Evidence of Early Onset of Antidepressant Effect in Randomized Controlled Trials

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Although antidepressant medications are effective in approximately 70% of patients with major depressive disorder, they have a delayed onset of therapeutic effect. This latency is problematic in that it prolongs the impairments associated with depression, leaves patients vulnerable to an increased risk of suicide, increases the likelihood that a patient will prematurely discontinue therapy, and increases medical costs associated with severe depression. No adequately designed prospective trials have been conducted to evaluate comparative time to onset of antidepressant effect. However, evidence suggests that some antidepressant agents may begin to work faster than others. Citalopram, venlafaxine, and mirtazapine each have exhibited statistically significant differences in some measures of antidepressant action within the first 2 weeks of treatment, both in placebo-controlled trials and in head-to-head comparisons with other antidepressants. This article reviews the data that hint at these drug-specific differences in time to onset of action. Given the potential benefits of early-acting antidepressant treatments, the possibility of superior speed of onset of citalopram, venlafaxine, and mirtazapine presented here merits further study in adequately designed, prospective clinical trials.

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Antidepressant medications are effective in approximately 70% of patients with major depressive disorder. An abiding shortcoming of antidepressant pharmacotherapy, however, is that available drugs have a delayed onset of action. In controlled trials, statistically significant differences between active treatment and placebo often require 4 weeks or more to emerge. In the clinic, where treatment is complicated by patient heterogeneity and other factors excluded from controlled trials, delays in clinically meaningful response may be even more pronounced.

The latent therapeutic effect of antidepressant treatment can be problematic for a number of reasons. In addition to prolonging the physical, psychological, and social impairment associated with depression, delayed onset of antidepressant action leaves patients vulnerable to an increased risk of suicide. Furthermore, it increases the likelihood that a patient will discontinue treatment prematurely,

missing altogether the potential benefits of sustained therapy. Finally, delayed onset may lengthen hospital stays and increase medical costs in patients with severe depression. As mentioned elsewhere in this supplement, the economic impact of depression is wide-ranging and profound, such that delays in response of several weeks can result in significant financial burdens for employers, insurers, and society in general. For all of these reasons, a long-standing goal of research has been to identify antidepressant medications or treatment strategies that demonstrate a more rapid onset of effect.

The vast majority of randomized controlled trials have shown that antidepressants are similarly efficacious at endpoint. However, a few studies have suggested that some drugs may begin to work faster than others. While no adequately designed, prospective trials have been conducted to evaluate comparative time to onset of effect, citalopram, venlafaxine, and mirtazapine each have exhibited statistically significant differences in at least some measures of antidepressant action within the first 2 weeks of treatment both in placebo-controlled trials and in head-to-head comparisons with other antidepressants. In this article, we review data from randomized controlled trials that hint at drug-specific differences in time to onset of action.
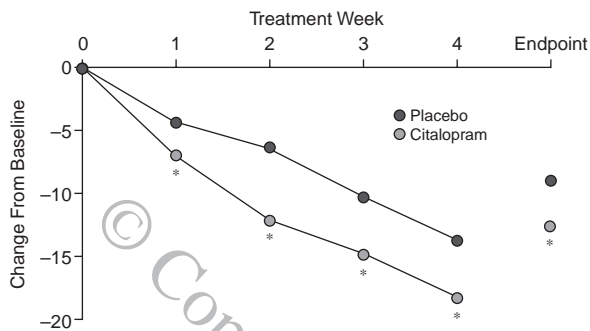
CITALOPRAM

Citalopram inhibits the activity of presynaptic serotonin transporters, potently blocking the reuptake of seroto-

Figure 1. Weekly Change in Baseline Hamilton Rating Scale for Depression Score in Patients Treated for 4 Weeks With Citalopram (20–80 mg/day) or Placebo[a]

[a]Adapted from Mendels et al.,[7] with permission.
*Significant difference, p < .05.

Figure 2. Weekly Change in Hamilton Rating Scale for Depression Depressed Mood Item Score in Patients Treated for 6 Weeks With Citalopram (10, 20, 40, or 60 mg/day) or Placebo[a]
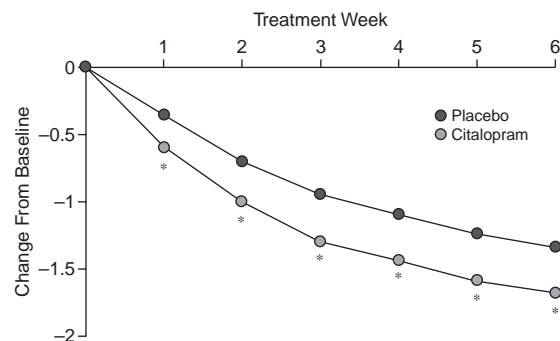

[a]Adapted from Feighner and Overø,[9] with permission.
*Significant difference, p < .05.

nin (5-HT) from the synaptic cleft while leaving other neurotransmitter pumps, receptors, and enzyme systems largely unaffected.[1,2] In fact, citalopram is the most selective of the available selective serotonin reuptake inhibitors (SSRIs). While this relatively "clean" pharmacodynamic profile does not appear to confer an efficacy advantage over other antidepressants, both preclinical and clinical data suggest that citalopram's unique properties may be associated with a comparatively early onset of action. For example, citalopram has been compared with imipramine using a well-validated[3] animal model of depression known as chronic mild stress, in which rats display antidepressant-reversible deficits in reward sensitivity when exposed to a series of unpredictable mild stressors. In 2 studies,[4,5] citalopram began to restore consummatory behavior to normal levels 1 to 2 weeks earlier than did imipramine. Although these results are difficult to extrapolate to patients with depression, they agree with data from several clinical studies.

Comparisons With Placebo

In an article published in 1984, Quitkin et al.[6] defined early onset of antidepressant effect as a statistically significant symptomatic improvement occurring by the end of the first or second week of treatment. Data from 2 randomized, double-blind, placebo-controlled trials of citalopram meet this criterion. In the first,[7] 180 depressed outpatients with melancholia were treated with a flexible dose of citalopram (20–80 mg/day) or with placebo. As shown in Figure 1, citalopram-treated patients exhibited significantly greater reductions in Hamilton Rating Scale for Depression (HAM-D) scores than placebo-treated patients starting at week 1. By week 2, the difference between the 2 treatment groups was both statistically and clinically significant, according to stringent standards suggested by Huitfeldt and Montgomery.[8]

In a second trial,[9] 650 patients with moderate-to-severe depression were randomly assigned to receive a fixed dose of citalopram (10, 20, 40, or 60 mg daily) or placebo. Pooled across all 4 dose groups, citalopram-treated patients displayed significantly greater reductions in depressive symptoms as measured by the HAM-D depressed mood item than did placebo-treated patients from week 1 of double-blind treatment through the end of the study (Figure 2).

Comparisons With Other Antidepressants

In randomized controlled trials, citalopram has exhibited an apparently faster time to onset compared with other SSRIs (fluoxetine and sertraline), imipramine, and mianserin.

Three hundred fourteen general practice patients with unipolar major depression were treated with 20 mg/day of either citalopram or fluoxetine in an 8-week, randomized, double-blind study.[10] In the endpoint analysis, the number of responders—defined as patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤ 12—was similar in both groups. However, as shown in Figure 3, a significantly greater proportion of citalopram-treated patients were responders at week 2 of the study, suggesting that citalopram had a faster onset of effect compared with fluoxetine in some patients.

Bougerol et al.[11] compared the efficacy of citalopram with that of fluoxetine in a randomized, double-blind study in a psychiatric setting (N = 316). A fixed dose of citalopram (40 mg/day) or fluoxetine (20 mg/day) was administered for 8 weeks, and HAM-D assessments were made after 1, 2, 4, 6, and 8 weeks of treatment. Again, citalopram appeared to have an improved onset of action relative to fluoxetine; the number of patients showing recovery (HAM-D score ≤ 7) was significantly higher at week 2 (Figure 4).

Figure 3. Patients Classified as Responder (MADRS score ≤ 12) After 1, 2, 4, 6, and 8 Weeks of Therapy With Citalopram (20 mg/day) or Fluoxetine (20 mg/day)[a]
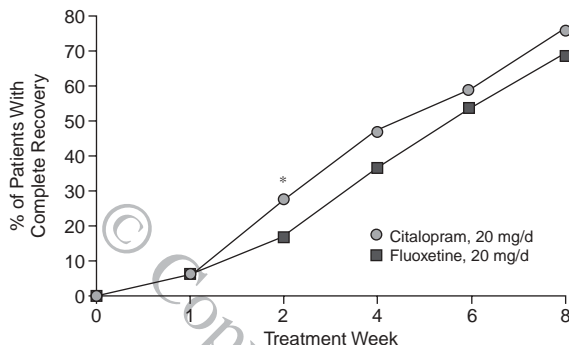
[a]Data from Patris et al.[10] Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.
*Significantly different from fluoxetine group, p < .05.

Figure 4. Patients Showing Recovery (HAM-D score ≤ 7) After 1, 2, 4, 6, and 8 Weeks of Therapy With Citalopram (40 mg/day) or Fluoxetine (20 mg/day)[a]
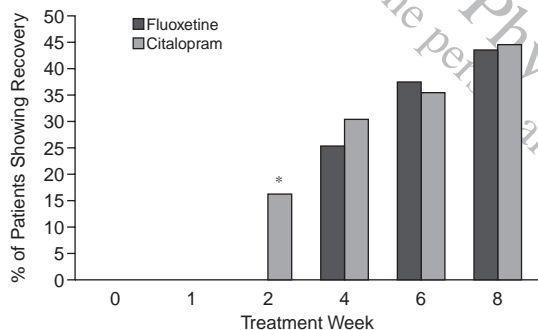

[a]Data from Bougerol et al.[11] Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
*Significant difference, p = .003.

Stahl[12] recently reported the results of a 24-week, randomized, double-blind, placebo-controlled comparison of citalopram (20–60 mg/day) and sertraline (50–150 mg/day) among 323 patients with major depression. As shown in Figure 5, mean HAM-D and MADRS scores in citalopram-treated patients were significantly improved at week 2. A significant therapeutic effect of sertraline was not observed until much later in the study.

As suggested by the preclinical studies described above, citalopram appeared to have a faster onset of action than the tricyclic agent imipramine in a 6-week, randomized, placebo-controlled study involving 46 inpatients with major depression.[13] At week 2, patients receiving citalopram (20–80 mg/day) displayed a numerically greater improvement on the HAM-D than patients receiving imipramine (50–300 mg/day) or placebo. However, the differences between the drugs did not reach statistical

Figure 5. Change in Baseline HAM-D (upper panel) and MADRS (lower panel) Scores Over Time in Depressed Patients Treated With Citalopram (20–60 mg/day), Sertraline (50–150 mg/day), or Placebo[a]
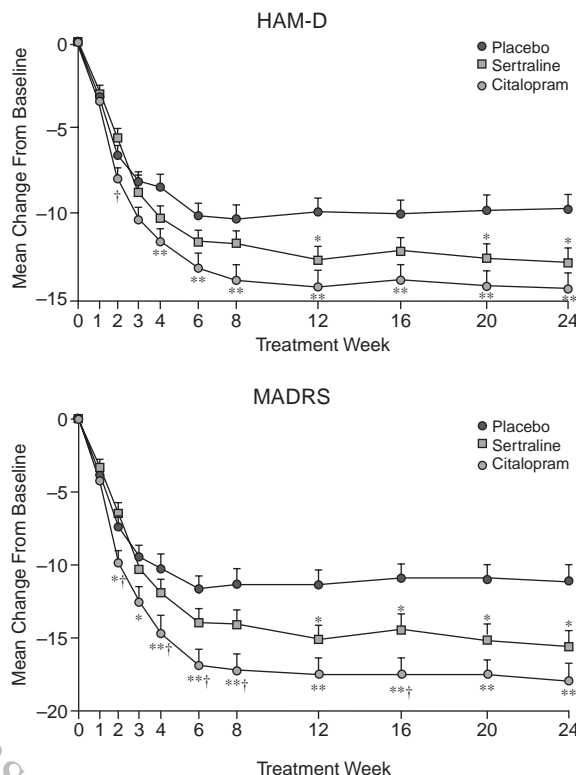
[a]Adapted from Stahl,[12] with permission.
*p < .05 compared with placebo.
**p < .01 compared with placebo.
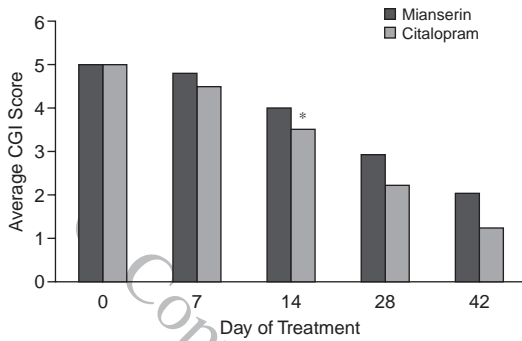†Significant difference between citalopram and sertraline, p < .05.

significance, owing in part to the small number of patients in each treatment group.

Finally, citalopram (20–80 mg/day) was compared with mianserin (60–120 mg/day) in a 6-week, double-blind trial involving 58 patients with endogenous depression.[14] Patients in both treatment groups exhibited significantly decreased Clinical Global Impressions scale (CGI) scores at the end of the trial. However, citalopram-treated patients showed significantly greater improvement than mianserin-treated patients at week 2 (Figure 6).

VENLAFAXINE

At the low end of its therapeutic dose range, venlafaxine acts primarily as a serotonin reuptake inhibitor.[15] At high doses, however, the drug blocks neuronal uptake of both serotonin and norepinephrine (and, to a lesser extent, dopamine).[15,16] It has been postulated that some depressed patients are more responsive to the blockade of 5-HT uptake, whereas others are more responsive to the blockade of norepinephrine uptake. Thus, some patients may

Figure 6. Mean Clinical Global Impressions Scale (CGI) Score After 1, 2, 4, and 6 Weeks of Citalopram (20–80 mg/day) or Mianserin (60–120 mg/day)[a]

[a]Data from de Wilde et al.[14]
*Significant difference, p < .05.

Figure 7. Survival Analysis of Clinical Global Impressions-Improvement Scale Score After 6 Weeks of Venlafaxine (200 mg/day) or Placebo[a]

[a]Reprinted from Derivan et al.[21]

Figure 8. Weekly Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score After 4 Weeks of Venlafaxine (mean dose = 350 mg/day) or Placebo[a]

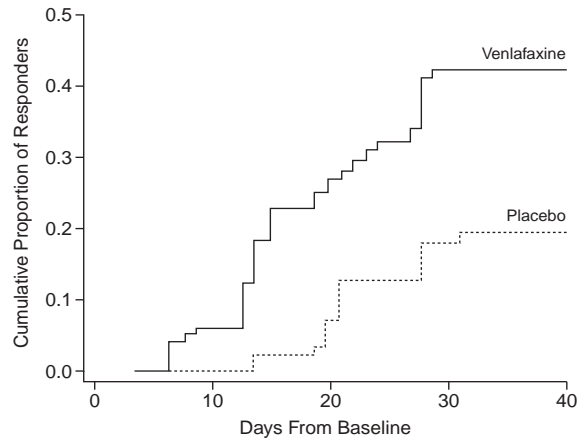[a]Adapted from Guelfi et al.,[24] with permission.
*p < .05.
**p < .001.

be more responsive to venlafaxine than to other antidepressant agents.[17–20] Placebo-controlled studies and 1 active-controlled randomized trial have suggested that venlafaxine's pharmacodynamic properties may contribute to a relatively early onset of action.

Comparisons With Placebo

Derivan et al.[21] retrospectively assessed 2 randomized, double-blind, placebo-controlled trials of venlafaxine[22,23] to evaluate the drug's time to onset. In both studies, venlafaxine was dosed aggressively. In the first study,[22] the mean daily doses were 200 and 340 mg/day after 1 and 2 weeks, respectively. In the second,[23] the mean dose after 1 week was 175 mg/day. The primary efficacy parameters in both studies were the HAM-D, MADRS, and CGI. Three different approaches were used to analyze the data: traditional analysis of depression rating scores, pattern analysis of timing and persistence, and survival analysis of sustained response.[21] All 3 statistical analyses showed that venlafaxine produced a statistically significant separation from placebo within the first 2 weeks of randomized treatment. For example, survival analysis of sustained response (as measured by CGI-Improvement score) demonstrated separation from placebo beginning on day 7 in patients taking 200 mg/day of venlafaxine (Figure 7).[23] It should be noted that over 40% of venlafaxine patients in one study[22] discontinued prematurely.

In a randomized, double-blind, placebo-controlled trial of 93 inpatients with major depression, Guelfi et al.[24] also used rapid up-titration of venlafaxine, with the mean dose reaching 350 mg/day after 1 week. After 4 days, MADRS scores of patients taking venlafaxine were significantly decreased in comparison with those of the placebo group (Figure 8). Venlafaxine-treated patients also exhibited statistically significant improvements in HAM-D scores relative to placebo-treated patients after 1 week, although the mean scores still were quite high (22.5 for venlafaxine and 25.5 for placebo).
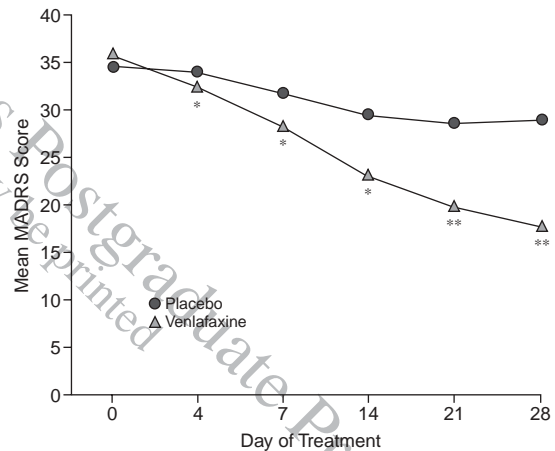
Comparison With Fluoxetine

Onset of action was prospectively compared in a head-to-head trial of venlafaxine versus fluoxetine. Again, aggressive dosing schedules were employed; venlafaxine was titrated to 300 mg/day and fluoxetine to 60 mg/day at the end of the first week. Ratings were initiated early in the study and performed frequently, and survival analysis was used to evaluate onset of action. The outcomes of several measures suggested that there was an earlier response to venlafaxine than to fluoxetine.[25]

Figure 9. Survival Analysis of Time to First Response on the Hamilton Rating Scale for Depression (reduction ≥ 50%), Intent-to-Treat Group[a]

[a]Data from Rosenbaum et al.[30]

Figure 10. Survival Analysis of Time to First Response on the Montgomery-Asberg Depression Rating Scale (reduction ≥ 50%), Intent-to-Treat Group[a]
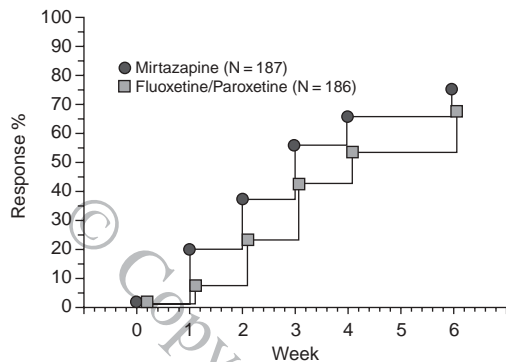
[a]Data from Rosenbaum et al.[30]

MIRTAZAPINE

Mirtazapine antagonizes α_2-adrenoceptors on norepinephrine and 5-HT neurons, and thereby affects both noradrenergic and serotonergic neurotransmission.[26,27] Via this dual mechanism of action, mirtazapine theoretically could avoid some of the early effects that are thought to delay the onset of action of serotonin and norepinephrine reuptake inhibitors (e.g., adaptation processes).
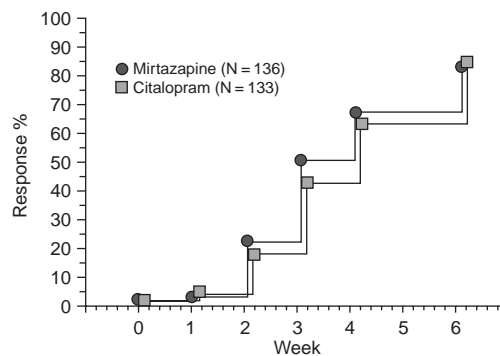
Comparison With Placebo

Mirtazapine displayed a relatively rapid onset of effect in a randomized, double-blind, placebo-controlled study[28] among 90 patients with moderate or severe major depression. According to HAM-D, MADRS, and CGI assessments, mirtazapine was significantly superior to placebo beginning at week 1 of the 6-week trial.

Comparisons With SSRIs

In a double-blind, randomized trial[29] in patients with major depression, mirtazapine (15–60 mg/day) appeared to have a faster onset of action than citalopram (20–60 mg/day). Whereas both treatment groups demonstrated significant and comparable improvement on Hamilton Rating Scale for Anxiety, CGI, and MADRS scores at endpoint, the mirtazapine group showed superior improvement relative to the citalopram group in all outcome parameters at week 2 of the study. It should be noted, however, that mirtazapine was up-titrated from 15 mg/day to 30 mg/day after 4 days of treatment, whereas the starting dose of clitalopram (20 mg/day) was not increased until week 2 of the study.

In contrast, a recent retrospective analysis of this trial and 2 other SSRI comparator studies[30] suggested that mirtazapine has a faster time to onset than fluoxetine and paroxetine, but not citalopram. This post hoc study used a conventional Kaplan-Meier survival analysis that assessed time to onset of response for those patients who not only responded or remitted but also experienced sustained improvement. Thus, the influence of a placebo-like rapid but unstable response was eliminated.[31] Time to response was defined as a 50% decrease in either the HAM-D or the MADRS total score, with no more than a 15% variation in this response during the trial. Remission was defined as either a HAM-D score ≤ 7 or a MADRS score ≤ 12. Intent-to-treat analysis was used to calculate the Kaplan-Meier product limits, a strategy that conservatively estimates the time to response. Because the trials that compared mirtazapine with fluoxetine and paroxetine used the HAM-D, these trials were pooled, while the trial with citalopram used the MADRS and was analyzed separately. As shown in Figure 9, the time to response for mirtazapine was about a week faster than either fluoxetine or paroxetine among patients who responded to treatment. No such difference was seen in the comparison of mirtazapine and citalopram (Figure 10).

Time to onset can be confounded by differences in rates of response; that is, 1 drug may simply be more effective than another drug at every timepoint, rather than faster acting.[32] To avoid this potential confound, an additional analysis was done for responders only, using a lower threshold of 20% improvement of onset for eventual 50% responders.[30] Thus, greater overall efficacy could be distinguished from greater speed of onset. For overall responders, the first sign of response (20% improvement) was faster for mirtazapine compared with all 3 SSRIs (data not shown). However, no statistically significant differences were found for time to remission between mirtazapine and the SSRIs.

DISCUSSION

The trials described in this review offer evidence that citalopram, venlafaxine, and mirtazapine may have a rela-

tively early onset of antidepressant effect compared with placebo and other antidepressants. However, because of various general and specific methodological shortcomings, the outcomes of these studies do not support definitive claims of "earlier" onset of effect for any of these drugs. For example, with the exception of the venlafaxine-fluoxetine comparison,[25] all of the trials discussed herein examined onset of action retrospectively and therefore failed to meet a basic requirement for speed-of-onset studies, as defined by Prien and colleagues,[33] namely, prospective definition of "onset." In addition, some of the studies were insufficiently powered to detect differences in time to onset.

Specific limitations of the trials include lack of equivalent dosing for compared drugs and clinically unrealistic dosing schedules. For example, the average clinician most likely would not increase the dose of venlafaxine as aggressively as was done in the studies by Schweizer et al.[22] and Guelfi et al.,[24] since high doses (> 200 mg/day) of this agent can cause clinically significant increases in blood pressure.[34,35] Aggressive dosing also creates a problem in the context of clinical trials; specifically, the rapid onset of telltale side effects can "unblind" both the patient and the assessor to the study drug. Patients who are certain they are receiving active treatment may report improvements sooner than patients who are not sure which treatment they are receiving. Raters, too, may be influenced by their belief that a patient has been randomly assigned to active drug. Thus, evaluations of efficacy may be inflated by expectations of improvement.

Studies showing apparent differences in time to onset among antidepressants are also problematic because they are difficult to interpret. Did the observed difference arise from the antidepressant action of the "superior" drug or from its side effects? For example, mirtazapine is moderately sedating because of its effects on histaminergic receptors. Fluoxetine, on the other hand, often produces activating effects during the acute phase of treatment. In a head-to-head trial involving these 2 drugs, mirtazapine might appear to be superior to fluoxetine during the first 2 weeks of double-blind treatment because of the sensitivity of rating instruments (e.g., the HAM-D) to changes in sleep, anxiety, and agitation.

Although existing data provide no proof of drug-specific differences in time to onset, they do suggest that such differences may exist. Given the potential benefits of early-acting antidepressant treatments, the hints of superior speed of onset presented here merit further study in adequately designed, prospective clinical trials.

Drug names: citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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