Prediction of Response Within the First 3 Days to Treatment With Paroxetine for Depression

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Objective: In the treatment of depression, clinical and psychopharmacologic aspects have been investigated to predict the response to antidepressants. Some trials have reported clinical improvement as early as the first week; however, few have investigated the early effects of selective serotonin reuptake inhibitors. The aim of this study was to investigate therapeutic efficacy of paroxetine within the first 3 days of therapy onset.

Method: Subjects included 29 outpatients diagnosed at first interview with major depressive disorder according to DSM-IV criteria (June 2003 to January 2007). Paroxetine 5–20 mg/day was administered for at least 2 weeks. Treatment efficacy was defined as a > 50% decrease in Hamilton Rating Scale for Depression (HAM-D) total scores from baseline to the end of the second week. To determine efficacy within the first 3 days, patients completed the HAM-D as a self-rated questionnaire on the first and third days and at the end of the first, second, and fourth weeks.

Result: Subjects were divided into 2 groups: successful (17 responders) and failed (12 nonresponders). There was a significant difference between the reduction rates of self-rated HAM-D total scores on the third day ($p < .01$).

Conclusion: In patients responding to paroxetine in the early stages of treatment, the prediction of response within the first 3 days using the self-rated HAM-D is suggested.

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If the effect of an antidepressant can be predicted during the early stage of therapy, medical treatment efficacy can be facilitated. It has been hypothesized that subjective initial reaction during the initial phase of treatment is a relatively good predictor.[1,2] The clinical benefit of such a prediction method promises to be significant because it can predict the efficacy of a specific drug within a short time compared with the current trial-and-error period of administering various antidepressants for several weeks before an effective drug is finally found.[3] Patients present to primary care physicians and psychiatrists, are diagnosed and started on medication, and usually return for follow-up after 1 or 2 weeks; therefore, primary care physicians and psychiatrists cannot observe the effectiveness of medication during the early stage of treatment (within the first week). This article reports the early clinical effectiveness of paroxetine within the first 3 days of therapy onset.

METHOD

Subjects included 29 patients who visited the Department of Psychiatry (Shimane University Hospital, Izumo, Japan) and 3 psychiatric outpatient clinics from June 2003 to January 2007. They were diagnosed at first interview with major depressive disorder according to DSM-IV criteria, excluding both bipolar disorder and personality disorder. All were clinically referred outpatients with no age restrictions, who gave written informed consent to participate in this prospective study. Almost all subjects had developed depression for the first time. Patients were objectively rated on the 21-item version of the Hamilton Rating Scale for Depression[4] (HAM-D) by psychiatrists at baseline and at the end of the second week. They had not taken any psychotropic drugs for at least 4 weeks before the study began. The maximum dose of paroxetine was 20 mg/day (range, 5–20 mg/day) for 4 weeks.

Efficacy was assessed on the basis of improvement in the severity of depression symptoms during the course of treatment (> 50% decrease in total HAM-D score from baseline to the end of week 2). In order to determine effi-

Table 1. Clinical Characteristics of Successful (responder) and Failed (nonresponder) Groups Treated With Paroxetine for Depression

Characteristic	Successful Group (N = 17)	Failed Group (N = 12)	p Value
Age, mean ± SD, y	51.9 ± 16.5	50.8 ± 16.7	.43
Gender, N			.49
Male	5	5	
Female	12	7	
Duration of current depressive episode, mean ± SD, mo	2.8 ± 1.7	2.3 ± 1.2	.18
HAM-D total score (first day), mean ± SD	30.4 ± 4.7	25.5 ± 9.0	.08
HAM-D total score (second week), mean ± SD	9.2 ± 3.3	15.9 ± 9.6	< .05
Paroxetine dose, mean ± SD (range), mg/d	10.9 ± 3.6 (5–20)	10.9 ± 3.0 (10–20)	.49

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 2. Comparison of Clinical Data of Successful (responder) and Failed (nonresponder) Groups Treated With Paroxetine for Depression

Variable	Successful Group (N = 17)	Failed Group (N = 12)	p Value
Self-rated HAM-D total score, mean ± SD			
First day (baseline)	33.4 ± 7.6	28.4 ± 8.7	.07
Third day	22.2 ± 7.2	25.5 ± 11.3	.16
First week	15.8 ± 5.3	24.0 ± 10.7	< .01
Second week	10.4 ± 5.5	22.4 ± 13.0	< .01
Reduction rate, mean ± SD			
Third day	0.67 ± 0.17	0.89 ± 0.22	< .01
First week	0.49 ± 0.17	0.83 ± 0.27	< .01
Second week	0.30 ± 0.14	0.78 ± 0.31	< .01
Self-rated HAM-D subscale score, mean ± SD			
Anxiety/somatization			
Third day	0.73 ± 0.20	0.85 ± 0.30	.09
First week	0.58 ± 0.23	1.05 ± 0.23	< .01
Core			
Third day	0.69 ± 0.21	1.05 ± 0.43	< .01
First week	0.46 ± 0.18	0.76 ± 0.41	< .05

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

cacy in the first 3 days, we used the HAM-D as a self-rated questionnaire. Patients completed the self-rated HAM-D on the first and third days and at the end of the first, second, and fourth weeks. Secondary efficacy measures included the HAM-D subscales: anxiety/somatization (items 10, 11, 12, 13, 15, and 17) and core (depressive mood/retardation; items 1, 2, 3, 7, and 8).[5] The unpaired t test (1-tailed) and χ^2 test were used to determine correlation coefficients.

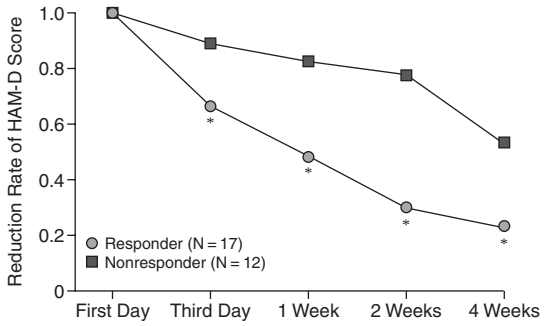
RESULTS

The 29 patients who completed the study were divided into 2 groups: 1 group in which the antidepressant treatment could be regarded as successful and 1 group in which treatment could be considered as having failed (Table 1). The successful group included 17 subjects (5 men and 12 women) ranging in age from 29 to 87 years (mean ± SD = 51.9 ± 16.5 years). The failed group included 12 subjects (5 men and 7 women) ranging in age from 19 to 73 years (mean ± SD = 50.8 ± 16.7 years).

The mean ± SD durations of the current depressive episode were 2.8 ± 1.7 months and 2.3 ± 1.2 months, respectively. The mean ± SD HAM-D total scores (assessed by psychiatrists) of the successful and failed groups were 30.4 ± 4.7 and 25.5 ± 9.0 ($p = .08$) on the first day and 9.2 ± 3.3 and 15.9 ± 9.6 ($p < .05$) at the end of the second week, respectively. The mean ± SD scores of the successful and failed groups on the self-rated HAM-D were 33.4 ± 7.6 and 28.4 ± 8.7 ($p = .06$) on the first day; 22.2 ± 7.2 and 25.5 ± 11.3 ($p = .16$) on the third day; 15.8 ± 5.3 and 24.0 ± 10.7 ($p < .01$) after the first week; 10.4 ± 5.5 and 22.4 ± 13.0 ($p < .01$) after the second week (Table 2); and 7.6 ± 4.2 and 15.0 ± 10.0 ($p < .05$) after the fourth week, respectively.

Improvement rates were expressed as the percentage reduction from baseline in self-rated HAM-D scores. The baseline value was 1. The mean ± SD percent reduction rates on the HAM-D of the successful and failed groups were 0.67 ± 0.17 and 0.89 ± 0.22 ($p < .01$) on the third day; 0.49 ± 0.17 and 0.83 ± 0.27 ($p < .01$) after the first week; 0.30 ± 0.14 and 0.78 ± 0.31 ($p < .01$) after the sec-

Figure 1. Improvement Rate on the Self-Rated Hamilton Rating Scale for Depression (HAM-D) Among Patients Treated With Paroxetine



*p < .01.

ond week; and 0.23 ± 0.13 and 0.53 ± 0.37 ($p < .01$) after the fourth week, respectively (Figure 1). There was a significant difference between the 2 groups on the reduction rate of the self-rated HAM-D total scores on the third day ($p < .01$) and continued improvement over 4 weeks.

The mean ± SD reduction rates of the self-rated HAM-D anxiety/somatization subscale of the successful and failed groups were 0.73 ± 0.20 and 0.85 ± 0.30 ($p = .09$) on the third day and 0.58 ± 0.23 and 1.05 ± 0.23 ($p < .01$) after the first week, whereas the mean ± SD HAM-D core subscales of both groups were 0.69 ± 0.21 and 1.05 ± 0.43 ($p < .01$) on the third day and 0.46 ± 0.18 and 0.76 ± 0.41 ($p < .05$) after the first week, respectively. There was a significant difference between the reduction rate of the HAM-D anxiety/somatization subscale and the core subscale on the third day. The reduction rate of the core subscale decreased significantly earlier than the anxiety/somatization subscale. The reduction rate of the change in core symptoms was greater than that in anxiety/somatization symptoms on the third day (Table 2).

DISCUSSION

Subjects with mild-to-moderate DSM-IV major depressive disorder were recruited for this study of the prediction of antidepressant treatment response using paroxetine. Although personality disorders appear to be common among patients with depression, whether personality disorders influence the treatment response is not clear and often shows a complicated prognosis.[6] We therefore excluded depressed patients with comorbid personality disorders.

Intensive research efforts have focused on the question of how to predict whether a given treatment will have a relatively favorable outcome.[2] In depression treatment, clinical and psychopharmacologic aspects have been investigated to predict the response to antidepressants. The clinical benefit of having an early prediction method promises to be significant. Clinically, we encountered patients who quickly responded to antidepressants and those who did not. Research into when a drug effect becomes noticeable is rare.

If we can investigate the clinically important early effects of antidepressants, these findings will have considerable significance for clinical practice. Early improvement may be predictive of a positive outcome at the end of treatment. Generally, outpatients return to their psychiatrist 1 or 2 weeks after the first visit; therefore, primary care physicians and psychiatrists cannot determine effectiveness in the early stages of treatment.

Randomized controlled trials comparing antidepressant agents with a placebo showed statistically significant benefits of SSRIs after as little as 1 week of use.[7,8] These studies were typically of a similar design and were often assessed weekly.[7,8] To our knowledge, few studies have investigated the effect of SSRIs within 1 week (i.e., on the third day from therapy onset). Our results suggest that the therapeutic efficacy of paroxetine may be predicted within the first 3 days of therapy onset.

Considering the results of the subscale scores of the HAM-D, Dunbar et al.[7] found that paroxetine improved retardation symptoms by 1 week and anxiety/somatization symptoms by 2 weeks when compared with placebo. However, recent studies indicate that SSRI treatment might be expected to improve, at least initially, the components of depression reflecting anxiety, agitation, and hostility.[8] The earliest improvement in paroxetine responders was anxiety, and depressed mood and cognitive impairment improved somewhat later.[10] In this study, the reduction rate of the core subscale decreased significantly earlier than that of the anxiety/somatization subscale on the third day. Although these findings suggest the earlier effect of paroxetine on core depressive symptoms, our results may have been insufficiently assessed because of smaller samples and because almost all subjects had mild-to-moderate depression.

A sufficient effect of antidepressants may be achieved in 2 to 4 weeks. Furthermore, some patients respond after 4 to 8 weeks following an appropriate increase in the antidepressant dose; therefore, it may be difficult to predict the final reactivity/effectiveness based on the early response. In this study, we judged treatment efficacy in the second week using low doses of paroxetine (5–20 mg/day); therefore, nonresponsive patients might have improved if we had administered a higher dose of the antidepressant over a longer period of time. Since we used a self-rating method to evaluate the patients, there might have been a problem in the precision of the assessment. However, in patients responding to antidepressants in the early stages of treatment, our results suggest that treat-

ment response may be predicted in the first 3 days using a self-rated HAM-D questionnaire.

From here, it is necessary to increase the accuracy of evaluation of efficacy using other monitoring psychometries. Except for the preliminary study and the small patient samples, we did not examine the validity of the self-rated HAM-D. The validity of the instrument in rating the depressive state should be examined. Moreover, further study is needed of the coincidence-of-effect evaluation between patients and psychiatrists.

Drug name: paroxetine (Paxil, Pexeva, and others).

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