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Efficacy and Mood Conversion Rate of Short-Term Fluoxetine Monotherapy of Bipolar II Major Depressive Episode

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Abstract

Objective—As part of a long-term, relapse-prevention study of anti-depressant versus mood stabilizer monotherapy of bipolar II major depressive episode, we prospectively examined the efficacy and mood conversion rate of initial fluoxetine monotherapy. We hypothesized that there would be a statistically significant reduction in depressive symptoms without a clinically meaningful increase in mood conversion symptoms.

Methods—Patients received open-label fluoxetine monotherapy 10 to 80 mg daily for up to 14 weeks. Primary outcome was change over time in Hamilton Depression Rating score, with secondary outcomes including the proportion of treatment responders and remitters, change over time in Young Mania Rating Scale (YMRS) score, and frequency of mood conversion episodes.

Results—One hundred forty-eight patients had at least 1 post-baseline measurement. Mean Hamilton Depression Rating score decreased by 9.0 points ($P < 0.0005$). There were 88 responder patients (59.5%; 95% confidence interval [CI], 51.1%–67.4%) ($P < 0.0005$) and 86 remitter patients (58.1%; 95% CI, 49.7%–66.2%) ($P < 0.0005$). Mean time to remission was 64.4 days (95% CI, 59.1–69.7 days). Six patients (4.1%; 95% CI, 1.5%–8.6%) ($P < 0.0005$) had hypomania, and 29 patients (19.6%; 95% CI, 13.5%–26.9%) ($P < 0.0005$) had subsyndromal hypomania, which did not result in treatment discontinuation. Six patients (4.1%; 95% CI, 1.5%–8.6%) had a YMRS score of 8 or greater ($P < 0.0005$), and 4 patients (2.7%; 95% CI, 0.7%–6.8%) ($P < 0.0005$) had a YMRS score of 12 or greater at any study visit.

Conclusions—Although design limitations constrain the interpretation of the current findings, fluoxetine monotherapy may be an effective short-term treatment of bipolar II major depressive episode with a relatively low rate of syndromal hypomanic episodes.

Keywords

bipolar; depression; antidepressant

The treatment of bipolar II major depressive episode remains a challenge for clinicians.¹ Although practice guidelines have been developed for treating bipolar II depression, these algorithms have generally been empirical and derived from studies of bipolar I patients or studies of mixed-diagnosis bipolar populations.^{2–8} Although several practice guidelines

disagree on how best to initiate treatment of bipolar depression,² none specifically addresses recommendations on treating bipolar type II depression, and only one recommends the use of antidepressant monotherapy as initial treatment of bipolar II depression.⁹ For example, one practice guideline recommends initial mood stabilizer monotherapy and avoiding serotonin reuptake inhibitor (SRI) therapy,⁵ whereas another guideline recommends initial mood stabilizer monotherapy in conjunction with a brief course of SRI therapy.⁷ Another guideline recommends starting mood stabilizer monotherapy for mild to moderate bipolar depression and reserving combined mood stabilizer plus SRI therapy for more severe bipolar depression.⁸ These recommendations are based on concerns over antidepressant-induced mood conversion episodes.¹⁰ Although the benefit of short-term antidepressant therapy in bipolar II depression is supported by some reports,^{11–18} other reports have either not confirmed this benefit or reported an increase in mood conversions.^{19–23} Several naturalistic studies have reported higher mood conversion rates during antidepressant monotherapy when compared with combination antidepressant plus mood stabilizer therapy,^{19,20} whereas a recent literature review found that antidepressant-induced mood conversions occurred with all antidepressant drug classes at a rate of 20% to 40%²¹ and that concurrent mood stabilizer therapy offered only limited protection against mood conversion episodes.²¹

Despite the general view that antidepressants may increase the rate of mood conversion episodes in bipolar disorder, clinicians continued to prescribe antidepressants for bipolar II depression. Results from the National Disease and Therapeutic Index study indicate that antidepressant medications are more widely prescribed than mood stabilizers for bipolar II depression.²⁴

We present efficacy and mood conversion rates during initial fluoxetine monotherapy of bipolar II major depressive episode. We hypothesized that there would be a statistically significant and clinically meaningful reduction in depressive symptoms over time without an appreciable increase in mood conversion episodes during fluoxetine monotherapy.

METHODS

Subjects

Outpatients 18 years or older with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I diagnosis of bipolar II disorder and current major depressive episode with a 17-item Hamilton Depression Rating (HAM-D)²⁵ score of 16 or greater were enrolled. Patients with a comorbid Axis I diagnosis other than depression were not excluded if the comorbid condition did not constitute the primary disorder. Exclusion criteria were a history of mania or psychosis, substance abuse or dependence within the preceding 3 months, nonresponse to fluoxetine within the current depressive episode, or sensitivity to fluoxetine. Other exclusion criteria were the presence of an unstable medical condition, being pregnant or nursing, serum thyrotropin level > 5 μ IU per ml, presence of hepatic or renal insufficiency, dementia, malignancy, or concurrent use of psychotropic drugs or chemotherapy.

Procedures

Patients provided written informed consent in accordance with the ethical standards of the institutional review board of the University of Pennsylvania. The study was conducted using the Good Clinical Practice guidelines with oversight by the local Office of Human Research and an independent Data & Safety Monitoring Board. A psychiatric history was obtained using the *Structured Diagnostic Interview for DSM-IV* format.²⁶ A medical history, physical examination, and laboratory evaluation (including complete blood count; electrolyte, hepatic, renal, and thyroid panels; pregnancy test in women; urinalysis; illicit drug screen; and

electrocardiogram) were performed. Estimates of the number of prior depressive and hypomanic episodes were obtained as defined by *DSM-IV* criteria.

Patients receiving ineffective or partially effective antidepressant therapy before enrolling in the trial had their medication discontinued for 7 days or more (14 days for monoamine oxidase inhibitor therapy) before starting fluoxetine mono-therapy. The purpose of this lead-in period was to avoid potential interaction between fluoxetine and prior psychotropic medication.

Structured ratings of the 28-item HAM-D and Young Mania Rating Scale (YMRS)²⁷ were obtained by a study doctor or nurse. Symptom ratings were obtained with attribution as to the origin of the symptom. For example, insomnia could be recorded on the HAM-D scale as a depressive symptom or recorded on the YMRS as a hypomanic symptom. It could be simultaneously recorded on both rating instruments as a mixed episode symptom if the evaluator attributed the insomnia to both depression and hypomania. This rating method sometimes resulted in baseline YMRS scores that were greater than zero. This procedure has previously been used in bipolar depression trials as a “real-world” mean of distinguishing mood conversion episodes from depressive symptom.^{14–16,28}

Treatment

Fluoxetine monotherapy was initiated at 20 mg daily and increased by 10 to 20 mg every other week to a maximum dose of 80 mg daily by week 6 of treatment. The dose could be reduced to a minimum of 10 mg daily, depending on response and tolerability. Participation of patients unable to tolerate 10 mg daily was discontinued from the trial. Remission was defined as a 50% or greater reduction in baseline HAM-D score plus a final HAM-D score of 8 or less at treatment week 6, 8, or 10, which was maintained for 2 additional weeks of consolidation therapy. Response was defined as a 50% or greater reduction in baseline HAM-D score by treatment week 10, with a final HAM-D score of 9 or greater. Nonresponse was defined as less than 50% reduction in baseline HAM-D score by treatment week 10. (Because it was not always possible to obtain outcome assessments within the designated 12-week study window, several patients received fluoxetine monotherapy for up to 14 weeks.)

Outcome Assessment

Outcome measures included the HAM-D, YMRS, and Clinical Global Impression severity item (CGI/S) and change item (CGI/C)²⁹ ratings. A treatment-emergent adverse event profile was obtained at each study visit.

Syndromal and subsyndromal hypomanic episodes were assessed via patient telephone reports of mood change and by clinician-elicited assessment of mood conversion symptoms in the preceding treatment period performed at each study visit. Hypomania was defined by *DSM-IV* criteria as an episode lasting 4 days or more with 4 symptoms or more. Subsyndromal hypomania was defined as an episode lasting 3 or less days with 4 symptoms or more, or as an episode lasting 4 days or more with 3 symptoms or less. Hypomania was also examined using a YMRS score cut points of 8 or greater and 12 or greater at any study visit.^{14–16,28} Patients experiencing syndromal or subsyndromal hypomania underwent rescue therapy via downward adjustment of their fluoxetine dose within the allowable dosage parameter.

Sample Size Justification

The study was powered to generate a sufficient sample size to test the hypothesis that continuation fluoxetine is superior to placebo in preventing depressive relapse after initial recover with fluoxetine monotherapy. The assumptions for our calculations were based on results from a prior study of fluoxetine monotherapy.³⁰ Using Kaplan-Meier analyses, the assumption of relapse was 0.7 on fluoxetine and 0.1 on placebo after 6 months and 0.6 and 0.1

after 12 months. We based our power analysis on an expected survival of 0.6 for fluoxetine and 0.18 for placebo. Thus, the sample size value that was needed for each treatment condition, to detect a significant difference in 0.6 versus 0.18 with the log-rank test at the $P < 0.05$ level with 80% power, was 23. Assuming a 50% remission rate during initial fluoxetine monotherapy, the number of subjects necessary was 184. However, because the number of treatment conditions was reduced from 4 to 3 at the outset of the trial, our sample size was adjusted to 168.

Statistical Procedures

All analyses were conducted in Stata 10.0 (College Station, Tex) with 2-sided tests of hypotheses and $P < 0.05$ as the criterion for statistical significance. Initial analyses were descriptive and summarized demographic and clinical outcome variables with means, medians, SDs, and 95% confidence intervals (CIs) for continuous variables and frequencies (with 95% CI) for categorical variables. Box plots and overlaid individual level plots of data (available on request) were displayed. Kaplan-Meier curves (available on request) were used to examine the time to remission or response. Additional estimates of the median time to remission or response (with 95% CI) were also obtained. We note that response was based on the last HAM-D measurement, so that the median time to response was greater than the median time to remission. (Because outcome assessments were not always obtained within the designated study visit window, the actual date of the measurement was used for statistical analysis.)

The proportion of patients (with 95% CI) who remitted and responded was obtained based on the binomial distribution. Change in HAM-D scores over time was examined using quasi-least squares (QLS)³¹ to fit a regression model that regressed HAM-D score on the time of measurement (days vs baseline), with adjustment for additional covariates in subsequent models. Quasi-least squares allow for application of the Markov correlation structure that is appropriate for measurements that are unequally spaced in time. We also fit other correlation structures to verify that the results were not unduly sensitive to the choice of correlation structure.³² To determine the extent of change in HAM-D scores over time, we examined whether the estimated regression coefficient for time was negative in the regression models (with and without adjustment for additional covariates) and tested whether this coefficient differed significantly from zero. Quasi-least squares models were also used to estimate the expected decline in HAM-D scores (with 95% CI) at 12 weeks after baseline and to estimate the change at 12 weeks in CGI/S and CGI/C ratings and in YMRS scores. Finally, the proportion of patients with elevated YMRS scores (with 95% CI and P values) at any study visit was examined.

RESULTS

Enrollment

One hundred sixty-seven patients enrolled in the study: 89 women (53.3%) with a mean (SD) age of 36.9 (12.7) years (range, 19–76 years) and 78 men (46.7%) with a mean age of 37.9 (12.9) years (range, 20–84 years). Mean illness duration was 18.4 (12.1) years (range, 1–66 years), and mean length of current depressive episode was 13.6 (17.6) months (range, 1–108 months). Mean number of prior depressive episodes was 8.9 (18.9) (range, 0–208), and mean number of prior hypo-manic episodes was 15.9 (29.4) (range, 0–208). Nineteen patients (11.4%) were screen failures: 10 for protocol exclusion and 9 for withdrawn consent. Of the 148 patients with at least 1 postbaseline measurement, 65 patients (43.9%) discontinued treatment: 26 (40.0%) for lack of efficacy, 5 (7.7%) for adverse events, 2 (3.1%) for noncompliance, 12 (18.4%) for withdrawn consent, and 20 (30.8%) lost to follow-up.

Efficacy

Figure 1 displays the box plots of HAM-17 scores by visit in this 12-week study. Eighty-six (58.1%) of 148 patients achieved remission (95% CI, 49.7%–66.2%) ($P < 0.0005$), with a median time to remission of 64.4 days (95% CI, 59.1–69.7 days), whereas 88 patients (59.5%) responded (95% CI, 51.1%–67.4%) ($P < 0.0005$), with a median time to response of 79.3 days (95% CI, 75.–3.4 days). The 2 responder patients who did not remit achieved final HAM-D scores of 10 and 11, respectively.

We observed a significant reduction over time in HAM-D scores ($P < 0.0005$), with the estimated reduction from baseline to week 12 being 13.5 (95% CI, 12.2–14.8), using a QLS model that did not adjust for additional covariates and 13.5 (95% CI, 12.2–14.8) in a model that adjusted for sex, age, race, and rapid versus nonrapid cycling. Quasi-least squares also found a significant decline over time in CGI/S ($P < 0.0005$) and CGI/C ($P < 0.0005$) scores. The estimated reduction in CGI/S scores was 2.2 (95% CI, 2.0–2.5), and the estimated reduction in CGI/C scores was 2.3 (95% CI, 2.–.5).

Fluoxetine Dosage

There was no statistically significant or clinically meaningful difference in the mean maximum dose prescribed for fluoxetine responders versus nonresponders by week 12 of therapy ($P = 0.834$).

Hypomanic Symptoms

There were 6 patients (4.1%; 95% CI, 1.5%–8.6%) ($P < 0.0005$) who had 1 hypomanic episode lasting a mean of 20.2 (23.3) days (range, 5–71 days), with a mean of 8.2 (2.9) (range, 6–13) symptoms. There were 29 patients (19.6%; 95% CI, 13.5%–26.9%) ($P < 0.0005$) who had a mean of 1.4 (0.72) (range, 1–4) subsyndromal hypomanic episodes lasting a mean of 4.1 (3.4) days (range, 1–15) days with a mean of 4.1 (1.1) (range, 2–13) symptoms. All hypomanic and subsyndromal hypomanic episodes resolved without treatment discontinuation.

There was no statistically significant or clinically meaningful increase in YMRS scores over time. The estimated change in YMRS scores between baseline and week 12 was 0.3 (95% CI, –0.03 to 0.6) ($P = 0.1$) with, or without, adjustment for additional covariates. Six patients (4.1%; 95% CI, 1.5%–8.6%) ($P < 0.0005$) had a YMRS score of 8 or greater, and 4 patients (2.7%; 95% CI, 0.7%–6.8%) ($P < 0.0005$) had a YMRS score of 12 or greater at any study visit.

Safety and Tolerability

Adverse events were reported or elicited in 145 patients (98.0%). Five patients (3.4%) discontinued treatment because of adverse events, including 2 serious adverse events: 1 suicide attempt and 1 manic episode (in a bipolar I patient who did not provide accurate information about the nature and severity of prior hypomanic episodes). The most frequent adverse occurrences ($\geq 10\%$) were headaches, yawning, nausea, reduced appetite, upper respiratory tract infection, decreased libido, and delayed orgasm. Table 1 displays the frequency of psychiatric adverse events. With the exception of an increase in resting systolic or diastolic blood pressure in 14 patients (9.5%), there were no other clinically meaningful physical or laboratory changes observed.

DISCUSSION

There is considerable controversy over the use of antidepressant monotherapy in patients with bipolar II disorder because of concerns over antidepressant-induced mood conversion episodes.^{10,14,20,22,24,33} In contrast to the current observations of a relatively low mood conversion rate

during short-term fluoxetine monotherapy of bipolar II depression, other investigators have reported higher mood conversion rates during antidepressant therapy.^{19–23,33} Most evidence for an increased risk of mood conversion episodes during anti-depressant therapy derives from retrospective analyses and prospective studies containing mixed populations of bipolar types I and II patients often taking a variety of antidepressant (including tricyclic antidepressants) and mood stabilizer medications.^{1,10,19–23,33}

In general, studies of antidepressant use in bipolar depression have shown good therapeutic efficacy,^{11–18,33} although this has not been a universal observation.^{10,19–23} For example, a retrospective study¹¹ observed good antidepressant response with no manic switch episodes in 30 bipolar I and II depressed patients treated with fluoxetine monotherapy or fluoxetine plus lithium therapy. In a prospective study of adjunctive citalopram therapy in bipolar I and II depressed inpatients unresponsive to initial mood stabilizer monotherapy, Kupfer et al¹⁸ found a 64% response rate with only a 6.7% mood conversion rate. A more recent randomized trial compared the efficacy and mood conversion rate of adjunctive venlafaxine, sertraline, or bupropion therapy in a mixed population of 228 bipolar I and II depressed patients taking various mood stabilizers and anti-psychotic drugs.¹⁰ Overall, 48.7% of the antidepressant trials were rated as “much improved” or “very much improved.” However, 19.3% of the antidepressant trials also resulted in a syndromal or subsyndromal mood conversion: 7.9% mania, 11.4% hypomania, and 11.8% subsyndromal hypomania. The risks of mood conversion were 30.8% in bipolar I patients and 18.6% in bipolar II patients, with the ratio of syndromal to subsyndromal conversions being greatest with venlafaxine.

Other studies have not found antidepressant therapy to be of benefit in bipolar depression.^{10,19–23} One prospective study compared the efficacy and safety of adjunctive bupropion versus desipramine therapy in 19 bipolar I depressed patients taking established lithium therapy³⁴ and found no difference in anti-depressant efficacy between treatments. However, a higher mood conversion rate was seen during desipramine (55%) versus bupropion (11%) therapy ($P < 0.012$). A subsequent, double-blind study examined the efficacy and mood conversion rate of bupropion or paroxetine therapy ($n = 179$) versus placebo ($n = 187$) in a mixed population of bipolar I and II depressed patients on established mood stabilizer therapy.²² Recovery rates were low during both antidepressant (23.5%) and placebo (27.3%) therapy. Interestingly, the rate of mood conversion episodes was also similar for the antidepressant (10.1%) and placebo (10.7%) groups. There were also no differences in recovery rates between bipolar I and bipolar II patients.

In contrast, studies of homogeneous bipolar II patient populations have found low antidepressant-induced mood conversion rates.^{13–16,28} For example, we observed a 3.8% mood conversion rate in 89 bipolar II (vs 0% in 89 unipolar) depressed patients receiving fluoxetine monotherapy 20 mg daily for up to 12 weeks.¹³ Fluoxetine also produced a similar response rate in bipolar II (61%) versus unipolar (51%) depressed patients ($\chi^2 = 1.41$, not statistically significant). Fewer bipolar II (24.3%) versus unipolar (39.7%) patients discontinued fluoxetine for lack of efficacy ($\chi^2 = 3.56$, $P < 0.07$).¹³

In a prior 2-phase, double-blind, placebo-substitution trial, we examined the efficacy and mood conversion rate of fluoxetine monotherapy in 37 bipolar II depressed patients.^{14,15} We observed no change over time in mean YMRS scores at any study visit versus baseline ($P = 0.93$), and only 3 patients met *DSM-IV* criteria for hypomania, none of which resulted in treatment discontinuation.

More recently, we compared the efficacy and safety of short-term venlafaxine ($n = 43$) versus lithium ($n = 40$) monotherapy in bipolar II depression.¹⁶ Venlafaxine produced a significantly greater reduction over time in HAM-D scores ($P = 0.017$), with no significant increase in mean

YMRS score over time in the venlafaxine versus lithium group. Similar findings were observed in rapid versus nonrapid cycling bipolar II depressed patients treated with venlafaxine versus lithium.²⁸ It is noteworthy that the rates of antidepressant-induced mood conversion episodes observed in these studies are less than the 8.6% natural mood conversion rate in unipolar and bipolar II disorders.³⁵

Several caveats should be considered in the interpretation of the current findings. The lack of a mood stabilizer condition constrained our ability to determine the true efficacy and mood conversion rate of fluoxetine monotherapy. It is possible that mood stabilizer monotherapy may have provided similar efficacy with a lower mood conversion rate. The lack of a placebo condition constrained our ability to determine if the observed mood conversion rate during fluoxetine may have represented the background frequency of mood conversion episodes in patients with bipolar II depression.

We did not use a patient-rated daily chrono-log for identifying ultra-short mood conversion episodes.²² Thus, it is possible that we missed the presence of some subsyndromal mood conversion episodes. Although the estimated difference in change in YMRS scores between baseline and week 12 was only 0.3 (95% CI, -0.03 to 0.6) ($P = 0.10$), a clinically insignificant change, we note the failure to find a difference over time is not proof that mood conversion episodes did not occur. In addition, we note that this study was not specifically powered to detect the true occurrence rate of mood conversion episodes during fluoxetine monotherapy. Moreover, low mean change in YMRS scores should be interpreted with caution, as this change is based on all patients, the majority of whom did not have hypomanic symptoms. Assessment of change in YMRS should not be based solely on average change per patient, but also on the proportion of patients with elevated YMRS scores. Furthermore, if we combine all 36 patients with any degree of mood conversion, the estimated frequency is $36 \div 148 = 24.3\%$ (95% CI, 17.7%–32.1%) ($P < 0.0001$). This suggests that the risk of having some degree of mood conversion symptoms is statistically significant.

It is possible that the frequency and severity of mood conversion episodes may have been greater had a longer treatment duration been used. Observations from prior studies of bipolar II depressed patients treated with SRI monotherapy indicate that most mood conversion episodes occur early in treatment and do not result in cycle acceleration or treatment discontinuation.^{13–16}

It is possible that the low syndromal mood conversion rate resulted from a patient sample with more mild bipolar II disorder with a low propensity for developing fluoxetine-induced hypomania. It is also possible that the frequency of mood conversion symptoms may have been higher had affective symptoms not been rated with attribution as to cause. However, rating symptoms (ie, insomnia) without attribution on both YMRS and HAM-D scale would have falsely inflated YMRS scores.

It is possible that some of the patients who were lost to follow-up experienced mood conversion episodes that were not recorded, resulting in a higher mood conversion rate than that reported. Finally, we acknowledge that the open-label study design may have introduced rater bias. Despite this limitation, our observation of a low syndromal hypomania conversion rate during short-term fluoxetine monotherapy supports similar observations from prior studies in bipolar II patients.^{11–16,18,35}

CONCLUSIONS

We examined the efficacy and mood conversion rate of short-term fluoxetine monotherapy of bipolar II depression. We observed a 58.1% remission rate (95% CI, 49.7%–66.2%) with a mean time to remission of 64.4 days (95% CI, 59.1–69.7 days). In contrast to prior reports of

an increase in syndromal mood conversion rates during SRI therapy, we observed only 6 patients (4.1%; 95% CI, 1.5%–8.6%) who had a hypomanic episode—none of which resulted in treatment discontinuation. These observations suggest that fluoxetine monotherapy may be a safe and effective short-term treatment of bipolar II depression with a relatively low syndromal mood conversion rate.

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FIGURE 1.

Box plot of median HAM-D scores, with the 25th and 75th percentile values at the bottom and top of each box, respectively. Dark circles indicate values that are more than 1.5 times the interquartile range away from the nearer quartile.

TABLE 1

Frequency of Treatment-Emergent Reported and Elicited Psychiatric Adverse Events From Fluoxetine Treatment
(n = 148)

Psychiatric Adverse Events	n (%)
Insomnia	34 (23.0)
Somnolence/oversleeping	29 (19.6)
Subsyndromal hypomania	29 (19.6)
Fatigue/lethargy	26 (17.6)
Agitation	21 (14.2)
Jitteriness	20 (13.5)
Concentration/memory problems	16 (10.8)
Abnormal dreams	8 (5.4)
Anxiety	7 (4.7)
Hypomanic episode	6 (4.1)
Mania	1 (0.7)
Irritability	5 (3.4)
Blunted affect/lassitude	3 (2.0)
Word finding problem	2 (1.4)
Tearfulness	1 (0.7)
Suicide attempt	1 (0.7)
Sensory disturbance	1 (0.7)
Coordination difficulty	1 (0.7)