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Induction of mania in depression by paroxetine

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Introduction An investigation of the proportion of patients who have experienced mania with antidepressant treatment and their characteristics would seem to be of clinical use.
Aims The purpose of this clinical study was to examine the predictors of induction of mania in depression patients as a result of paroxetine treatment.
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 and 2001. Some 79 patients were identified who were receiving paroxetine to treat depression. A variety of clinical factors including gender, the type of depression, frequency of episodes, family history, age and daily dose were examined as possible predictors of induction of mania by paroxetine.
Results Seven (8.86%) of the 79 paroxetine-treated patients developed mania. A Cox proportional hazards analysis showed the type of depression and the history of family psychiatric illness to be independent predictive factors of the induction of mania by paroxetine treatment.
Conclusions The rate of mania induction of paroxetine is not substantially different from that found for conventional antidepressants. The type of depression and the history of family psychiatric illness may be considered as predictors of mania induction in depression patients taking paroxetine treatment.

KEY WORDS — paroxetine; antidepressant; depression; mania; predictor

INTRODUCTION

Antidepressants have been recognized as potential inducers of mania since their introduction in the 1950s. Bunney (1978) reported a 9.5% incidence of mania or hypomania in 3922 treatments with tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors. Presumably, TCAs may provoke the manic episode. There were early reports suggesting that TCAs could induce mania, not only in bipolar patients but also in those with an apparently unipolar presentation (Ball and Kiloh, 1959). Subsequent reports suggested that selective serotonin reuptake inhibitors (SSRIs) appeared capable of producing mania (Howland, 1996; Preda *et al.*, 2001). Peet (1994) also reported that the mania induced by SSRIs occurred substantially more often in bipolar depression than in unipolar depression.

Some reports indicated that paroxetine, an SSRI, was associated with mania and/or hypomania (Christensen, 1995; Landry and Roy, 1997; Oldroyd, 1997; Preda *et al.*, 2001; Ramasubbu, 2001). Paroxetine is an effective SSRI, which has been approved for the treatment of depression in several countries. In Japan, paroxetine was introduced in 2000 as an antidepressant SSRI. However, the proportion of patients being treated with paroxetine who have experienced mania is not known, nor are the characteristics of such patients. Therefore, an investigation of the proportion of patients who have experienced mania with paroxetine treatment and their characteristics would seem to be of clinical use. This clinical study was carried out to examine the proportion of patients who experienced mania when treated with paroxetine for depression and the predictors of this mania.

MATHERIALS AND METHODS

Patients

A retrospective cohort analysis was made of outpatients treated in the Department of Psychiatry,

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Kawasaki Medical School Hospital, Kurashiki, Japan, between December 2000 and November 2001. During this study period, 846 outpatients met the DSM-IV criteria for major depressive disorder or bipolar disorder depression. Patients were treated by five doctors in the same clinical team. The medical records of the patients receiving paroxetine to treat depression were also reviewed. For inclusion in this study, patients diagnosed with depression who were being treated with paroxetine were required to meet all of the following criteria.

Inclusion criteria. All outpatients had already been evaluated by the 21-item Hamilton depression rating scale (HAM-D) (Hamilton, 1960). Before treatment, patients were required to have a total HAM-D score of 22–32 after at least 14 days without psychotropic medication. Paroxetine was administered orally once daily without any augmentation drugs including other antidepressants, lithium, mood stabilizers or tryptophan. The maintenance or treatment daily dose was 10–40 mg (mean 19.2 mg). The induction of mania or hypomania was observed during the continued paroxetine treatment period. The manic or hypomanic episodes had to fulfil DSM-IV criteria and the required duration.

Exclusion criteria. Patients were excluded from the study if they had a history of seizure or myoclonus, comorbid anxiety, obsessive–compulsive disorder, mixed state, rapid cycling bipolar disorder or other psychiatric disorders.

Seventy nine patients were identified who met the above criteria and they were included in the analysis (Table 1).

Table 1. Baseline characteristics of 79 patients

Male/female	41/38
Unipolar/bipolar	69/10
First episode/recurrence	37/42
Positive family history/negative	20/59
Age	20–75 (mean 47.0)
Daily dose (mg)	10–40 (mean 19.2)
Observation period (week)	1–60 (mean 22.8)

Statistical analyses

The following six clinical factors (Table 1) were derived from the 79 patients. These clinical factors were easily derived from the medical records. Therefore, these six clinical factors were compared as possible predictors for induction of mania: gender; the type of depression (unipolar and bipolar); frequency of episodes (first and recurrence); history of family psychiatric illness (positive and negative); age (50 years or older and 49 years or younger); daily dose when patient developed mania or hypomania (20 mg or under and 21 mg or higher).

These clinical factors were subsequently used in a multivariate analysis employing a Cox proportional hazards model to test their significance as predictors of mania induction resulting from paroxetine treatment.

A computer software program, StatView for Macintosh (version 5.0), was used for all analyses in this study. The level of significance was set at $p < 0.05$.

RESULTS

Seven (8.86%) of the 79 patients receiving paroxetine developed mania or hypomania. One of the seven was mania, and the others were hypomania. Their characteristics are given in Table 2.

The rates of mania induction for each clinical factor are shown in Table 3. A Cox proportional hazards analysis showed the type of depression ($p = 0.0107$) and the history of family psychiatric illness ($p = 0.0497$) to be independent predictive factors for induction of mania due to paroxetine treatment. The induction rate in bipolar depression patients was higher than that in those with unipolar depression. A positive history of

Table 2. Paroxetine-induced mania ($n = 7$ of 79)

Pre-diagnosis	Gender	Onset age	Frequency	Dose (mg)	Duration (week)	Family history	Type of mania
Unipolar	F	33	First	20	9	Positive	Hypomania
Unipolar	F	54	Recurrence	40	30	Positive	Mania
Unipolar	M	35	Recurrence	20	4	Negative	Hypomania
Bipolar	M	44	Recurrence	20	24	Negative	Hypomania
Bipolar	M	72	Recurrence	20	4	Positive	Hypomania
Bipolar	F	47	Recurrence	20	4	Negative	Hypomania
Bipolar	F	66	Recurrence	20	5	Negative	Hypomania

Table 3. Cox proportional hazards analysis of six clinical factors

	Rate (%) of mania induction	χ^2	p value	Odds ratio
Gender	7.32 : 10.53 (male : female)	1.000	0.3172	0.384
Type	4.35 : 40.0 (unipolar : bipolar)	6.519	0.0107[a]	0.049
Frequency	2.70 : 14.29 (first : recurrence)	0.862	0.3531	0.269
Family history	15.0 : 6.80 (positive : negative)	3.851	0.0497[a]	11.020
Age (years)	8.70 : 9.09 ($50< : \leq 50$)	0.467	0.4943	0.522
Dose (mg/day)	8.22 : 16.67 ($20\leq : < 20$)	0.067	0.7957	1.545

[a]Significant difference was $p < 0.05$.

family psychiatric illness resulted in a higher rate of induction of mania than a negative history of family psychiatric illness. The remaining clinical factors, gender, frequency of episodes, age and dose, were not significantly different (Table 3).

DISCUSSION

The rate of mania induction (8.86%) was not substantially different to that found in previous studies (9.0%–9.5%) (Preda *et al.*, 2001; Bunney, 1978). Six patients who experienced mania appeared to be hypomanic. Their psychiatric symptoms were slight. Therefore, there may not be a high incidence of a switch to mania.

The predictors of paroxetine-induced mania have been much less studied. To the best of our knowledge, this is the first report on predictors in mania induced by treatment with paroxetine in depression patients.

A multivariate analysis showed that the type of depression and the history of family psychiatric illness were important in predicting the induction of mania.

The difference in the response between unipolar depression patients and bipolar depression patients supposes that the underlying abnormality in unipolar depression is not the same as that in bipolar depression (Goodwin *et al.*, 1972; Morishita and Aoki, 2002; Silverstone, 1984). It has been reported that a positive history of family psychiatric illness was associated with a poor prognosis (Duggan *et al.*, 1998; Ohaeri and Otote, 2002). The result in this study supposed that a positive history of family psychiatric illness would be a risk factor for poor prognosis in paroxetine treatment. The remaining clinical factors, gender, frequency of episodes, age and daily dose, were not important for the induction of mania with paroxetine.

In this study, the incidence and predictors of induction of mania by paroxetine were shown. This clinical study was retrospective, and so did not have a placebo control group or a comparison group. According to a review of medical records, any psychotherapy to patients would be apparent. The treatment dose was increased if the patients had a low response to the start dose within 2 weeks. However, some limitations still remain. Two of the seven had been treated for a very long time (24 and 30 weeks) before the manic symptoms appeared. However, there is not sufficient evidence that the paroxetine treatment affected the developing mania. Therefore, the result strictness was evaluated and long time treatment cases were included. The results may reflect differences in the speed of dose escalation. Tolerability may influence the results. It is always difficult to attribute causality when there is no control or comparison group. Although these limitations should be investigated using stricter methods in future studies, these results would seem to present useful information in regard to the use of paroxetine for depression.

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