes, weight gain) that are more clinically significant than extrapyramidal symptoms (EPS) with atypical antipsychotics were not systematically examined. For example, multiple reports have described impaired glucose metabolism that in some instances was life-threatening in patients receiving olanzapine.<sup>4-6</sup> Weight gain, in addition to being associated with excess morbidity and mortality, is also associated with reduced compliance with antipsychotic therapy.<sup>7</sup> This study reported no cases of impaired glucose tolerance despite the large number of patients in the olanzapine group, thus raising the possibility of overreporting, in both groups, of the events for which systematic data collection was performed and of underreporting of other events. The large number of patients and the unequal distribution between olanzapine and non-olanzapine subjects could easily make a clinically insignificant difference appear statistically significant.

The haloperidol dose also appears much larger than that typically used for schizophrenia. EPS would not be unexpected with such large haloperidol doses and would skew the findings in favor of a safety advantage for olanzapine. The finding that 10.2% and 19.9% of patients taking olanzapine and risperidone, respectively, were given anticholinergics, while 36.9% and 49.6%, respectively, were identified as having EPS, again suggests that single ratings of patients on an elevated dose of risperidone were responsible for the differences in EPS and accounts for the apparent better safety profile of olanzapine.

Unfortunately, because of these limitations, this study did not fulfill its potential. Besides identifying, in a naturalistic manner,

the larger weight gain associated with olanzapine therapy, this comparison yielded very little in useful clinical observation obtained from an authentically naturalistic experience.

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### Drs. Sacristán and Gómez Reply

**Sir:** We appreciate the opportunity to respond to the comments made in print by Dr. Masand. We agree with Dr. Masand that the main objective of the EFESO study was to assess the safety of olanzapine and confirm differences regarding extrapyramidal symptoms (EPS) between the olanzapine group and the control group. This is acknowledged in the introduction section of the article.<sup>1</sup> We consider that this was a reasonable main objective for the study, taking into account when the study was designed and the low incidence of EPS observed in the pivotal controlled clinical trials during treatment with olanzapine in comparison with other antipsychotics.

Since this study was initiated, there have been reports in the literature of metabolic adverse events observed in temporal association with treatment with olanzapine and other atypical antipsychotics. A number of research initiatives are currently underway to investigate changes in metabolic parameters and treatment with atypical antipsychotics.

As stated in the Method section of the article, the naturalistic design of this study did not dictate that glucose levels, weight, or other laboratory procedures be systematically performed since the intent of the study was to reflect actual clinical practice for patients with schizophrenia. As in clinical practice, these procedures would have been performed if the patient presented with complaints or symptomatology warranting the

performance of the procedure. Obviously, this naturalistic approach may cause underreporting of some adverse events, but, on the other hand, the adverse events reported are probably the most frequent and relevant from a clinical perspective.

Although the UKU Side Effect Rating Scale<sup>2</sup> was used to identify EPS, it is important to note that all adverse events mentioned spontaneously by the patients or elicited in the patient-investigator interviews were recorded. Weight gain was reported with statistically significant difference in the olanzapine group compared with the control group. No cases of impaired glucose tolerance were documented in either the olanzapine or control group.

Contrary to Dr. Masand's subjective opinion that adverse events such as weight gain are more clinically significant than EPS, the results of a study conducted in parallel with EFESO showed that for Spanish psychiatrists, EPS is of greater clinical relevance than weight gain.<sup>3</sup> During the start-up meetings for the EFESO study, participating psychiatrists were asked to assign scores of clinical relevance to each of the adverse effects on a list of the most frequent adverse events of antipsychotics, according to their experience. The scores ranged from 1 (insignificant) to 5 (extremely severe). The researchers considered that weight gain has a lower severity (mean  $\pm$  SD = 2.6  $\pm$  0.79) than EPS such as dystonia (3.21  $\pm$  0.85), hypokinesia (3.01  $\pm$  0.68), akathisia (3.05  $\pm$  0.77), tremor (2.74  $\pm$  0.68), or hypertonia (3.16  $\pm$  0.75).

We strongly disagree with Dr. Masand's suggestion that the doses of risperidone and haloperidol somehow impeded the study from achieving its "potential." Relying solely on a risperidone dose provided by the manufacturer of risperidone as "data on file" from Janssen, Dr. Masand finds "unrealistically high" the dose of risperidone and suggests that the elevated dose of risperidone may be responsible for the differences in EPS. However, the median risperidone dose in the EFESO study was 6 mg/day, meaning that at least half of the risperidone-treated patients received an average daily dose of 6 mg or less. Further, the mean risperidone dose in the EFESO study was 5.39 mg/day. In studies using naturalistic or flexible-dose ranges, investigators have often found that mean daily doses of risperidone exceeded 6 mg.<sup>4-6</sup>

With respect to haloperidol, Dr. Masand claims that the dose used in the EFESO study (mean dose = 13.64 mg; range, 2–40 mg) "... appears much larger than that typically used for schizophrenia." The American Psychiatric Association Practice Guidelines for the Treatment of Patients With Schizophrenia<sup>7</sup> recommend that the effective daily dose of haloperidol is most likely in the range of 5 to 20 mg. However, higher doses are still commonly used.<sup>8</sup>

We disagree with Dr. Masand's view of the purpose of post-marketing naturalistic studies. Naturalistic studies are not typically the vehicle by which previously undetected but infrequent adverse events are identified. Rather, such studies are most useful in confirming or revising in a naturalistic setting the incidence and clinical relevance of adverse events reported in previous randomized controlled trials. The EFESO study did just this in confirming that olanzapine-treated patients were less likely to experience EPS than patients treated with other antipsychotics.

In summary, the primary objective of the EFESO study was to assess whether the lower incidence of EPS seen in olanzapine-treated patients in clinical trials was observed in a clinical practice setting. The results of this naturalistic study confirmed those findings. Naturalistic trials may also be useful in demonstrating that a priori perceptions regarding drug utilization and effectiveness may not reflect clinical practice. It appears that in this case, Dr. Masand's perceptions regarding the

dose of risperidone used in patients with schizophrenia and subsequent EPS profile are not in agreement with clinical practice in Spain. We would encourage Dr. Masand and other investigators to conduct similar observational prospective and controlled studies using different endpoints in order to improve the knowledge about the performance of drugs in actual practice.

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#### Should We Keep Calling Antidepressants Antidepressants?

**Sir:** In his recent comprehensive review "New Indications for Antidepressants," Schatzberg<sup>1</sup> finely points out the therapeutic efficacy of serotonin reuptake inhibitors, nefazodone, venlafaxine, mirtazapine, and bupropion for a wide range of disorders beyond major depression, such as generalized anxiety disorder, obsessive-compulsive disorder (OCD), social phobia, panic disorder, posttraumatic stress disorder, bulimia nervosa, aggressive behavior, and nicotine dependence, not to mention the efficacy of some so-called antidepressant drugs in migraine, chronic pain, and attention-deficit/hyperactivity disorder. Moreover, a few studies suggest that improvement of certain specific endpoints was independent of changes in depression.<sup>1</sup> So, why keep calling these drugs antidepressants?

This label is solely based on a historical perspective and dismisses the fact that some neurotransmitters, such as serotonin and monoamines, have diverse actions in several brain regions that seem not to be preferentially related to mood as compared to anxiety, impulse control, appetite, stress reaction, drug craving, or attention. There is clear overlap between some of these

categories, but there is also some degree of specificity regarding indications, such as serotonergic agents for OCD, dopaminergic/noradrenergic drugs for smoking cessation and attention-deficit/hyperactivity disorder, and norepinephrine uptake inhibition for poststroke depression.<sup>2</sup> Moreover, this inaccuracy can be puzzling and misleading for the increasing number of patients who are advised to take an “antidepressant,” despite not being at all depressed, subtly implying an additional diagnosis and its unnecessary burden if not properly clarified by the physician. Maybe it is time we called these drugs by their main mechanism of action (i.e., serotonergic agents or enhancers, dual agents, or dopaminergic agonists), or merely say such drug can be used to treat depression if the patient is depressed or social phobia, OCD, nicotine dependence, or whatever may be the case if the patient is not depressed.

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#### Dr. Schatzberg Replies

**Sir:** Lara and Souza make an excellent point in their letter to the editor. There is no question that these “antidepressants” have effects in many nondepressive disorders, and we agree that it is time to begin to reclassify agents by their pharmacologic properties. This would indeed be more accurate pharmacologically, but to really make sense of our treatments, we need a deeper understanding of the biology of specific symptoms and disorders. Ultimately, we need to combine the specific pharmacologic effects of drugs with a much better biological description and classification of our patients. Hopefully, genetics will help inform a new classification system. When this occurs, a pharmacologic reclassification will be more informative both theoretically and practically.

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