Do Some Antidepressants Work Faster Than Others?

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The clinical utility of antidepressant drugs is impaired by the delay in onset of their therapeutic action. It is becoming increasingly clear that differences exist between antidepressants with respect to this property, both within and between pharmacologic classes. Post hoc analyses of comparisons between selective serotonin reuptake inhibitors and dual-action antidepressants such as mirtazapine and venlafaxine indicate that the dual-action drugs may have a faster onset of action. At least in the case of mirtazapine, the earlier onset appears to be via a specific antidepressant effect and not an effect on sleep or other accessory symptoms. Studies that compare mirtazapine and venlafaxine are relatively rare and lack sufficient statistical power to determine a difference in the onset of action. Although these differences have been shown in clinical efficacy studies not specifically designed to detect differences in onset of action, a definitive demonstration of early onset of action awaits the results of appropriately designed and powered clinical studies currently planned or in progress.

(J Clin Psychiatry 2001;62[suppl 15]:22–25)

Antidepressants have a delay in therapeutic effect that ranges from 1 to 10 weeks. No antidepressant has been firmly established as having a substantial and clinically relevant faster time of onset, nor are clear predictors of time to onset used in clinical practice. Data on the time to onset of antidepressant action would be helpful: it would allow practicing physicians to better predict the course of recovery at the start of treatment. Patients can be educated about the combination of early side effects and lack of symptom improvement that so often accompanies the beginning of treatment. If patients expect such a course, they can be more easily encouraged to persist in taking the medication for the time necessary to achieve clinical improvement. A good model of the time of onset allows clinicians to estimate the course of treatment and communicate this estimate to patients and their family. Moreover, an accurate model of the time course of antidepressant action allows timely intervention if a patient does not respond after an appropriate duration of treatment.

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Presented at the satellite symposium "Depression: The Relevance of the Time Factor," which was held at the XXIInd Collegium Internationale Neuro-Psychopharmacologicum Congress in Brussels, Belgium, July 9, 2000, and supported by an unrestricted educational grant from NV Organon.

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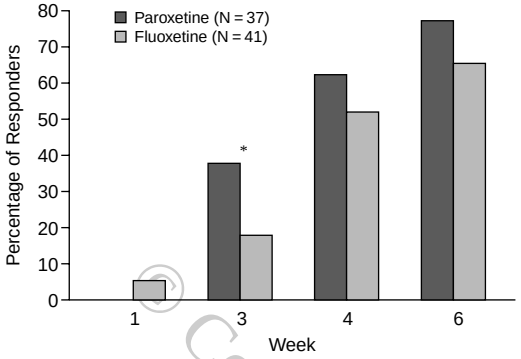
DIFFERENCES IN ONSET OF ACTION OF ANTIDEPRESSANTS

Although the results of specifically designed onset-of-action studies are awaited, at least some evidence suggests that differences exist among antidepressants. Pharmacologic studies suggest possible reasons for these differences: the firing rate of serotonin (5-HT) cell bodies in the raphe and 5-HT concentrations in the cortex decline during acute treatment and then increase slowly over several weeks of treatment. One theory suggests that the increase in the 5-HT firing rate and concentration is the mechanism of action of antidepressants. This phenomenon is subject to a number of potential sites for intervention, and antidepressants with different pharmacologic actions may accelerate the process.

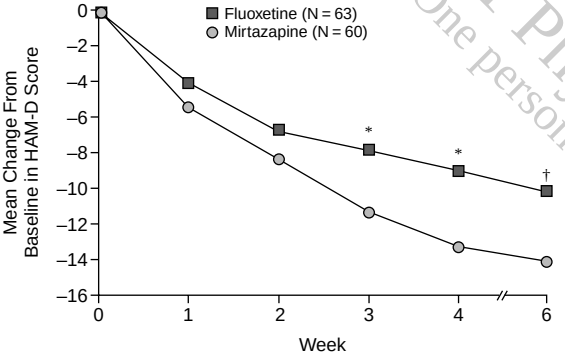
The precise measurement of the delay in onset of therapeutic action of antidepressants depends critically on the definition of onset of action. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors appear to share a delay in onset of between 2 and 4 weeks. Differences may exist, however, between antidepressant classes and even between the members of a class. Figure 1 shows the results of a comparison of paroxetine and fluoxetine in which paroxetine shows a statistically significant advantage over fluoxetine in the proportion of patients who achieve a response during the first 3 weeks of treatment.[1] Not surprisingly, differences can also be shown between classes of antidepressants. Figure 2 illustrates results from a double-blind randomized comparison of mirtazapine and fluoxetine given to patients with moderate-to-severe (Hamilton Rating Scale for De-

Figure 1. Percentage of Responders With Paroxetine Versus Fluoxetine[a]



[a]Reprinted, with permission, from De Wilde and colleagues.[1] Response defined as ≥ 50% decrease in Hamilton Rating Scale for Depression score from baseline.
*p ≤ .05.

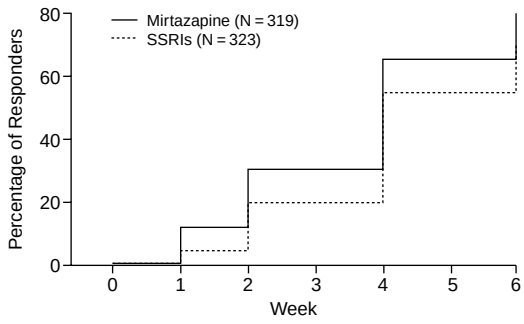
Figure 2. Mean Change in Hamilton Rating Scale for Depression (HAM-D) Score for Mirtazapine Versus Fluoxetine[a]



[a]Adapted, with permission, from Wheatley and colleagues.[2]
†p = .054.
*p < .05.

pression [HAM-D] ≥ 21 at entry) major depressive disorder.[2] There is a statistically significant difference between mirtazapine and fluoxetine in the mean change from baseline in HAM-D score by week 3 in a population of patients with more severe depression. The difference at week 3 is more than 3.5 points on the HAM-D and clinically relevant. A similar statistically significant early advantage for mirtazapine was demonstrated in a double-blind comparison versus paroxetine[3] (a difference of 2.3 points on the HAM-D). This result was supported by responder and remitter analyses; the proportion of responders (decrease in HAM-D score ≥ 50%) and remitters (HAM-D score ≤ 7) was significantly higher in the mirtazapine group than in the paroxetine group at week 1 (23.2% vs. 8.9% and 8.8% vs. 2.4%, respectively). Similarly, a double-blind comparison of mirtazapine versus citalopram[4] revealed a statistically significant advantage for mirtazapine at week 2 (a difference of 2.3 on the Montgomery-Asberg Depression Rating Scale [MADRS]).

Figure 3. Meta-Analysis of 3 Studies of Mirtazapine Versus SSRIs (Citalopram, Fluoxetine, or Paroxetine) in Depression[a]



[a]Data from references 2–4. Abbreviation: SSRI = selective serotonin reuptake inhibitor. Kaplan-Meier analysis, log rank test p = .0178.

The studies described here were all double-blind, controlled efficacy studies and were not specifically designed to distinguish differences in onset of action. However, in all of the mirtazapine studies, the differences were consistently in the direction of an advantage for mirtazapine. A combined analysis[5] of these 3 mirtazapine studies (a total of 323 mirtazapine-treated patients and 319 SSRI-treated patients) has shown an onset-of-action advantage for mirtazapine in terms of remission and response. The proportion of patients achieving remission (HAM-D total score reduced to 7 or less or MADRS total score reduced to 12 or less) was statistically significantly greater in the mirtazapine group during weeks 3 and 4 (12.4% vs. 8.2% [p < .05] and 32.2% vs. 12.8% [p < .05], respectively). Furthermore, by week 1, more than twice as many mirtazapine-treated patients as SSRI-treated patients had responded (12.1% vs. 5.3%); this difference was statistically significant (p < .05) and remained so until week 4.

The Kaplan-Meier survival analytic method has been found to be the best to analyze time-to-event series for onset of action for electroconvulsive therapy[6]; such a meta-analysis of the mirtazapine-versus-SSRI data set is illustrated in Figure 3. For this analysis, the Kaplan-Meier approach was used to analyze the time to first response (defined as a 50% or greater reduction in HAM-D or MADRS score). As can be seen, the curve for the combined SSRI group lags behind the mirtazapine group by 1 week. In other words, patients given mirtazapine were considered responders an average of 1 week earlier than those given SSRIs, a clinically important difference.

Early Onset With Mirtazapine: Role of Sleep and Anxiety

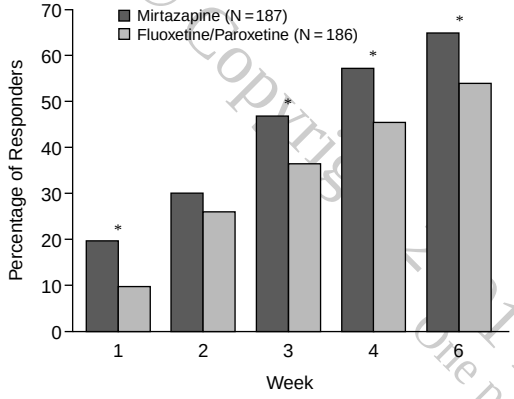
Mirtazapine is known to have beneficial effects on sleep in depressed patients as well as an anxiolytic ef-

Table 1. Hamilton Rating Scale for Depression Items Constituting the Bech Melancholia Factor[a]

Depressed mood
Feelings of guilt
Work and activities
Retardation
Psychic anxiety
General somatic symptoms

[a]Based on Bech and colleagues.[9]

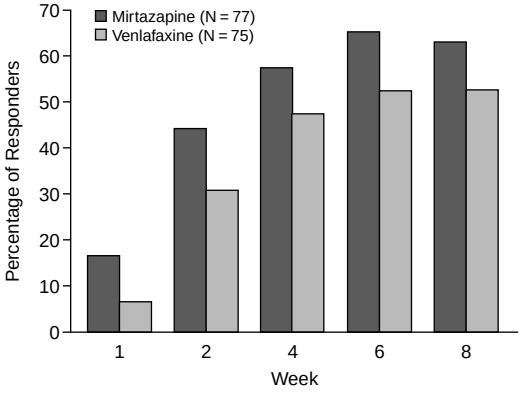
Figure 4. Responder Rates for Mirtazapine Versus the SSRIs Fluoxetine and Paroxetine[a]



[a]Data from Wheatley and colleagues[2] and Benkert and colleagues.[3] Abbreviation: SSRI = selective serotonin reuptake inhibitor. Response defined as ≥ 50% reduction in Bech Melancholia Factor score from baseline.
*p < .05.

fect.[7,8] It is therefore possible that the apparently more rapid onset of action of mirtazapine compared with the SSRIs could be due to early restoration of sleep and diminution of the patient's anxiety, rather than a specific early antidepressant effect. The Bech Melancholia Factor is a subset of 6 HAM-D items (Table 1) that are considered to reflect the core symptoms of depression.[9] Thus, if a drug has an effect on scores on the Bech Melancholia Factor, this would most likely represent a specific antidepressant effect, rather than an effect on accessory symptoms of depression. Figure 4 shows the results from a meta-analysis of 2 double-blind studies of mirtazapine versus either fluoxetine or paroxetine (the mirtazapine vs. citalopram study was excluded from this analysis because it employed the MADRS rather than the HAM-D). A responder was defined by a 50% or greater reduction in the Bech Melancholia Factor score. In the mirtazapine group, the proportion of responders was significantly higher than in the combined SSRI group at the end of the first week of treatment, as well as at some subsequent timepoints. This finding suggests that the early antidepressant effect of mirtazapine is not due simply to an effect on sleep or anxiety, but to a specific antidepressant effect.

Figure 5. Percentage of Responders With Mirtazapine Versus Venlafaxine[a]



[a]Data from Guelfi.[14] Response defined as ≥ 50% decrease in Hamilton Rating Scale for Depression score from baseline.

Mirtazapine Versus Venlafaxine

Similar post hoc analyses have shown that venlafaxine also appears to have an early onset of action, particularly when aggressive dose schedules are used.[10] As well as statistical separation between venlafaxine and placebo as early as week 2,[11] pattern analysis and Kaplan-Meier analysis have provided supporting evidence for venlafaxine's early onset of action.[12,13]

Comparisons between active treatments in illnesses with high placebo responder rates such as depression require large numbers of patients to provide sufficient statistical power. To date, only a single study has undertaken a head-to-head comparison of mirtazapine and venlafaxine. The results from this double-blind, randomized study in 157 severely depressed hospitalized patients show no statistically significant difference in time to onset, but it is possible that the numerical reduction in HAM-D total score occurs sooner with mirtazapine than with venlafaxine. It is also possible that responder and remitter rates may be higher with mirtazapine than with venlafaxine during the early phase of treatment (Figure 5).[14] However, the number of patients in this study was not sufficient to provide adequate statistical power, and conclusions can be drawn only with great caution until the results of larger studies specifically designed to detect the timing of onset of action are available.

ONGOING ONSET-OF-ACTION STUDIES WITH MIRTAZAPINE

A trial is already underway in Europe to compare the onset of action of mirtazapine with that of sertraline. A second, parallel study comparing mirtazapine and fluoxetine will soon begin in the United States. Both trials are 8-week double-blind studies using rapid titration of the anti-

depressants to doses that approach their highest approved doses. Interim 4- and 10-day assessments will be used to increase the temporal resolution of the study to detect the onset of antidepressant action. To avoid bias from rating scales that may favor a particular drug, patients will be evaluated using the HAM-D, MADRS, and Clinicians Global Impressions scales.

CONCLUSION

The available evidence suggests that some antidepressants may act faster than others. Mirtazapine and venlafaxine appear to have a faster onset of action than at least some SSRIs, and the early effects of mirtazapine are seen across a broad range of symptoms (not just insomnia and anxiety). The available data are, however, not adequate to make firm conclusions, and the results of ongoing studies are awaited with interest.

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

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