Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study
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Current guidelines for the treatment of bipolar type II (BP II) major depressive episode (MDE) recommend using either mood stabilizer monotherapy or the combination of a mood stabilizer with a selective serotonin reuptake inhibitor (SSRI). These guidelines are the result of concern over SSRI-induced manic switch episodes. We previously showed that fluoxetine monotherapy may be effective as an initial treatment for BP II and BP NOS MDE with a low manic switch rate. We now present the results of a double-blind, placebo-substitution continuation study of fluoxetine monotherapy in BP II and BP NOS patients who have recovered from their MDE. This was a two-phase study. In study phase I, patients received open-label fluoxetine monotherapy 20 mg daily for up to 8 weeks. Responders with a final 17-item Hamilton Rating Scale for Depression (HAM-D) score $\leq 9$ were enrolled into study phase II which consisted of double-blind, placebo-substitution continuation therapy with fluoxetine 20 mg daily for up to 6 months. Outcome measures included the 17-item HAM-D and Young Mania Rating (YMR) scales. Changes in YMR scores were assessed using generalized estimating equation analysis. Relapse was assessed using Kaplan–Meier survival analysis and Fisher’s exact test. In study phase II, 43% of fluoxetine-treated patients and 100% of placebo-treated patients relapsed during continuation therapy ($P=0.08$). The mean increase in YMR score in study phase II was slightly higher in the fluoxetine-treated patients (3.0 $\pm$ 1.8) versus placebo-treated patients (0.2 $\pm$ 0.4) ($P=0.01$). However, this difference was not clinically meaningful. No hypomanic switch episodes were observed during study phase II. Despite the limited sample size resulting in insufficient power to detect statistical significance in relapse rates or change in YMR scores between treatment conditions, these preliminary data appear to support previous observations demonstrating that initial and continuation fluoxetine monotherapy may be safe and effective for some patients with BP II or BP NOS MDE with a low manic switch rate. Larger-scale studies are needed to confirm these findings. Int Clin Psychopharmacol 20:257–264 @ 2005 Lippincott Williams & Wilkins.

Introduction

Bipolar type II (BP II) disorder is the most common phenotype of BP disorder (Simpson et al., 1993; Benazzi et al., 1997; Akiskal and Pinto, 1999; Benazzi, 1999; Akiskal, 2003; Berk and Dodd, 2005). Its clinical course is characterized by a preponderance of depressive episodes with a lifetime history of one or more hypomanic episodes lasting at least 4 days (Dunner et al., 1976; Akiskal, 1996). BP II disorder is diagnostically stable over time (Akiskal, 1996, 2003) and rarely evolves into BP type I (manic-depressive) disorder (Ayuso-Gutierrez and Ramos-Brieva, 1982; Faedda et al., 1993; Coryell et al., 1995). BP II disorder is often difficult to recognize, and frequently goes undiagnosed (Benazzi, 1997, 1999; Cassano et al., 1999; Akiskal, 2003; Goldberg, 2003; Berk and Dodd, 2005). BP II patients often do not recognize the presence of their hypomanic symptoms or, if recognized, they rarely consider them to be in need of treatment (Cassano et al., 1999) and, as a result, BP II disorder is generally diagnosed when the patient seeks treatment for a major depressive episode (MDE) (Benazzi, 1997; Cassano et al., 1999; Ghaemi et al., 2001). The incidence of BP II MDE may vary widely depending upon the ascertainment method used (Benazzi, 1997; Goodwin and Ghaemi, 1998; Ghaemi et al., 1999; Ghaemi et al., 2000). Surveys of clinical populations have found the rates of BP II disorder to be as high as 45% of patients who were previously diagnosed with unipolar MDE (Benazzi, 1997; Goodwin and Ghaemi, 1998). This is largely the result of a failure to recognize previous hypomanic episodes that can frequently be of short duration and characterized by an enhanced sense of well-being, or by symptoms of irritability and agitation. These brief hypomanic episodes stand in stark contrast to the more frequent and prolonged BP II MDEs.

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Although some investigators have suggested that BP I and BP II disorders may be distinct clinical and biochemical entities (Goodwin and Jamison, 1990), the majority of treatment studies have grouped BP I and BP II disorders together. This has resulted in a paucity of information about the most appropriate initial and continuation treatment for BP II MDE (Berk and Dodd, 2005).

There is debate as to whether antidepressant therapy is even effective for BP MDE (Montgomery et al., 2000; Geddes and Goodwin, 2001; Ghaemi et al., 2004). Several controlled trials of antidepressant add-on therapy in BP I and BP II MDE patients taking established mood stabilizer therapy have failed to demonstrate clear-cut antidepressant efficacy (Young et al., 2000; Nemeroff et al., 2000), although this contention has not been a universal finding (Kupfer et al., 2001).

Current treatment recommendations for the use of antidepressants in BP II MDE are largely based upon the treatment approach to BP I MDE, which discourages the use of antidepressants due to concern over the risk of drug-induced manic switch episodes (Wehr and Goodwin, 1979; Wehr and Goodwin, 1987; Prien et al., 1994; Boerlin et al., 1998; Ghaemi et al., 1999). Current guidelines for the treatment of BP II MDE suggest initiating mood stabilizer monotherapy for patients with mild depressive symptoms, and using a mood stabilizer in combination with a selective serotonin reuptake inhibitor (SSRI) for more severe depressive symptoms (American Psychiatric Association, 1994; Treatment of Bipolar Disorder Expert Consensus Panel, 1996; Yatham et al., 1997; Sachs et al., 2000; American Psychiatric Association, 2002). It is further recommended that SSRI therapy be limited to a low dose for the briefest possible time. Tricyclic antidepressants are to be avoided altogether in BP MDE (American Psychiatric Association, 1994; Treatment of Bipolar Disorder Expert Consensus Panel, 1996; Yatham et al., 1997; Sachs et al., 2000; American Psychiatric Association, 2002). A BP disorder's expert panel has suggested initiating treatment for BP MDE with a mood stabilizer alone and to avoid antidepressant monotherapy altogether (Yatham et al., 1997). More recently, Sachs et al. (2000) published treatment guidelines recommending starting mood stabilizer therapy alone for BP MDE of mild to moderate severity, and combining a mood stabilizer and an antidepressant for patients with severe BP MDE. None of these treatment algorithms recommend the use of antidepressant monotherapy for BP MDE, and none of the guidelines appear to make the distinction between therapy for BP I and BP II MDE.

The use of SSRI monotherapy for the treatment of BP II MDE is an area of current controversy (Ghaemi et al., 2000; Amsterdam and Brunswick, 2003; Post et al., 2003). Nevertheless, many patients with undiagnosed BP II MDE do receive antidepressant monotherapy (Benazzi, 1997, 1999; Cassano et al., 1999; Berk and Dodd, 2005), and some studies have suggested that the rate of drug-induced mania in BP II MDE may be considerably lower than previously thought (Amsterdam and Brunswick, 2003). Although cases of SSRI-induced mania have been reported (Feder, 1990; Stoll et al., 1994; Heimann and March, 1996), controlled clinical trials of SSRI monotherapy in BP II MDE patients have reported good efficacy and a relatively low manic switch rate (Benfield et al., 1986; Cohn et al., 1989; Simpson and DePaulo, 1991; Maj, 1997; Amsterdam et al., 2004). Unfortunately, many of these studies have included patients with BP I disorder as well, and many of the patients were also taking a mood stabilizer.

In the present study, we present data from a prospective, double-blind, placebo-substitution study of the safety and efficacy of initial and continuation fluoxetine monotherapy 20 mg daily in BP II MDE and BP NOS MDE patients.

**Methods**

**Study design**

All subjects were provided with a detailed description of the purpose and procedures of the study in accordance with the ethical standards set forth by the Institutional Review Board of the University. All subjects provided their written informed consent before enrolling in the trial.

This was a two-phase trial. Phase I of the study consisted of all patients receiving open-label fluoxetine monotherapy 20 mg daily for 8 weeks. During this study phase, the fluoxetine dose could be reduced to 10 mg daily for adverse events during weeks 1-4 of treatment. However, the dose of fluoxetine had to be maintained at 20 mg daily during the final 4 weeks of study phase I. Efficacy and safety measures were obtained after weeks 1, 2, 4, 6 and 8 of treatment. Remission was defined as a final 17-item Hamilton Depression Rating (HAM-D) (Hamilton, 1960) score ≤ 9, or a final 17-item ‘atypical symptom’ HAM-D score ≤ 9 (Reimherr et al., 1998) after week 8 of treatment. Patients with a final HAM-D score ≤ 99 were eligible to be enrolled into study phase II, which consisted of randomized, double-blind, placebo-substitution, continuation treatment with fluoxetine monotherapy for 6 months. Patients randomized to fluoxetine monotherapy condition continued their dose at 20 mg daily. Patients randomized to the placebo condition were provided with identically appearing medication capsules.

During study phase II, efficacy and safety measures were obtained after weeks 2, 4, 8, 12, 16, 20 and 26 of double-blind therapy. However, the actual measurement times varied slightly between subjects and, accordingly, the
actual day of measurement after the study phase II baseline visit was used for statistical analysis. Relapse was defined as an increase in the week 8 (phase II baseline) 17-item HAM-D score ≤ 14 plus DSM-IV criteria of MDE. Concomitant use of lorazepam 0.5–1.0 mg or chloral hydrate 250–1500 mg at bedtime was permitted for severe insomnia during study phase I (but was rarely used). All efficacy and safety measures were performed by study doctors who had undergone inter-rater reliability training with the 17-item HAM-D and Young Mania Rating (YMR) (Young et al., 1978) scales.

**Patient selection**

Outpatients aged ≥ 18 years, with a DSM-IV Axis I diagnosis of BP II or BP NOS disorder and a current diagnosis of MDE were eligible for the trial. All patients had a baseline 17-item HAM-D score ≥ 18. Patients were excluded from the study if they had a history of mania, psychosis, rapid cycling affective disorder with ≥ 4 affective episodes in the preceding year, current alcohol or substance abuse, alcohol or substance dependence within the preceding 3 months, non-response to fluoxetine therapy in the current MDE, or a previous sensitivity to fluoxetine. Pregnant or nursing women were excluded, as were patients with an unstable medical condition, or a serum thyrotropin level ≥ 5 μU. Other exclusion criteria were the presence of any clinically significant cardiac disease, malignancy, presence of central nervous system disorder (e.g. Parkinson’s disease, dementia), presence of significant hepatic or renal disease, use of chemotherapy, use of over-the-counter preparations (e.g. St. John’s Wort), use of tranquilizers, barbiturates or other sedative and hypnotic medications.

**Evaluation and outcome procedures**

A complete psychiatric and medical history was obtained using the Structured Diagnostic Interview for DSM-IV (SCID) format (First et al., 1994). All patients had a physical examination including blood pressure, pulse and weight, along with a complete blood count, blood chemistry profile, a serum pregnancy test in pre- and peri-menopausal women, urinalysis, urine drug screen and a 12-lead electrocardiogram. A listing of previous psychotropic drug treatment preceding study enrollment, and a list of concomitant medication was obtained.

Outcome measures included the 28-item HAM-D rating (Williams, 1988) with the embedded 17-item HAM-D rating (Reimherr et al., 1998) and the YMR scale. The HAM-D and YMR ratings were scored by the study rater without attribution as to the origin of the particular symptom. For example, the symptom of insomnia or agitation that were scored on the HAM-D rating were also scored on the YMR as hypomanic ratings at the same study visit, even though the patient may not have demonstrated hypomania at the time. This rating method resulted in YMR scores that were above zero at many visits.

Patients receiving ineffective antidepressant therapy before enrolling in the trial had their medication discontinued for at least 7 days [14 days for a monoamine oxidase (MAO) inhibitor] before starting fluoxetine monotherapy. None of the patients were taking a mood stabilizer or an atypical neuroleptic agent immediately preceding enrollment in the study. The purpose of this lead-in period of up to 14 days was to avoid a drug interaction from previous psychotropic medication (e.g. MAO inhibitors).

**Treatment procedures**

Phase 1 of the study has been described elsewhere (Amsterdam et al., 2004). Patients who responded during study phase I were randomly assigned to continuation therapy with either fluoxetine 20 mg daily or placebo for up to 6 months. Double-blind study conditions were maintained until the end of the trial.

**Statistical analysis**

Descriptive statistics for the assessment of demographic and clinical variables included frequencies, means, medians, SDs and ranges (Table 1). Time to relapse during double-blind treatment was compared between treatment conditions using Kaplan-Meier analysis (Fig. 1) and the log-rank test for equality of survival distributions. The proportion of patients who relapsed when taking fluoxetine monotherapy versus placebo was compared using Fisher's exact test. Change in YMR scores over time were assessed using generalized estimating equation (GEE) analysis that included the
treatment condition (fluoxetine versus placebo), time (measured in days after phase II baseline), and a group-time interaction variable in the regression model. The GEE analysis is equivalent to a regression analysis, but allows for more than one observation per subject and adjusts for any intra-subject correlation of measurements. A group-time interaction term that deviates significantly from zero would indicate that the change in YMR scores over time differs significantly for patients taking fluoxetine versus placebo. Because subjects were treated after relapse, for a fair comparison of placebo versus fluoxetine, the GEE analysis was limited to YMR observations made up to the time of relapse. For subjects who did not relapse during double-blind therapy, all YMR scores were included in the GEE analysis. In addition, Students t-test was used to compare the mean change from each patient's study phase II baseline YMR score to their largest phase II YMR score between treatment groups. The mean changes for each group, with 95% confidence intervals, were also computed. Table 2 shows the mean YMR score (and number of patients) during study phase II together with YMR scores exceeding zero. Table 2 includes all positive YMR scores measured in phase II, including scores after relapse. Statistical analyses were conducted using STATA 8.0, with a two-sided $P < 0.05$ considered statistically significant.

Results

Study enrollment

A total of 43 patients were enrolled into phase I of the trial. Of these, six patients (14%) were screen failures who did not receive study medication because they either withdrew their consent to participate in the study ($n = 5$) or were non-compliant ($n = 1$) with the study protocol. Thirty-seven patients received fluoxetine monotherapy: 34 had BP II MDE and three had BP NOS MDE. Of the 37 patients, 14 (37.8%) discontinued treatment before the completing study phase I: two (5.4%) for adverse events, three (8.1%) for lack of efficacy, two (5.4%) for non-compliance and seven (18.9%) who withdrew their consent. Fourteen patients responded during study phase I with a final 17-item HAM-D score $\leq 9$. Of these, two patients withdrew their consent to participate in the double-blind study phase, and 12 patients were randomized to continuation treatment with either fluoxetine monotherapy 20 mg daily ($n = 8$) or placebo ($n = 4$).

Patient characteristics

The clinical and demographic characteristics of the patients' samples in study phase I and study phase II are shown in Table 1.

Study phase I

Results of study phase 1 have been described previously (Amsterdam et al., 2004) and are briefly summarized here. Of the 37 patients in study phase I, 14 (37.8%) responded to initial fluoxetine monotherapy with a final week 8 17-item HAM-D score $\leq 9$. There was an overall reduction of the mean baseline 17-item HAM-D score from $21.7\pm 3.9$ to $14.8\pm 8.3$ by study week 8, using last observation carried forward analysis ($P < 0.001$, Wilcoxon paired sample test). A similar finding was also observed using the GEE analysis ($P < 0.001$). Three patients (8.1%) had an elevated YMR score on at least two consecutive study visits. Using a moderately conservative total YMR cut-off score of $\geq 12$ for the presence of hypomanic symptoms, five (13.5%) of the patients had a YMR score $\geq 12$ at any point during treatment. None

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<th>Visit</th>
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*Patient number at each study visit reflects the available sample size with a Young Mania Rating (YMR) score $>0$. 

Kaplan-Meier survival curves during continuation fluoxetine monotherapy or placebo.
of the patients discontinued fluoxetine therapy due to hypomanic symptoms.

**Study phase II**

**Efficacy**

Twelve patients participated in the randomized, double-blind, continuation phase with either fluoxetine monotherapy (n = 8) or placebo (n = 4). Relapse of MDE during double-blind therapy was observed in 43% of fluoxetine-treated patients and in 100% of placebo-treated patients (P = 0.08, Fisher's exact). Although this difference did not achieve statistical significance, it appears to indicate a trend towards treatment differences between conditions. Figure 1 indicates that the median time to relapse was slightly shorter in the fluoxetine-treated patients compared to that observed in the placebo-treated group, although the difference was not statistically significant (P = 0.19).

**Safety**

Table 2 displays the mean ± SD YMR scores at phase II baseline visit (week 8) and at subsequent phase II study visits.

The mean change in YMR score (highest YMR score versus baseline YMR score) during study phase II was 3.0 ± 1.8 [95% confidence interval (CI) = 1.3–4.7] for the fluoxetine condition versus 0.2 ± 0.45 (95% CI = –0.4–0.8) for the placebo condition (P = 0.01, t-test). Despite the modestly higher YMR scores in the fluoxetine-treated patients (versus the placebo group), this small difference was not clinically meaningful. Moreover, when all YMR scores were examined over time using the GEE analysis, no difference in the rate of increase in individual YMR scores was observed between treatment conditions. Similarly, when patients were examined for YMR scores ≥ 8 (a very conservative estimate of hypomanic syndrome), no patient in either treatment condition had a YRM score ≥ 8. Thus, no patient in study phase II had a YMR score that was considered to be clinically meaningful. None of the patients in study phase II met DSM-IV diagnostic criteria for hypomanic episode. Finally, there were no treatment-related serious adverse events in study phase II.

**Discussion**

A recent expert clinician panel on the treatment of BP MDE concluded that the efficacy of SSRI monotherapy, or combined SSRI and mood stabilizer therapy, has not been established (Prien and Rush, 1996). Most expert consensus panels recommend the cautious use of SSRIs for the treatment of BP MDE, and that SSRIs be prescribed only in combination with a mood stabilizer for more severely ill patients (American Psychiatric Association, 1994; Treatment of Bipolar Disorder Expert Consensus Panel, 1996; Yatham et al., 1997; Sachs et al., 2000; American Psychiatric Association, 2002). This recommendation is based upon concerns arising from TCA-induced manic switch episodes (Wehr and Goodwin, 1979; Wehr and Goodwin, 1987; Prien and Rush, 1996; Montgomery et al., 2000; Goldberg and Truman, 2003; Ghaemi et al., 2004). In this context, a recent retrospective comparison of antidepressant treatment in 41 BP MDE patients found a substantially higher manic switch rate in the BP patients taking antidepressant monotherapy (84%) compared to BP patients taking an established mood stabilizer (32%) (Ghaemi et al., 2004). Similarly, a recent review on the subject of antidepressant-induced mania found a 20–40% drug-induced manic and hypomanic switch rate in published BP MDE studies (Goldberg and Truman, 2003). In these studies, manic switch episodes occurred with a similar frequency in the presence, or absence, of mood stabilizer therapy, especially in BP patients with previous drug-induced mania and in BP patients taking multiple antidepressants (Goldberg and Truman, 2003).

Despite these cautionary recommendations, SSRI monotherapy has been used in patients with BP MDE for more than 25 years (Saletu et al., 1997). Results from more recent, controlled prospective trials have confirmed these early findings and have found that SSRIs may be safe and effective for the short term a treatment of BP MDE (Benfield et al., 1986; Cohn et al., 1989; Simpson and DePaulo, 1991; Maj, 1997; Amsterdam, 1998; Grunze et al., 2000; Kupfer et al., 2001; Amsterdam and Brunswick, 2003). For example, a multi-site study of citalopram as an add-on therapy for BP MDE patients who were resistant to initial 4-week mood stabilizer monotherapy found that 64% of citalopram-treated patients responded, with a only a 6.7% manic switch rate (Kupfer et al., 2001). By contrast, a double blind, placebo-controlled add-on study of paroxetine versus imipramine in patients with BP I MDE taking established lithium or valproic acid therapy did not demonstrate superior antidepressant efficacy compared to placebo, although this study was not adequately powered to detect a drug versus placebo difference (Nemeroff et al., 2001). Similarly, Post et al. (2003) found a relatively poor antidepressant efficacy in all BP MDE patient groups studied.

Although combination SSRI and mood stabilizer therapy may represent an advance in the treatment of BP II MDE over mood-stabilizer therapy alone (Kupfer et al., 2001), mood stabilizer therapy may also expose patients to additional side-effects (Young et al., 2000) and the need to monitor plasma drug levels, hepatic enzyme levels and thyroid hormone levels. A recent retrospective study of more than 2000 patients found that SSRIs were equally effective in unipolar and BP MDE (Grunze et al., 2001). Similarly, we observed good short-term efficacy of fluoxetine monotherapy 20 mg daily in 89 unipolar versus
89 BP II and NOS MDE patients, with the BP patients showing a hypomanic switch rate of only 3.8% (Amsterdam et al., 1998).

There are fewer data available on the efficacy and safety of SSRI monotherapy of BP II disorder during continuation treatment. In a two-phase, multi-site, placebo-substitution study (Amsterdam et al., 1998), we examined the efficacy and safety of continuation fluoxetine monotherapy 20 mg daily after 6 months in 28 recovered BP II MDE and BP NOS MDE patients (compared with 27 recovered unipolar MDE patients). We observed a slightly lower relapse rate in the BP (22%) versus the unipolar (33%) patients (chi squared = 0.5; d.f. = 1; P = not significant, Kaplan-Meier survival) during continuation fluoxetine monotherapy.

Although, in the present study, we were unable to demonstrate a statistically significant difference in relapse rates during continuation fluoxetine monotherapy (43%) versus placebo therapy (100%) (P = 0.08, Fisher's exact test), there was a trend towards greater relapse in the placebo-treated patients. Moreover, the relapse rate for the continuation fluoxetine monotherapy group in the present study was similar to the relapse rate observed in recovered unipolar patients during continuation fluoxetine monotherapy in an earlier long-term fluoxetine study (Reimherr et al., 1998).

Our original estimate for treatment response in phase I of the present study was 60% (after a 20% drop out for screen failures or side-effects). This would have resulted in 10 patients per treatment condition during phase II double-blind therapy and would have resulted in greater statistical power to detect potential differences in group survival. However, only 14 patients (38%) met the HAMD criteria of ≤ 9 for response in study phase I, which resulted in smaller than expected cohort samples in study phase II. Despite this shortcoming, our findings do suggest a substantial trend towards fluoxetine superiority over placebo during continuation therapy. The strict application of a P < 0.05 cut-off value for statistical significance has sometimes been criticized as being arbitrary and overly dependant on sample size. We would suggest that that the results of the present study, although not statistically significant at the P < 0.05 level, should also be interpreted in terms of the actual group differences that were observed in relapse rates during continuation therapy. We are presently conducting a larger, follow-up study to verify what is suggested by these preliminary results.

There is a paucity of data on the rate of manic switch episodes during long-term SSRI monotherapy of BP II disorder. In a previous double-blind, placebo-substitution study (Amsterdam et al., 1998), we observed a hypomanic switch rate of 3.6% in 28 BP II patients and a hypomanic switch rate of 0.8% in 241 unipolar MDE patients taking fluoxetine monotherapy for 6 months. The results from the present study also suggested the presence of a low hypomanic switch rate in recovered BP II MDE patients during continuation fluoxetine monotherapy. Although we observed a slightly higher mean YMR score of 3.0 ± 1.8 in the fluoxetine condition versus 0.2 ± 0.5 in the placebo condition (P = 0.01), this difference was not clinically meaningful because YMR scores ≥ 16 are generally considered to define mild manic symptoms. Moreover, a longitudinal GEE analysis found no significant difference in the rate of change in YMR scores between treatment conditions during continuation therapy. Using a conservative total YMR cut-off score of ≥ 8 to identify patients with mild symptoms of hypomania, we observed no patient in either treatment group with a YMR score ≥ 8 during continuation therapy. Furthermore, we observed no DSM IV hypomanic episodes during continuation therapy.

Several caveats should be considered in the interpretation of the present data. The cohort sizes in study phase II were limited, resulting in insufficient power to detect statistical significance in relapse rates or to detect a significant difference in the rate of change in YMR scores between treatment conditions during continuation therapy. This occurred despite the fact that 100% of placebo-treated patients versus 43% of fluoxetine-treated patients relapsed. This lack of power resulted from an unanticipated low response rate to initial fluoxetine treatment in study phase I. It is possible that the response rate to initial fluoxetine therapy would have been higher if the treatment duration had been longer (Quitkin et al., 2003), or if the dose of fluoxetine had been higher. However, a recent analysis by our group of 71 BP II MDE patients taking fluoxetine monotherapy up to 80 mg daily for 10 weeks found a remission rate of only 38% (Shults and Amsterdam, 2004).

Three patients in the present study had BP NOS MDE. These patients had a history of definite mood swings characterized by at least one episode of elevated mood with additional manic symptoms; however, these patients could not endorse an episode duration lasting at least 4 days. In this regard, the gradation between BP syndromes is often difficult to establish (Simpson et al., 1991; Benazzi, 1997; Cassano et al., 1999; Ghaemi et al., 2001; Akiskal, 2003). It is possible that patients with BP NOS disorder may be clinically distinct from patients with BP II disorder and that they may be less likely to experience fluoxetine-induced manic symptoms.

We did not employ a patient-recorded daily chrono-record to identify sub-syndromal manic episodes. As a result, it is possible that we missed the presence of ultra-short or
mild hypomanic episodes that occurred between study visits. As a result, the rate of hypomanic symptoms may have been higher than those detected. Furthermore, a higher fluoxetine dose may have resulted in a higher frequency of manic switch episodes.

Finally, we did not measure plasma levels of fluoxetine and norfluoxetine, which may have provided additional information on the low response rate in study phase I and the difference in relapse rates in study phase II. However, a previous study in 839 unipolar and BP II MDE patients treated with fluoxetine monotherapy 20 mg daily for up to 9 months found no relationship between plasma levels and initial response efficacy (Amsterdam et al., 1997) or between plasma levels and relapse rates during continuation therapy (Brunswick et al., 2002). Similarly, in a previous study, Brunswick et al. (2001) also observed the presence of substantial residual fluoxetine and norfluoxetine plasma levels in some patients many weeks after they were randomized to double-blind placebo therapy. This factor suggests that, in the present trial, the fairly rapid relapse of patients in both treatment conditions was not simply the result of the absence of circulating plasma concentrations of fluoxetine.

In summary, we examined the safety and efficacy of fluoxetine monotherapy 20 mg daily for BP II MDE and BP NOS MDE. As reported previously (Amsterdam et al., 2004), we observed a 38% remission rate with a HAM-D score ≤ 9, and 8.1% hypomania switch rate, during study phase I. During continuation therapy, 43% of fluoxetine-treated patients and 100% of placebo-treated patients relapsed (P < 0.08). There were slightly more hypomanic symptoms reported in the fluoxetine-treated patients compared to the placebo group (P < 0.01), although this difference was not clinically meaningful. Despite the limited sample size of the continuation study phase resulting in insufficient power to detect statistical significance in relapse rates or change in YMR scores between treatment conditions, these preliminary data appear to support previous observations that initial and continuation fluoxetine monotherapy may be safe and effective for some patients with BP II or BP NOS MDE with a low manic switch rate. Larger-scale studies are needed to confirm these findings.

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