Does Mirtazapine Have a More Rapid Onset Than SSRIs?

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Background: A single study utilizing a cross-sectional analysis of scores on the Hamilton Rating Scale for Depression (HAM-D) suggested that mirtazapine has a more rapid onset than selective serotonin reuptake inhibitors (SSRIs). Analysis based on the HAM-D may favor drugs with sleep-producing effects. The purpose of the present study was to determine if a review of all studies comparing an SSRI with mirtazapine, utilizing persistent improvement as the dependent variable, would suggest that mirtazapine had a more rapid onset than SSRIs.

Method: All double-blind studies comparing mirtazapine with SSRIs were analyzed. Included in the analysis to determine speed of onset were 298 patients taking mirtazapine and 285 taking an SSRI. Pattern analysis, which has been described and used by other researchers, was employed to study speed of onset.

Results: At the end of each of the 3 studies, the total number of responders for each of the drugs did not differ. However, the proportion of responders with onset of persistent improvement in week 1 was greater for mirtazapine (13%, 38/298) than for the SSRIs (6%, 18/285; $\chi^2 = 6.95$, df = 1, p = .008).

Conclusion: These data support the possibility that mirtazapine may have a more rapid onset than SSRIs. This observation should be considered preliminary because of the retrospective nature of the analysis and the absence of a placebo group.

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Depending on how they are categorized, antidepressants can be divided into at least 4 classes: tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and novel antidepressants such as venlafaxine and mirtazapine. For patients who do not respond to a first trial with an antidepressant, clinical wisdom and some empirical data support the strategy of an interclass, rather than an intraclass, antidepressant switch.[1] Any single class of drugs offers only a modest effect size, approximately 30% better than placebo. However, if the clinician and patient are steadfast and persevere through several treatment trials, 90% of patients may eventually benefit.[2] The development of multiple classes of drugs provides us with more therapeutic options, but our ability to characterize different symptom profiles for predicting response to different classes of drugs is at best imprecise.[3–5] This imprecision has increased interest in defining time parameters to guide clinicians,[6] including time to onset of patient improvement with antidepressant treatment and the length of time required to determine whether further improvement is unlikely without a treatment change. Defining these relevant time parameters may shorten the time required to identify which treatment is more likely to benefit the individual patient.

The purpose of this study was to determine if the onset of improvement with mirtazapine is more rapid than onset of improvement with SSRIs. Interest in this question was stimulated by a recent report by Wheatley et al.[7] suggesting that mirtazapine, which increases serotonergic and noradrenergic transmission, had an earlier onset of beneficial effect than fluoxetine. The initial analysis had limitations in that it was primarily supported by a cross-sectional approach using the Hamilton Rating Scale for Depression (HAM-D), which favors antidepressants with sleep-enhancing effects.

There are 2 approaches to determine the point at which antidepressant effects first occur. In the first, a cross-sectional approach,[8–10] any statistically significant drug-placebo difference is considered evidence of the onset of antidepressant effect. However, this approach does not consider the issue of whether the observed improvement persists and therefore is clinically relevant. We observed that early transient responses were equally likely to occur

with drug and placebo, suggesting this type of response is probably attributable to placebo effects.[11] In contrast, responses that persist over time would appear to be more clinically relevant and more likely to reflect true antidepressant effects.[11] Approaches that consider a longitudinal as well as a cross-sectional perspective include classical survival analysis (as reported in the work by Stassen et al.[12]) and pattern analysis.[11,13,14]

Pattern analysis was proposed as a means of differentiating true drug and placebo effect,[11] but it also offers a means of identifying the onset of first antidepressant response. This method has previously been used by others as a tool in identifying early onset of drug effect.[13,14] Pattern analysis considers the time of onset of response and whether responses persist. Each study week is rated (applicable for studies lasting for 4 to 12 weeks). All patients much or very much improved as determined by the Clinical Global Impressions-Improvement scale (CGI-I) (score of 1 or 2) are considered improved and are given a score of "1" for that week; all others are considered unimproved and given a score of "0." A response is considered persistent if improvement of 1 or 2 on the CGI is not followed by a score of 3 or worse. A pattern is made for each patient consisting of a 0 or 1 for each study week. A comma is added to simplify the examination of the digit pattern. Thus the course of a 5-week study can be characterized by 5 digits, for example, 111,11 or 000,00 or any combination of zeros or ones. A patient with a pattern of 111,11 was judged a responder in week 1 and never relapsed; a patient with 000,00 never responded; a patient with 010,00 was judged to achieve responder status in week 2 but was a nonresponder in all other weeks. Further details of the method are available.[11] If a particular drug shows a higher proportion of patients with early persistent response than other antidepressants, it may have an earlier onset of action. Pattern analysis by definition is not applied to patients missing ratings for more than 1 week. Since our interest is in examining speed of onset rather than a total view of efficacy, analysis involving all data, such as a last-observation-carried-forward analysis, is less critical for the purpose of this report.

METHOD

All double-blind studies comparing mirtazapine with SSRIs were examined; SSRIs studied included fluoxetine,[7] paroxetine,[15] and citalopram.[8] Table 1 summarizes the main aspects of design and results for each study. All 3 studies had virtually identical designs, with a 3- to 7-day single-blind placebo washout period followed by a double-blind randomized parallel design. Two studies lasted 6 weeks, and the citalopram comparative study lasted 8 weeks. The fact that 1 study lasted 8 weeks should not affect determination of the speed of onset or persistence. To make the 8-week study comparable to the 6-week studies, only ratings through week 6 were used in making patterns. In all studies, patients were evaluated weekly except for week 5. Therefore, their patterns consist of 5 digits. Entrance requirements included a diagnosis of major depressive disorder (according to DSM-III-R or DSM-IV criteria) and a 17-item HAM-D minimum score of 18 or 21 or a Montgomery-Asberg Depression Rating Scale minimum score of 22 (see Table 1). Further details of the inclusion and exclusion criteria can be found in the original publications.[7,8,15]

Table 1. Design of 3 Studies Comparing Mirtazapine With an SSRI[a]

Variable	Mirtazapine vs Fluoxetine[7]	Mirtazapine vs Paroxetine[15]	Mirtazapine vs Citalopram[8]
Diagnosis	MDD (DSM-III-R)	MDD (DSM-IV)	MDD (DSM-IV)
Inclusion criteria	HAM-D-17 ≥ 21; item 1 ≥ 2	HAM-D-17 ≥ 18	MADRS ≥ 22
Duration, wk	6	6	8
Patients, N (ITT)			
Mirtazapine	60	127	136
SSRI	63	123	133
Dose, mg/d			
Mirtazapine	15–60	15–45	15–60
SSRI	20–40	20–40	20–60
HAM-D/MADRS mean score at baseline			
Mirtazapine	26.0	22.4	29.6
SSRI	26.1	22.4	29.1
Responders[b] at endpoint, %			
Mirtazapine	66.7	58.3	85.3
SSRI	46.0	53.7	88.0

[a]Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.
[b]Responder defined as having at least a 50% decrease in HAM-D or MADRS (last observation carried forward).

The study comparing mirtazapine and citalopram was found to have an unusually high response rate. More than 80% in both treatment groups were judged to be much or very much improved as determined by the CGI, 10% to 20% higher than that response rate usually found in active comparative studies. Another aberrant characteristic is that only 10% of the citalopram group never improved (pattern of all zeros), lower than the 20% seen in published reports.[10] These high rates of response and low rates of total absence of response suggest that patients entered into the citalopram-mirtazapine study may not be representative of patients usually included in this type of study. A quandary in post hoc analysis is how to deal with such aberrant data while avoiding biased post hoc data manipulation. It was decided to analyze the overall data for this study on the basis of 2 subsets: with and without data from this citalopram-mirtazapine study.

To compare the speed of onset between mirtazapine and SSRIs, we analyzed the proportion of persistent responses by week using pattern analysis.

Table 2. Persistent and Nonpersistent Responders for Mirtazapine vs. Fluoxetine, Paroxetine, and Citalopram Groups[a]

Status	Proportion of Patients (%)			
	Mirtazapine (N = 298)	Fluoxetine (N = 46)	Paroxetine (N = 110)	Citalopram (N = 129)
Persistent responders				
Week 1	13	9	6	5
Week 2	20	20	25	20
Week 3	15	15	14	28
Week 4	10	9	9	15
Week 6	9	7	9	12
Nonpersistent responders[b]	7	13	8	5
Nonpersistent nonresponders[c]	9	9	4	4
Never improved	15	20	25	10
Total responders	75	72	71	86

	Mirtazapine	SSRIs	
Week 1 responders	38	18	$\chi^2 = 6.95$, df = 1, p = .008
All others	260	267	

[a]Response determined by Clinical Global Impressions-Improvement Scale score. Abbreviation: SSRI = selective serotonin reuptake inhibitor.
[b]Responded, relapsed, rated responder at week 6.
[c]Responded, relapsed, not rated responder at week 6.

Table 3. Persistent and Nonpersistent Responders for Mirtazapine vs. Fluoxetine and Paroxetine Groups[a]

Status	Proportion of Patients (%)		
	Mirtazapine (N = 169)	Fluoxetine (N = 46)	Paroxetine (N = 110)
Persistent responders			
Week 1	17	9	6
Week 2	16	20	25
Week 3	12	15	14
Week 4	10	9	9
Week 6	8	7	9
Nonpersistent responders[b]	8	13	8
Nonpersistent nonresponders[c]	11	9	4
Never improved	17	20	25
Total responders	72	72	71

	Mirtazapine	SSRIs	
Week 1 responders	29	11	$\chi^2 = 7.68$, df = 1, p = .006
All others	140	145	

[a]Response determined by Clinical Global Impressions-Improvement Scale score. Abbreviation: SSRI = selective serotonin reuptake inhibitor.
[b]Responded, relapsed, rated responder at week 6.
[c]Responded, relapsed, not rated responder at week 6.

RESULTS

Data are presented in Table 2 for mirtazapine versus all 3 SSRIs and in Table 3 for mirtazapine versus fluoxetine and paroxetine. These tables include the proportion of patients with a persistent response by week of onset, as well as total percentage of patients rated as responders using CGI-I criteria. There were no differences in the total proportion of responders for any of the drugs. The proportion of responders for completers in the fluoxetine-mirtazapine and paroxetine-mirtazapine studies is consistent with other drug-drug comparisons, i.e., 72% of mirtazapine-, 72% of fluoxetine-, and 71% of paroxetine-treated patients responded (Table 3). In the citalopram-mirtazapine study, the proportion of responders was 86% and 80%, respectively.

Turning to the question of speed of onset, for the analysis including all 3 studies, the proportion of persistent response with onset in week 1 for patients receiving mirtazapine was 13% (38/298), whereas the combined group of patients receiving SSRIs had 6% (18/285) persistent response with onset in week 1 ($\chi^2 = 6.95$, df = 1, p = .008; see Table 2).

Examination of 2 studies, excluding the possibly aberrant study (mirtazapine vs. citalopram), suggests the proportion of persistent responders in week 1 was 17% with mirtazapine (29/169) and 7% (11/156) with fluoxetine or paroxetine ($\chi^2 = 7.68$, df = 1, p = .006; see Table 3). The fact that these differences were measured using the CGI-I suggests that this improvement reflects mood improvement and not merely improvement in sleep.

DISCUSSION

These data suggest that mirtazapine may have a more rapid onset of action compared with SSRIs. The approximately 10% difference in first-week persistent responders when mirtazapine is compared with fluoxetine and paroxetine is clinically relevant. If we include the citalopram study, the difference in first-week persistent responders with mirtazapine is statistically significant but less robust. Others have used pattern analysis to examine onset of therapeutic effect and suggest that venlafaxine's benefit exceeded that of placebo by the second treatment week but not the first.[13,14]

Intent-to-treat (ITT) analysis is frequently used and is considered a standard. Pattern analysis could be converted into a type of ITT analysis by adding dropouts as a separate category. Doing so would increase the total number of patients included in the analysis and would thereby slightly decrease the proportion in each category. In the original study comparing mirtazapine with fluoxetine,[7] patients were categorized as early persistent, late persistent, early nonpersistent, and late nonpersistent responders and nonresponders (dropouts were excluded). Since it would be anticipated that the proportion of dropouts would be approximately equal in each of the study arms, including them would not significantly alter pattern analysis. A study with unequal dropouts in the different treatment groups would pose the same problems in interpretation for pattern analysis as for other types of analysis. In these data, there were 25 dropouts in the combined mirtazapine group and 34 in the combined SSRI group. If we include dropouts and do a modified ITT analysis, there is still a significant advantage at week 1 for patients receiving mirtazapine (onset at week

1: 11.8% [38/323] for mirtazapine vs. 5.6% [18/319] for SSRIs, $\chi^2 = 7.56$, df = 1, p = .006).

These data should be interpreted cautiously. Since the prediction that week 1 persistent responders would be greater with mirtazapine was not made a priori, we may be capitalizing on a fortuitous post hoc finding. The absence of a placebo group also supports cautious interpretation. However, if we attribute early improvement in the mirtazapine group to a placebo effect, it becomes necessary to explain why this was not observed with SSRIs. Furthermore, the increase in first week persistent response is numerically greater for mirtazapine in all 3 studies, decreasing the likelihood of a fortuitous observation.

Earlier, we questioned whether the sample included in the mirtazapine-citalopram study was representative of the modal patient with major depression because of the overall high response rate. Two studies that suggested a rapid onset of response with citalopram compared with other SSRIs did not find a higher response rate at study end.[16,17] Therefore, they do not help to explain the very high response rates with citalopram (> 85% in an ITT analysis) observed in the mirtazapine-citalopram study.

In summary, the apparently greater effect of mirtazapine in the first treatment week should be considered a preliminary observation requiring prospective validation in subsequent studies including a placebo group and active comparator. The fact that the number of persistent responders with onset in week 1 is greater for mirtazapine in each of the 3 studies supports the possibility that this observation is valid. Future studies planned include a mirtazapine, fluoxetine, and placebo study with evaluation using standard clinical and interactive voice response measures done frequently during an 8-week period. Prospectively demonstrating a rapid onset of benefit with mirtazapine would add to the validity of the post hoc observations reported in this article.

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

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