

## Letters to the Editor

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### Fluoxetine-Induced Sexual Dysfunction Reversed by Loratadine

**Sir:** Sexual dysfunction as a side effect of antidepressant treatment occurs at a rate of roughly 50% of treated patients.<sup>1</sup> Fluoxetine is no exception. Attempts at reversing sexual side effects in selective serotonin reuptake inhibitors (SSRIs) have included dosage reduction, change to a different SSRI or non-SSRI, and adding bupropion, *Ginkgo biloba*, cyproheptadine, yohimbine, trazodone, and sildenafil, all with varying degrees of success.<sup>2</sup> In this study, loratadine, a long-acting tricyclic antihistamine with selective peripheral histamine H<sub>1</sub> receptor antagonistic activity, appeared to be very helpful in reversing fluoxetine-induced sexual dysfunction.

About 12 months ago, one of my male clients with major depression who previously had experienced sexual dysfunction with fluoxetine, 5 mg/day, restarted taking fluoxetine, 5 mg/day, while also taking loratadine, 2.5 mg/day, for allergic rhinitis. The patient was taking these low doses because of being a slow metabolizer of medication in general. Whereas before with fluoxetine he had reported dulling of penile sensation and delayed erection and ejaculation, in the presence of loratadine none of these side effects were present and he reported normal sexual function, which continued at last report.

Due to this initial success with loratadine, over the next 9 months I prescribed, with informed consent, loratadine for fluoxetine-induced sexual dysfunction in 9 additional patients (5 men and 4 women) with a diagnosis of major depression. No sexual dysfunction assessment scales were employed, just the verbal report of each patient within the confines of a typical 15-minute medication review. Before-and-after reports were noted concerning level of sexual interest, delay or absence of erection, and delay or absence of orgasm. Two male patients reported delayed or absent erection and orgasm; 1 male patient reported impotence, anorgasmia, and no sexual interest; 2 male patients had anorgasmia and low sexual interest; 3 female patients reported anorgasmia and no sexual interest; and 1 female patient experienced anorgasmia only. No change in general or psychiatric medications was made. Dosage of loratadine ranged from 2.5 to 15 mg, depending on side effects and efficacy. Most patients were started on 10 mg/day. Seven of 9 patients had complete reversal of sexual dysfunction within 2 days, and the other 2 experienced significant improvement of sexual side effects. One male patient, who had partial impotence and low libido, had function restored to a prefluoxetine state by taking loratadine, 10 mg, 1 day before planned sexual activity. Side effects of loratadine ranged from none to mild-to-moderate dry mouth and sedation, which responded to bedtime dosing or reduction in dose. No change was seen on effectiveness of fluoxetine for depression, although the patients were happy to have their sexual function restored.

Furthermore, a female patient taking nefazadone and sertraline responded nicely to the addition of loratadine for low

sexual interest and anorgasmia. I also prescribed loratadine for low sexual interest and anorgasmia to a female patient taking paroxetine and a male patient experiencing impotence who was being treated with citalopram, but neither had a positive response. I have no explanation for this lack of efficacy.

It appears from this small open study that loratadine is a promising agent for reversing fluoxetine-induced sexual dysfunction. These results are subject to the limitations of a retrospective report and the possibility of a placebo-like effect. A larger double-blind controlled study could confirm a generalization of these findings. If confirmed, these findings could prompt an investigation into the mechanism of action of loratadine in reversing sexual dysfunction in patients treated with fluoxetine and possibly lead to development of antidepressants without this side effect. Whether loratadine could be useful for sexual dysfunction induced by other SSRIs awaits further study.

*Dr. Brubaker reports no financial affiliation or other relationship relevant to the subject matter of this letter.*

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### Rapid Onset of Antidepressant Activity With Venlafaxine

**Sir:** In their recent article, “How Fast Are Antidepressants?”<sup>1</sup> Drs. Gelenberg and Chesen rightly acknowledged the benefits of novel, fast-acting antidepressants. These benefits include alleviating patient suffering, reducing hospital stay length, and, most importantly, preserving life by decreasing the risk of suicide.<sup>1</sup> The availability of venlafaxine may reduce the several-week therapeutic delay associated with other available antidepressants.

Benkert et al.<sup>2</sup> reported a median response time (time to achieve 50% decreases from baseline Hamilton Rating Scale for Depression [HAM-D] and Montgomery-Asberg Depression Rating Scale [MADRS] scores) of 14 days for venlafaxine-treated patients, compared with 21 days for those treated with imipramine. A separate but related study of response rates in 93 inpatients with major depression and melancholia demonstrated significantly greater improvement in MADRS scores for patients treated with venlafaxine versus placebo after only 4 days and in HAM-D scores after 1 week.<sup>3</sup>

Head-to-head studies comparing venlafaxine with fluoxetine support the overall conclusions of Benkert et al.<sup>2</sup> and the view of venlafaxine as a novel, rapid-acting antidepressant. In a recent multicenter, randomized, double-blind study<sup>4</sup> designed specifically to compare the speed of onset of venlafaxine with that of fluoxetine, adult patients with major depression (minimum MADRS score of 26) received venlafaxine titrated rapidly to 300 mg/day, fluoxetine titrated rapidly to 60 mg/day, or placebo on an outpatient basis for 7 days. By day 7, venlafaxine demonstrated a statistically greater sustained response than did placebo (17% versus 5%,  $p < .001$ ), as determined by the Clinical Global Impressions-Improvement scale score; there was no statistical difference between response to fluoxetine and placebo at week 1 ( $p = .144$ ) or week 2 ( $p = .419$ ).

A separate double-blind study<sup>5</sup> addressed early response to venlafaxine in the geriatric population by comparing venlafaxine with fluoxetine and placebo in 300 patients with major depression. Patients receiving venlafaxine experienced a more rapid onset of action (significantly greater response) by week 3.

The rapid onset of action of venlafaxine could be explained by evidence that combining antidepressants with single mechanisms of action may reduce the lag in response time associated with a single agent. For example, combining desipramine (a relatively selective noradrenergic reuptake inhibitor) and fluoxetine (a selective serotonin reuptake inhibitor) has produced a more rapid improvement in patients with major depression and melancholia than has desipramine alone. Significant antidepressant effects were observed within 1 week of initiating the combined regimen.<sup>6</sup> Venlafaxine, a potent inhibitor of serotonin and norepinephrine reuptake, achieves as a single agent the dual-neurotransmitter effect obtained by combining desipramine and fluoxetine.

Dual-neurotransmitter agonism (as provided by venlafaxine and mirtazapine<sup>7</sup>) may elicit a more rapid onset of antidepressant efficacy than that provided by an agent with a single mechanism of action. However, this advantage is not observed in the older tertiary tricyclic or monoamine oxidase inhibitor agents, which also have an agonistic effect on more than one neurotransmitter.<sup>8</sup> Data on venlafaxine suggest that its relative rapid onset of action may also be due to rapid desensitization of the  $\beta$ -adrenergic receptor.<sup>9,10</sup>

Compared with achieving a more rapid response with combination therapy with 2 separate antidepressant agents, using a single compound with dual activity could improve compliance, reduce the likelihood of drug-drug interaction, and achieve a cost advantage. Providing rapid relief while maximizing efficacy and minimizing adverse effects is the goal of any physician prescribing pharmacotherapy.

*Financial disclosure: Dr. Weisler and Dr. van Meter have financial associations with many companies, including Wyeth Ayerst, that produce psychoactive pharmaceutical agents. The associations include grant/research support and participation on speakers/advisory boards.*

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#### Drs. Chesen and Gelenberg Reply

**Sir:** We are grateful to Drs. Weisler and van Meter for giving us an opportunity to reflect on and respond to their letter regarding our recent article. They presented several examples in the literature of possible “more rapidly acting” antidepressants, some of which we had not specifically addressed in our recent review and critique.<sup>1</sup> They point out that the availability of venlafaxine and mirtazapine, both dual-acting antidepressants, may provide a more rapid response than the selective serotonin reuptake inhibitors (SSRIs), unlike that seen with the tricyclic antidepressants and monoamine oxidase inhibitors. While the examples chosen by our colleagues are interesting and certainly call for more research designed to look for relative differences in time to action of antidepressants, we reiterate that none of the published examples meet the rigorous requirements that would truly indicate that one antidepressant is faster than another. The poster data discussed in their letter are a welcome addition to this area of study, and we would hope to see such data submitted for peer review and publication in the near future.

In their letter, Drs. Weisler and van Meter bring our attention again to the study by Benkert et al.,<sup>2</sup> which we discussed in our article in the section on dose and dosing strategy. The study compared rapidly escalating doses of imipramine versus venlafaxine in hospitalized depressed patients, with results indicating that venlafaxine-treated subjects demonstrated an earlier onset and sustained response as measured only by the Hamilton Rating Scale for Depression (HAM-D), not the Montgomery-Asberg Depression Rating Scale (MADRS).<sup>2</sup> Because results were inconsistent depending on the rating scale used, these results are ambiguous at best. As we discussed in our article, the HAM-D may be less sensitive to mood-specific symptoms than the MADRS. The venlafaxine versus placebo study by Guelfi and colleagues<sup>3</sup> discussed by our colleagues should have no place in the discussion of relative rates of onset of action

between antidepressants, as placebo studies are useful only for establishing efficacy.

The head-to-head studies<sup>4,5</sup> (poster data) discussed by Drs. Weisler and van Meter are more pertinent to the question of relative rate of onset of action. The venlafaxine versus fluoxetine outpatient depression study by Rudolph et al.<sup>4</sup> includes a placebo arm, which may be helpful in discerning between early response due to some aspect of a specific antidepressant agent and such response due to placebo effect of a given agent. The study was also randomized and double-blind and used the MADRS and Clinical Global Impressions scale to measure changes in symptoms. The study suggests that venlafaxine-treated subjects demonstrated a sustained response earlier than did fluoxetine- and placebo-treated subjects (17% response rate at week 1 with venlafaxine compared with only 5% with placebo, and where the difference between response rates for placebo- and fluoxetine-treated subjects was not statistically significant). We find the choice of fluoxetine to be interesting, given its long half-life compared with other SSRIs, which may or may not be related to its apparently slower onset of action. Rigorous studies between SSRIs designed to look for differences in onset of action would help clarify whether fluoxetine is the best SSRI comparator for investigators to use when attempting to look for more rapid onset of action in novel antidepressants.

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**Surprising Results in the Study of Paroxetine for Generalized Anxiety Disorder**

**Sir:** I read with interest the recent article titled "Paroxetine in the Treatment of Generalized Anxiety Disorder: Results of a Placebo-Controlled, Flexible Dosage Trial."<sup>1</sup>

Much was made of the fact that paroxetine achieved statistically significant efficacy over placebo after week 6. What was not mentioned, but seems substantially more interesting, is that this advantage was trivial in comparison to the dramatic improvement over 6 weeks on placebo alone.

If generalized anxiety disorder (GAD) is a disorder "in which 'uncontrollable' anxiety or worry, chronicity, and functional impairment are emphasized,"<sup>1(p350)</sup> one may wonder how placebo alone resulted in an almost 40% improvement on the

total Hamilton Rating Scale for Anxiety (HAM-A). This response is even more glaring when one considers that at week 8, the paroxetine group's HAM-A score was only 3 points better than that of the placebo group, but by that point, placebo had resulted in an overall 9-point improvement. Although the remission rate in the paroxetine group was 36%, placebo was hardly laughable with a 23% remission rate.

This study appears to indicate that placebo is surprisingly effective for the treatment of GAD. It is unfortunate that, due to rigorous U.S. Food and Drug Administration standards, placebo can only be prescribed within the confines of an internal review board-approved investigation.

*Dr. Ballas reports no financial affiliation or other relationship relevant to the subject matter of this letter.*

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**Dr. Pollack and Colleagues Reply**

**Sir:** We do not share Dr. Ballas' surprise over the placebo-response rate (47%) in the course of the short-term treatment of generalized anxiety disorder (GAD) described in our article.<sup>1</sup> As we point out in the Discussion, other authors using similar response criteria have reported response rates of approximately 40%.<sup>2,3</sup> Response rates of 40% to 50% or more using various response criteria are not unique to studies of GAD treatments and have been reported for clinical trials of treatments for major depression,<sup>4</sup> panic disorder,<sup>5</sup> and social anxiety disorder.<sup>6</sup> The fact that paroxetine demonstrated significant efficacy despite a substantial placebo-response rate further strengthens the assertion of its effectiveness. In addition, the selection of efficacy parameters in our study was such that the discrimination of drug-placebo differences was enhanced by consideration not only of general improvement (as measured by the Hamilton Rating Scale for Anxiety [HAM-A] total score and Clinical Global Impressions scale), but also of improvement of GAD-specific symptoms (HAM-A items "anxious mood" and "tension") as well as improvement of illness-related disability (Sheehan Disability Scale). We feel that, taken together, the results confirm that those patients taking active drug are improving more than those taking placebo. We emphasize "are improving" for it is only in the context of continued treatment that the full benefit of treatment with medication (versus treatment with placebo or no treatment at all) will become manifest, as evidenced from the results of a 32-week relapse prevention study in GAD, in which the remission rate for patients taking paroxetine increased from 43% at week 8 to 73% at week 32 compared with 34% for patients switched to placebo at week 8.<sup>7</sup>

Dr. Ballas' espousal of the efficacy of placebo is puzzling. To quote Schatzberg and Kraemer, "in the absence of an appropriate control group against which to compare the placebo response, the placebo response is not the efficacy of the placebo."<sup>4(p736)</sup> In other words, the placebo response is most certainly not due to just the absence of drug or the ritual of taking medicine, but is influenced, for example, by the care-giving aspects of the clinical trial itself and perhaps by the patients' hope

that they are receiving an active and effective treatment. This is a given in psychopharmacology research and likely pertinent in the clinical practice of psychopharmacology itself. Therefore, it is uncertain that the placebo response would be as acutely robust if patients were aware that they were definitely receiving a placebo.

*Dr. Pollack has financial associations with many companies that produce psychoactive pharmaceutical agents. Dr. Zaninelli is a major stock shareholder with GlaxoSmithKline.*

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#### Design and Interpretability of Findings in a Family Study to Investigate Posttraumatic Stress Disorder

**Sir:** The study by Dierker and Merikangas<sup>1</sup> (September 2001 issue) contained many shortcomings that make the results difficult to place within the growing body of literature about associations between posttraumatic stress disorder (PTSD) and other psychiatric disorders. A lack of standardization in study design, from the selection and categorization of the

sample to data-gathering methods, renders this study difficult to comprehend.

While the authors defended the use of 2 different methods for recruiting the proband sample by asserting that it reduced sample bias, they apparently did not run an analysis comparing the different recruitment groups to detect any significant differences that might invalidate the results of subsequent analyses. Further, the screening process by which the proband group was assigned to psychiatric diagnosis groups was not well specified, leaving the reader unsure of how, when, and by whom or what instrument they were diagnosed. This ambiguity throws into question the validity of the data analysis. Many similar studies about PTSD or comorbid disorders use standardized instruments and diagnostic interviews that make their data more uniform and invulnerable to dispute.<sup>2–5</sup>

The authors did address the omission of physical or sexual abuse or victimization from the format of the PTSD gate question, stating that “This narrow list quite likely caused an underestimation of trauma exposure and PTSD symptoms in both probands and relatives.”<sup>1(p719)</sup> That they would use a data set lacking this category of traumatic events to study PTSD is surprising, given that an epidemiologic study found that 32% of women and 43% of men were exposed to assaultive violence in their lifetimes and that 54% of women and 15% of men developed PTSD as a result of that violence.<sup>6</sup>

Finally, a curious inconsistency in the data about the relatives of the control proband group was not addressed. The control group probands, with no history of an Axis I disorder, had significantly lower rates of exposure to trauma and PTSD than the other proband groups, as one would expect. Their relatives, however, had rates higher than or equal to those of the other groups of relatives—a counterintuitive finding. Although this was not statistically significant, it is an inconsistency in the data that should be recognized. Cottler et al.,<sup>2</sup> in their 1992 study of PTSD among substance users from the general population, found that younger cohorts were more likely to be exposed to a traumatic event than older cohorts. They suggested that this likelihood of exposure, in combination with a similar finding from an earlier study,<sup>7</sup> may indicate a greater prevalence of traumatic events and PTSD in younger cohorts, a trend that might be verified by tracking over time.

The intent of this article was to add to our knowledge about associations between PTSD and other psychiatric disorders. A family study such as this is important to our learning about genetic and environmental vulnerabilities to psychopathology. It is unfortunate that this study was not more rigorously designed, so that we might add its findings to our small but growing knowledge base about these vulnerabilities.

*Ms. Droege reports no financial affiliation or other relationship relevant to the subject matter of this letter.*

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### **Drs. Dierker and Merikangas Reply**

**Sir:** Droege's critique of the rigors of the design and interpretability of findings in our article<sup>1</sup> is unfounded.

First, proband recruitment source (clinic vs. community) was included in each model-building step that formed the bases of the final analyses along with a number of other potential confounders (e.g., socioeconomic status). The exclusion of these confounding variables from the final tables was based on their lack of impact on either the magnitude or significance level of findings and our desire to preserve model power for familial transmission variables given low base rates of posttraumatic stress disorder (PTSD).

Second, diagnoses for probands and relatives were determined with identical and rigorous procedures. The diagnostic interview was a modified version of the DSM-III-R semistructured Schedule for Affective Disorders and Schizophrenia (SADS), current and lifetime versions. The final diagnoses were "best-estimate" diagnoses based on all available information, including the diagnostic interview, family history reports on each proband and relative, and medical records. Assignment to a proband group was based on a blind and independent review by clinicians with extensive experience in the evaluation and treatment of substance abuse.

Criticism of the probe question used to enter the PTSD interview module is better left to a more general debate over the appropriate degree of structure for psychiatric interviews. In other words, while a more exhaustive list of traumatic experiences is common in highly structured instruments,<sup>2</sup> the more general nature of the present probe, followed by a list of illustrative examples, is in fact a widely used approach among more

semistructured interviews.<sup>3</sup> The suggested superiority of the former assumes that valid responses to trauma are exclusively dependent on the number and types presented to the subject. In fact, valid reporting of painful and sensitive issues is likely highly dependent on the rapport developed by the interviewer, possibly a more achievable goal among those with clinical experience who engage in semistructured interview procedures.

Finally, the statistically equivalent rates of traumatic exposure among relatives in case and control proband groups are not surprising. Empirical work has yet to demonstrate elevated rates of trauma (presence vs. absence) in lifetime measurement based on familial psychiatric status. Droege's reference to elevated rates of trauma among younger cohorts seems out of place, as analyses by cohort were not presented in the original article.

Family studies designed to investigate PTSD have been relatively scarce. While this represents the ideal context in which to examine issues of familiarity of traumatic exposure and PTSD, the resources involved, as well as the emerging concern over ethical issues surrounding proxy informants, make the adequate proliferation of these studies uncertain. Secondary analyses conducted on samples that may shed an additional light on the association among psychiatric disorders and environmental exposures should not be overlooked. While these analyses require more cautious interpretation, our article provides the appropriate cautions throughout by articulating the secondary nature of our hypotheses within the title, abstract, and body of the article.

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