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Possible predictors of response to fluvoxamine for depression

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Introduction An investigation of the characteristics of patients being treated with antidepressants would seem to be useful in determining which patients would be most likely benefit from antidepressant medication.
Aims The purpose of this preliminary study was to examine the possible predictors of response to fluvoxamine for depression.
Method A retrospective cohort analysis was carried out among depression patients treated in the Department of Psychiatry, Kawasaki Medical School Hospital, Kurashiki, Japan, in 2000. Seventy two patients were identified who were receiving fluvoxamine to treat depression.
Results A variety of clinical factors including age, gender, type of depression, frequency of episodes, family history and daily dose of fluvoxamine were examined as possible predictors of the response to fluvoxamine. A Weibull regression analysis showed age, frequency of episodes and daily dose to be the independent predictive factors of improvement in fluvoxamine treatment. The most influential factor was age (ecoef = 2.109), followed by daily dose (ecoef = 0.648) and frequency of episode (ecoef = 0.512). An age of 49 years or younger ($\chi^2 = 6.767$, df = 1, $p = 0.0093$), a first episode ($\chi^2 = 9.079$, df = 1, $p = 0.0026$) and a daily dose of 100–150 mg ($\chi^2 = 5.353$, df = 1, $p = 0.02$) were significantly better predictors of improvement.
Conclusions Age, the frequency of episodes and the daily dose of fluvoxamine may be considered as predictors of the response to fluvoxamine treatment for depression. This result should be examined in future prospective study.

KEY WORDS — fluvoxamine; antidepressant; selective serotonin reuptake inhibitor; depression; predictor

INTRODUCTION

Depression is the most common major mental illness and affects 5%–12% of men and 10%–25% of women during their lifetime (Kessler *et al.*, 1994). Of all medical disorders seen in primary care, depression appears to be the most common and has been found to cause more functional disability than diabetes, chronic lung diseases, hypertension or arthritis (Panzaro, 1998). Recently, many patients with depression have been treated successfully with antidepressants including tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors and/or selective serotonin reuptake inhibitors (SSRIs).

All antidepressants do not have the same effect on all patients at any time. It is important to predict which patients would be most likely to benefit from each antidepressant. Although investigation of the characteristics of patients being treated with antidepressants would seem to be useful in determining which patients would be most likely to benefit from antidepressant medication, it is a task of great difficulty. Recently, a relationship between antidepressants and predictors was reported (Gex-Fabry *et al.*, 1999; Kornstein *et al.*, 2000; McGrath *et al.*, 2000). This information is very useful in antidepressant treatment.

Fluvoxamine, an SSRI, is an effective antidepressant (Ware, 1997), which acts by facilitating serotonergic neurotransmission (Claasen, 1983). It has been approved for depression in several European countries since 1983 and in Australia since 1997. In Japan, fluvoxamine was introduced in 1999 as the first antidepressant SSRI. Ansseau *et al.* (1991) reported that

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depressive patients with an underlying compulsive personality respond better to a serotoninergic antidepressant such as fluvoxamine than do depressive patients without an underlying compulsive personality. However, the characteristics of patients expected to respond to treatment with fluvoxamine have not been thoroughly elucidated.

Therefore, a preliminary trial explored the possible predictors of response to fluvoxamine for depression.

METHODS

Patients

A retrospective cohort analysis was made among depression patients treated in the Department of Psychiatry, Kawasaki Medical School Hospital, Kurashiki, Japan, between January and December 2000. During this study period, 672 patients met the DSM-IV criteria for major depressive disorder or bipolar disorder depression. The medical records of the patients receiving fluvoxamine to treat depression were also reviewed. To be included in this study, patients diagnosed with depression who were being treated with fluvoxamine were required to meet all of the following criteria.

The inclusion criteria. Patients, who were already evaluated by the 21-item Hamilton depression rating scale (HDRS) (Hamilton, 1960), were reviewed. Before treatment, patients were required to have a total HDRS score of 22–32 (mean 26.7) after at least 14 days without psychotropic medication. Fluvoxamine was administered orally once or twice daily without any other antidepressants or mood stabilizers. The daily dose of fluvoxamine did not change during the treatment period. The clinical symptoms were evaluated for improvement or nonimprovement before and every week after fluvoxamine treatment using the HDRS. Patients with a 50% reduction from baseline total scores on the HDRS were evaluated as improved (Prien *et al.*, 1991), whereas, others were not improved.

Exclusion criteria. Patients were excluded from the study if they had a history of seizure or myoclonus, comorbid anxiety, obsessive-compulsive disorder, or other psychiatric disorders.

Seventy-two patients met the above criteria and were included in the analysis.

Table 1. Baseline characteristics of 72 patients

Age	Mean 51.8 (range 18–81)
Gender (M/F)	53/37
Type of depression (unipolar to bipolar)	64/8
Frequency of episode (first to recurrence)	34/38
History of family psychiatric illness (positive to negative)	18/54
Daily dose (50–75 mg to 100–150 mg)	34/38

Statistical analyses

The following six clinical factors (Table 1) were derived from the 72 patients. These clinical factors were easily derived from the medical records. Therefore, these six clinical factors were compared as possible improvement predictors; age (50 years or older and 49 years or younger); gender; type of depression (unipolar and bipolar); frequency of episodes (first and recurrence); history of family psychiatric illness (positive and negative), and daily dose of fluvoxamine (50–75 mg and 100–150 mg).

The Weibull regression model and the chi- square test were used to test the significance of these clinical factors as predictors of improvement resulting from fluvoxamine treatment.

A computer software program, StatView for Macintosh (version 4.11), was used for all analyses in this study. The level of significance was set at $p < 0.05$.

RESULTS

A Weibull regression analysis showed age, the frequency of episodes and daily dose to be independent predictive factors of improvement resulting from fluvoxamine treatment (Table 2).

Table 2. Weibull regression analysis of six clinical factors

	χ^2	df	*p*-value	Odds(ecoef)	95% confidence interval
Age	13.259	1	0.0003	2.109	1.411 to 3.153
Gender	1.771	1	n.s.	—	—
Type	1.191	1	n.s.	—	—
Frequency	9.717	1	0.0018	0.512	0.336 to 0.780
Family history	2.530	1	n.s.	—	—
Daily dose	3.886	1	0.0487	0.648	0.421 to 0.998

Table 2 shows the odds ratio (ecoef) and 95% confidence interval of age, frequency of episode and daily dose. Of these three clinical factors, the most influential factor was age (ecoef = 2.109), followed by daily dose (ecoef = 0.648) and frequency of episodes (ecoef = 0.512).

Of the 72 patients, 29 patients were aged 49 years or younger and the remaining 43 patients were aged 50 years or older. The proportion of patients showing improvement among those aged 49 years or younger (79.3%) was significantly greater than that among patients aged 50 years or older (48.4%) by the chi-square test ($\chi^2 = 6.767$, df = 1, $p = 0.0093$).

Of the 72 patients, 34 patients were experiencing their first episode of depression, while the other 38 patients were having a recurrent episode. The proportion of patients showing improvement among those having a first episode (79.4%) was significantly greater than that among those experiencing a recurrent episode (44.7%) by the chi-square test ($\chi^2 = 9.079$, df = 1, $p = 0.0026$).

Of the 72 patients, 34 patients were given a dose of 50–75 mg of fluvoxamine, while the other 38 patients received a dose of 100–150 mg. The proportion of patients showing improvement among those receiving a 100–150 mg dose (73.7%) was significantly greater than that among those given a 50–75 mg dose of fluvoxamine (47.1%) by the chi-square test ($\chi^2 = 5.353$, df = 1, $p = 0.02$).

DISCUSSION

Since imipramine was developed in 1956, many patients with depression have been cured with antidepressants including tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors and/or SSRIs. However, all antidepressants do not have the same effect on all patients at any time. Therefore, it is important to predict which patients would be most likely to benefit from each antidepressant.

Kornstein *et al.* (2000) reported that women were significantly more likely to show a favourable response to sertraline, whereas men were significantly more likely to show a favourable response to imipramine. McGrath *et al.* (2000) reported that a neurovegetative symptom pattern was a predictor for fluoxetine. Gex-Fabry *et al.* (1999) hypothesized that the delayed response of clomipramine might be concentration dependent. However, the clinical predictors of response to fluvoxamine have been much less studied.

To the best of our knowledge, this is one of the few reports on clinical predictors in the treatment response to fluvoxamine in patients with depression.

The most influential factor was age. There was significantly more improvement in the 49 years or younger group than in the 50 years or older group. Organic changes in the brain may increase in older people. These changes including brain infarction, brain bleeding and brain atrophy influence the symptoms of affect. These organic changes are based on molecular death and are not reversible. Antidepressants do not affect the cell in death. Therefore, depression in senile people with organic change does not show sufficient improvement. However, not brain CT or EEG data were obtained. Further work is needed in the future. The second influential factor was the daily dose of fluvoxamine. The daily dose of 100–150 mg resulted in significantly more improvement than that of 50–75 mg. Many clinical trials (DeWider and Doogan, 1982; Guelfi *et al.*, 1983; Lapierre *et al.*, 1987) testing the efficacy of fluvoxamine in depression have been carried out with a daily dose of 100 mg and over, and those trials showed good results. The results of the present study support those findings. The third influential factor was the frequency of episodes. There was significantly more improvement in the patients experiencing a first episode than in those having a recurrent episode. Therefore, it is recommended that fluvoxamine be the first choice for depression.

These factors should be considered when fluvoxamine is selected for depression. However, some limitations should also be considered. This preliminary report was a retrospective study, and so did not have stricter criteria and methods. The family history of psychiatric illness was assessed retrospectively, hence underestimation is possible. The number of patients with bipolar depression was only eight, which may be not sufficient for analysis. There was no placebo control group. Therefore, a placebo response may be included in the improved patients. Although these limitations should be examined in future prospective study, it seems that age, daily dose and the frequency of episodes are useful predictors for determining the response to fluvoxamine treatment for depression.

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