

The Use of Maprotiline for Major Depression: A Clinical Report of 62 Cases

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ABSTRACT

Objective: The purpose of this clinical study was to examine the utility of maprotiline in the treatment of a wide spectrum of patients with depression.

Methods: A retrospective cohort analysis of outpatients with major depressive disorders was performed. Sixty-two patients receiving maprotiline were identified and included in the analysis.

Results: After 6 weeks the cumulative percentage of responders receiving maprotiline was over 80%. A variety of clinical factors including age, gender, frequency of episodes, family history, and psychiatric symptoms were examined as possible predictors of the response to maprotiline. Although there were no significant differences among these clinical factors by Cox proportional hazards analysis and chi-square test, patients with these clinical factors showed a good response to maprotiline.

Conclusion: Maprotiline showed a good response in patients with a variety of clinical factors. Therefore, maprotiline

appears to be useful in the treatment of therapy-resistant depression.

INTRODUCTION

Depression is the most common major mental illness and affects 5% to 12% of men and 10% to 25% of women during their lifetime.¹ Recently, many patients with depression have been successfully treated with selective serotonin reuptake inhibitors (SSRIs) and/or dual serotonin and noradrenaline reuptake inhibitors (SNRIs). However, the number of therapy-resistant patients, who show lesser responses with SSRIs and SNRIs, is on the increase. Therefore, it is important to be able to treat therapy-resistant depression. Kielholtz² has reported that maprotiline has been proven to be particularly effective in treating such therapy-resistant depression. Maprotiline is a tetracyclic drug, distinguished from the tricyclic antidepressants only by the rigid flexure of its molecular skeleton, and its ability to block noradrenaline uptake while having no apparent influence on 5-HT metabolism. Maprotiline appears to have a broad spectrum of activity in the various types of depression.³ In Japan, although maprotiline has been prescribed for over 20 years to treat depression, the types of patients that could be expected to respond to treat-

Table 1. Baseline Characteristics of 62 Patients

Age	Mean 53.1 (range 23-77)
Gender (male/female)	29/33
Frequency of episodes (first/recurrence)	39/23
History of family psychiatric illness (positive/negative)	12/50
Psychiatric symptoms (Inhibited depression/agitated depression)	22/40

ment with maprotiline have not yet been thoroughly elucidated. Therefore, it seemed necessary, in order to fully understand the treatment of therapy-resistant depression, to examine the clinical characteristics of patients on maprotiline treatment. Thus, this clinical study was carried out to determine which types of patients with major depression benefit from maprotiline treatment.

METHODS

Patients

A retrospective cohort analysis of depressed patients treated in the Department of Psychiatry, Kawasaki Medical School, Kurashiki, Japan was conducted. The medical records of the patients receiving maprotiline to treat depression were also reviewed. This study included patients diagnosed with depression, who were being treated with maprotiline and were required to meet all of the following criteria: patients met the DSM-III-R or DSM-IV criteria for major depressive disorder; patients had to have been already evaluated by the 21-item Hamilton Depression Rating Scale (HAM-D),⁴ and needed a total HAM-D score of 22 to 32 after at least 14 days without psychotropic medication before treatment; maprotiline must have been administered orally without any other antidepressants or mood stabiliz-

ers with a daily dose of maprotiline, 30 to 75mg (the recommended treatment dose in Japan); patients needed to be observed for 10 weeks; and using the HAM-D, their clinical symptoms had to be evaluated to rate them as either being responders or non-responders before and every week after maprotiline treatment (patients with a 50% reduction from baseline total HAM-D scores were rated as responders,⁵ otherwise they were considered non-responders).

Patients were excluded from the study if they had a history of seizures, comorbid anxiety disorder, obsessive-compulsive disorder, mixed state, or other psychiatric disorders, and received psychotherapy.

Sixty-two patients met the above criteria and were included in the analysis (Table 1).

Statistical Analyses

To determine the period of the onset of action, the point in time during the treatment period when the cumulative percentage of responders reached more than 80% was noted. This was selected as the critical value, since a lower probability with 1 SD (standard deviation) contained 84.4% of the normal distribution. Consequently, the 80% cut-off contained almost all the data of the statistical distribution.

Table 2. Cox Proportional Hazards Analysis of Five Clinical Factors

	χ^2	df	P value
Age	0.017	1	0.8960
Gender	0.778	1	0.3779
Frequency	0.106	1	0.7448
Family history	0.038	1	0.8451
Psychiatric symptoms	0.292	1	0.5887

The following 5 clinical factors (Table 1) were obtained from the 62 patients: age, gender, frequency of episodes (first or recurrent), history of family psychiatric illness (positive or negative), and major psychiatric symptoms (inhibited depression or agitated depression). These clinical factors were easily extracted from the medical records and were studied as possible predictors of improvement. A Cox proportional hazards model and the chi-square test were used to test the significance of these clinical factors as predictors of the response. A computer software program, StatView for Macintosh (version 5.0), was used for all the analyses. The level of significance was set at $P < 0.05$.

RESULTS

At the end of the 10-week treatment period, 54 (83.1%) of the 62 patients showed a response to maprotiline treatment.

Of those responding to maprotiline treatment, the cumulative percentage of responder patients is shown in Figure 1. The cumulative percentage of responder patients reached more than 80% after 6 weeks.

A Cox proportional hazards analysis showed that the 5 clinical factors were not independently predictive of improvement resulting from maprotiline treatment (Table 2).

The response rate for males was 79.3% (23 of 29), while that of females was 87.9% (29 of 33). The response rate of patients having their first episode of

depression was 79.5% (31 of 39), and the response rate for patients having a recurrent episode was 91.3% (21 of 23). The response rate for patients with a positive family history was 83.3% (10 of 12), while for those with a negative family history it was 84.0% (42 of 50). Finally, the response rate for patients with inhibited depression was 82.5% (33 of 40), while for patients with agitated depression the response rate was 86.4% (19 of 22). There were no statistically significant differences for any of the clinical factors.

Table 3 showed the maprotiline response rate of each clinical factor by gender. There was no significant gender difference in the maprotiline response rate for any of the clinical factors.

DISCUSSION

In this study, we examined the clinical characteristics associated with a positive response to maprotiline treatment for major depression.

When providing antidepressant treatment it is important to determine whether the regimen should be altered after several weeks. This can be addressed by knowing the onset of action of a particular treatment regimen.

During the last few years, some investigators have studied the onset of action of antidepressant medication. Stassen et al⁶ found that 70% of subjects who showed improvement of at least 20% at 10 days reached the conventional 50% symptom reduction responder criteria at 4 weeks. Quitkin et al⁷ investi-

Table 3. Response Rate of Clinical Factors Among Patients by Gender

	Male	Female
Frequency		
First	72.2%	85.7%
Recurrence	90.9%	91.7%
Family history		
Positive	50.0%	100%
Negative	84.0%	84.0%
Psychiatric Symptom		
Inhibited	72.2%	90.9%
Agitated	90.9%	81.8%

gated at what point a patient is not likely to receive any further benefit from the current antidepressant and should be switched to another medication. They recommended that patients who are tolerant of an adequate dose but whose condition has not been even minimally improved by the end of 4 weeks should have their treatment regimen altered. Our previous studies have reported that the minimal suitable treatment duration for fluvoxamine, paroxetine, and low dose milnacipran is 6 weeks.⁸⁻¹⁰ Thus, our findings suggest that antidepressant treatment for depression must be tried for at least 6 weeks. We also recommend that the treatment regimen should be

altered if a patient does not show a response within 6 weeks of maprotiline treatment.

It would be important to be able to predict which patients are most likely to benefit from maprotiline. Until now, the clinical predictors of the response to maprotiline have not been thoroughly studied. This study showed that 5 clinical factors were not associated with the response to maprotiline treatment. This finding offers an important clinical insight. Recently, we reported that the response rate to SSRIs and SNRIs was lower among females with a recurrent episode of depression than among patients with a first episode of depression.¹¹ Although several studies have suggested that female gender is associated with poor response to antidepressant treatment,¹²⁻¹⁴ treatment with maprotiline appears to be effective in women with depression and/or women with a recurrent episode of depression. Therefore, one can recommend maprotiline for refractory depression in both men and women.

Kielholz and Poeldinger^{15,16} reported that distinguishing between inhibited and agitated depression could facilitate the choice of pharmacotherapy. They proposed that different antidepressants have varying effects on the individual symptoms of the depression syndrome, such as psychomotor retardation, sadness, depressive mood, anxiety, agitation

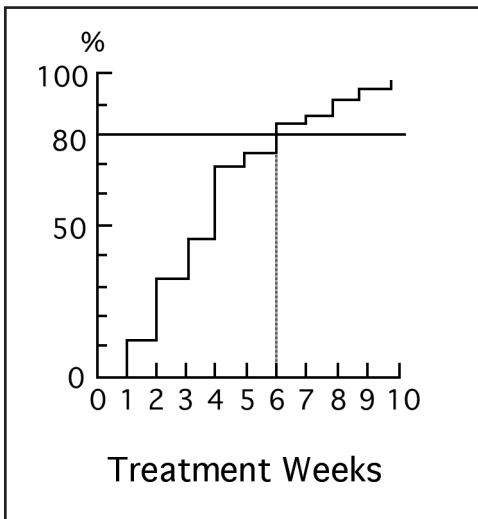


Figure 1. Cumulative percent of patients showing response to maprotiline.

and hypochondriasis. Since the spectrum of action of antidepressant substances is important for the treatment of depression, Kielholz² recommended that maprotiline be used for therapy-resistant agitated depression. In fact, the present study showed that maprotiline had a good response in patients with the agitated type of depression. Therefore, maprotiline can be recommended for all patients with therapy-resistant depression.

However, this study did have some limitations. This was a retrospective study, and so lacked the stricter criteria and methods of a prospective study. Since there was no placebo control group, a placebo response may be included in the responder patients. Patients with a bipolar disorder depression were not included, and patients with bipolar depression may have a different response from patients with a major depressive disorder. These findings warrant a future prospective study that would overcome the limitations of this study. However, the current results can already help guide clinicians in determining the selection of antidepressants for therapy-resistant depression.

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