Efficacy, Adverse Events, and Treatment Discontinuations in Fluoxetine Clinical Studies of Major Depression: A Meta-Analysis of the 20-mg/day Dose

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Background: The efficacy and safety of fluoxetine in adults with moderate-to-severe major depression are well established. However, most analyses combined dosages (20–80 mg/day) of the compound. We hypothesized that in patients taking 20 mg/day, efficacy would be maintained but the incidence of adverse events would be lower. We present a meta-analysis of efficacy and safety data for fluoxetine, 20 mg/day.

Method: Data were from 3 double-blind studies (N = 417) that included patients with moderate-to-severe major depression (DSM-III or DSM-III-R criteria) who received placebo or fixed-dose 20-mg/day treatment with fluoxetine. Efficacy was assessed using the Hamilton Rating Scale for Depression (HAM-D; HAM-D-17 total score and anxiety/somatization, retardation, sleep disturbance, and cognitive disturbance factors) and response and remission rates. Safety assessments included treatment-emergent adverse events, reasons for discontinuation, and adverse events leading to discontinuation. Adverse events were evaluated to determine the emergence of activation and/or sedation.

Results: At 20 mg/day, fluoxetine-treated patients demonstrated significantly greater remission and response rates and mean changes on HAM-D-17 total score and anxiety/somatization, retardation, and cognitive disturbance factor scores than placebo-treated patients ($p < .001$). The incidence of specific adverse events leading to discontinuation and the frequency of study discontinuations due to adverse events were similar among fluoxetine-treated and placebo-treated patients (6.1% vs. 5.8%, $p = .879$). Several adverse events (insomnia, asthenia, somnolence, gastroenteritis, decreased libido, chills, and confusion) occurred significantly more frequently among fluoxetine-treated patients. A significant change in sedation, but not activation, occurred in patients in the fluoxetine 20-mg/day group compared with the placebo group.

Conclusion: These data affirm that fluoxetine at 20 mg/day is efficacious, safe, and of similar activation potential when compared with placebo in patients with major depression.

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The early, major, pivotal studies of fluoxetine in adults that demonstrated its efficacy and safety in major depression used escalating dosages of up to 80 mg/day.[1–4] The majority of the patients were in fact treated with 60 mg/day. Wernicke and colleagues[5,6] subsequently reported 2 multiple fixed-dose studies, a 20-40-60–mg/day study and a 5-20-40–mg/day study, which demonstrated that 20 mg/day of fluoxetine is effective in moderate-to-severe major depressive disorder. Since then, another fixed-dose study has demonstrated the efficacy and tolerability of fluoxetine 20 mg/day in the treatment of depression.[7] The analyses by Beasley et al.[8] of fluoxetine's activating and sedating effects using multiple fixed-dose studies of fluoxetine suggested that the incidence of activation was relatively flat between 5 and 40 mg/day and increased relative to placebo, whereas the incidence of sedation increased linearly to 40 mg/day. With respect to the analysis of activation, the data were complex. There was an initial rise in the incidence from placebo to 5 mg/day, and then the incidences observed with 20 mg/day and 40 mg/day were relatively similar to that observed with 5 mg/day in one study. However, in the comparison of placebo and fluoxetine, 20 mg/day, 40 mg/day, and 60 mg/day, no difference was shown in incidence of activation between placebo and fluoxetine, 20 mg/day.

The perception of the efficacy and tolerability of 20 mg/day of fluoxetine has been confounded by the experience of clinicians with the higher doses reported in the earlier literature. To demonstrate the efficacy and potentially improved safety and tolerability with 20 mg/day, we present a meta-analysis of efficacy and safety data of fluoxetine, 20 mg/day. Special attention was given to adverse events, discontinuations due to adverse events, and changes along the psychomotor activity continuum.

METHOD

Patient Population

Patients were adult male or female outpatients with a primary psychiatric diagnosis of nonpsychotic major depression as defined by either the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III),[9] or the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R).[10] Patients had a score ≥ 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D-21) in 2 studies and ≥ 15 on the 17-item HAM-D (HAM-D-17) in one study. Patients had no serious medical conditions and had normal clinical laboratory findings. Written informed consent was sought and obtained as appropriate in all cases.

Additional exclusion criteria generally included a history of substance misuse within the previous year, psychotic or organic mental disorder, serious suicidal risk as clinically assessed by the investigator, concomitant use of psychotropic medications, and any medical condition that was unstable or might preclude the use of one of the drugs evaluated in the studies.

Study Design

Data were from studies in nongeriatric patients without significant comorbid medical disease who had moderate-to-severe major depressive disorder. The studies included a fixed dose of 20 mg/day of fluoxetine, were sponsored by Eli Lilly and Company, and were conducted in the United States. The 3 studies included in this analysis[5–7] were randomized, double-blind, and placebo-controlled and compared fluoxetine at 20 mg/day with placebo in adult patients with moderate-to-severe major depression (fluoxetine, N = 245; placebo, N = 172).

One of the studies included in our analysis (a placebo-controlled study using fixed doses of fluoxetine of 20, 40, and 60 mg/day)[5] was actually 1 of 2 studies conducted in parallel by the same group of investigators. The other study,[11] which included mildly depressed patients (HAM-D-21 score of 14–19), was excluded from our analysis. In addition, 1 study in the geriatric population that included a fixed dose of 20 mg/day of fluoxetine[12] has been excluded from this analysis. Furthermore, 3 small studies in patients with specific comorbid medical illnesses that included the fixed dose of 20 mg/day of fluoxetine (reference 13 and C.M.B., data on file, Eli Lilly and Company, Indianapolis, Ind.) were also excluded. The exclusion of these studies allowed this meta-analysis to focus on a population of patients with relatively homogeneous demographic and illness characteristics.

Before starting randomized treatment, 2 of the studies excluded patients for whom scores improved by 20% or more during a 1-week run-in period of single-blind placebo treatment and the other study excluded patients for whom scores improved by 25% or more during a 2-week placebo run-in period.

Assessments

A variety of efficacy assessments were used in the individual studies. This meta-analysis focuses on the HAM-D and includes HAM-D-17 total score and anxiety/somatization, retardation, sleep disturbance, and cognitive disturbance factor scores. If 1 or more items were not scored on a specific scale or subscale, the scale or subscale score was treated as missing.

Safety was assessed by the evaluation of treatment-emergent adverse events and discontinuations for adverse events. Throughout all of the individual studies, adverse events were elicited by nonprobing inquiry. All events were recorded regardless of perceived causality. An event was considered treatment emergent if it occurred for the first time or worsened during the double-blind therapy period.

Statistical Methods

Efficacy differences between fluoxetine and placebo-treated patients were assessed by comparison of mean changes from baseline to endpoint in HAM-D (HAM-D-17 total score and anxiety/somatization, retardation, sleep disturbance, and cognitive disturbance factor scores). At least 1 visit beyond baseline was necessary for a patient to be considered for endpoint analysis. When analyzing efficacy data for individual studies, analysis of variance (ANOVA) of changes, with treatment in the model, was used to compare mean changes between treatments, and confidence intervals were constructed. For the meta-analyses assessing efficacy, confidence intervals were constructed and p values were calculated for the pooled studies by way of a fixed-effects model for mean absolute differences between treatments using the meta-analysis method derived by Whitehead and Whitehead.[14] The fixed-effects model assumes homogeneity of treatment effects over all studies. When heterogeneity of treatment effects across studies was detected, a random-effects model was used that allowed for treatment effects that varied between studies.[14]

The percentages of patients achieving response and remission were also used to compare efficacy between fluoxetine- and placebo-treated patients. Patients who experienced at least a 50% reduction in HAM-D-17 total scores from baseline to endpoint were considered responders. Remission was defined as a HAM-D-17 total score ≤ 7 at endpoint. Analyses of response and remission were conducted using 2 methods: (1) patients treated for more than 3 weeks (minimal therapeutic exposure) and (2) intent-to-treat.

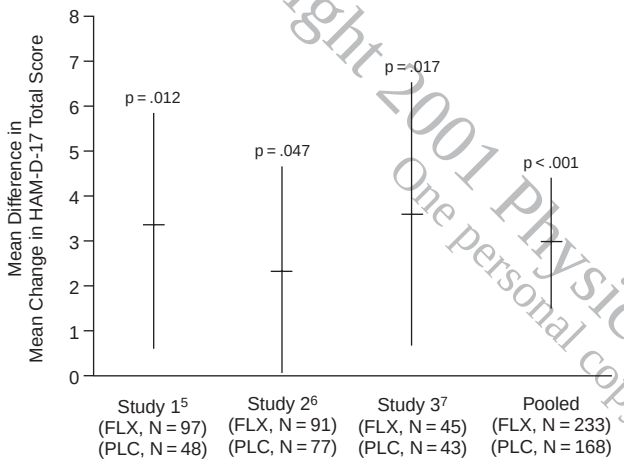
Safety differences between fluoxetine and placebo were assessed by comparison of treatment-emergent adverse events, discontinuations, and adverse events lead-

Table 1. Patient Demographics and Baseline Scores[a]

Variable	Fluoxetine, 20 mg/d (N = 245)	Placebo (N = 172)
Age, y	39.2 ± 11.6	38.4 ± 10.4
White, N (%)	214 (87.3)	156 (90.7)
Female, N (%)	151 (61.6)	106 (61.6)
HAM-D score		
17-Item total	21.7 ± 3.4	22.2 ± 3.8
Anxiety/somatization	6.5 ± 1.8	6.7 ± 1.8
Retardation	7.9 ± 1.7	8.2 ± 1.7
Cognitive disturbance	5.0 ± 2.1	5.1 ± 2.3
Sleep disturbance	3.7 ± 1.7	3.6 ± 1.7

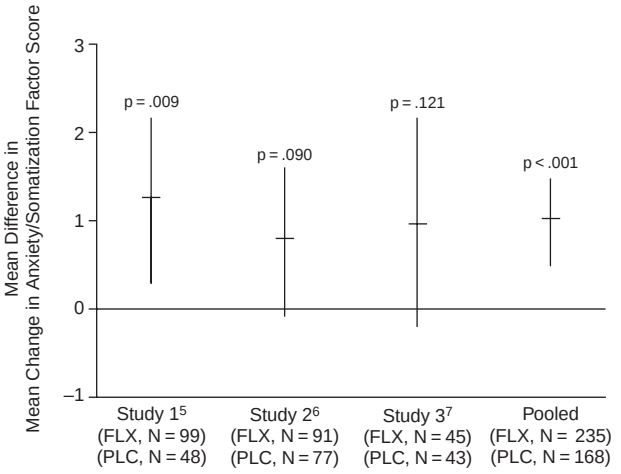
[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. All values shown as mean ± SD unless otherwise specified.

Figure 1. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Change in HAM-D-17 Total Score[a]



[a]Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression. Change from baseline to endpoint; endpoint values based on last observation carried forward. Small horizontal lines represent mean differences between fluoxetine and placebo groups in mean change scores; vertical lines depict 95% confidence intervals. All p values result from analysis of variance.

Figure 2. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Change in HAM-D Anxiety/Somatization Factor Score[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Change from baseline to endpoint; endpoint values based on last observation carried forward. Small horizontal lines represent mean differences between fluoxetine and placebo groups in mean change scores; vertical lines depict 95% confidence intervals. All p values result from analysis of variance.

ing to discontinuation. Analyses included all randomized patients. Adverse events were also evaluated to determine the emergence of activation or sedation during therapy. The adverse event terms *agitation, akathisia, anxiety, CNS [central nervous system] stimulation, insomnia,* and *nervousness* were grouped to indicate activation; the terms *apathy, asthenia, CNS depression,* and *somnolence* were grouped to indicate sedation. Activation and sedation were not mutually exclusive. A patient could report a treatment-emergent sedation event and a treatment-emergent activation event at the same visit; alternatively, a patient could report sedation events at one visit and activation events at another.

Safety differences and differences in response and remission were analyzed using the Mantel-Haenszel incidence difference stratified by study[15,16] in cases where heterogeneity of incidence differences across studies was not statistically significant. The DerSimonian-Laird incidence difference method was used in cases where heterogeneity across studies was statistically significant (Cochran test, $p < .10$).[17] When analyzing individual studies, the Pearson chi-square test was used.

RESULTS

Demographics and Baseline Characteristics

A total of 417 randomized patients were included in this patient population. Baseline characteristics of the patients in the 2 groups analyzed are summarized in Table 1. No statistically significant differences were found between the treatment groups.

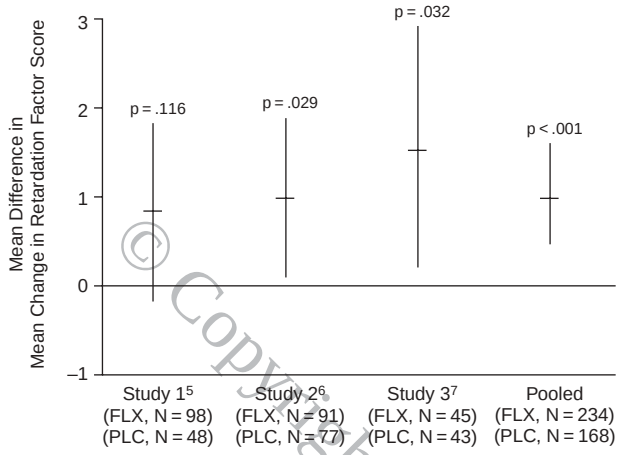
Endpoint Analysis

As indicated by improvement on the HAM-D, fluoxetine at a dose of 20 mg/day was statistically significantly superior to placebo on all outcome measures (total score and anxiety somatization, retardation, and cognitive disturbance factor scores) except sleep disturbance in the meta-analytic pooling of studies (Figures 1–5).

Response and Remission Rate Analyses

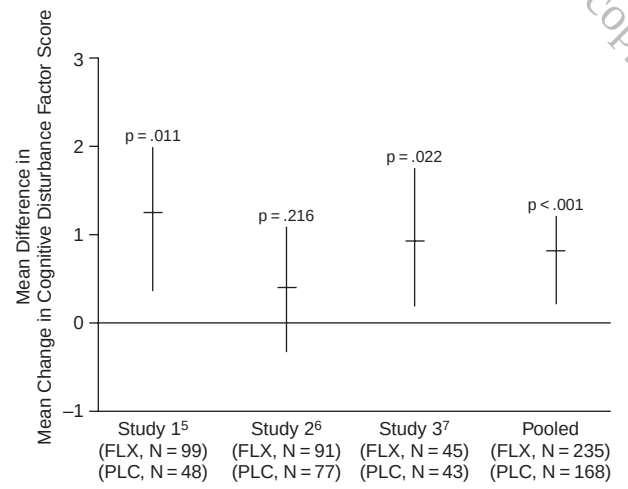
Patients who experienced at least a 50% reduction in HAM-D-17 scores from baseline were considered responders. Remission was defined as a HAM-D score of ≤ 7 at the last visit. Three hundred eleven patients were included in the analysis, which was restricted to the subset of patients treated for more than 3 weeks (minimal therapeutic exposure), and 401 were included in the intent-to-

Figure 3. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Change in HAM-D Retardation Factor Score[a]



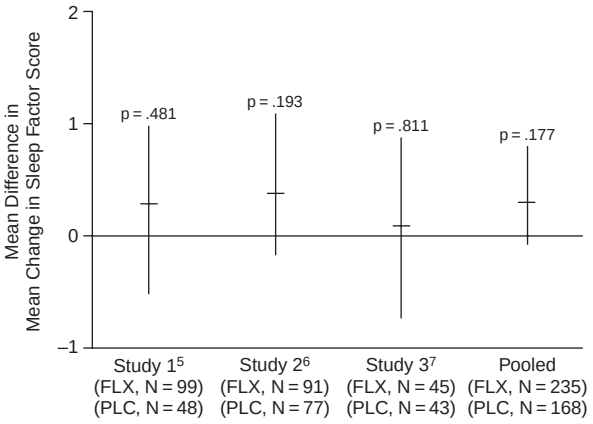
[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Change from baseline to endpoint; endpoint values based on last observation carried forward. Small horizontal lines represent mean differences between fluoxetine and placebo groups in mean change scores; vertical lines depict 95% confidence intervals. All p values result from analysis of variance.

Figure 4. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Change in HAM-D Cognitive Disturbance Factor Score[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Change from baseline to endpoint; endpoint values based on last observation carried forward. Small horizontal lines represent mean differences between fluoxetine and placebo groups in mean change scores; vertical lines depict 95% confidence intervals. All p values result from analysis of variance.

Figure 5. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Change in HAM-D Sleep Disturbance Factor Score[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Change from baseline to endpoint; endpoint values based on last observation carried forward. Small horizontal lines represent mean differences between fluoxetine and placebo groups in mean change scores; vertical lines depict 95% confidence intervals. All p values result from analysis of variance.

treat analyses. In both subsets of patients, fluoxetine at 20 mg/day produced statistically significantly greater response and remission rates than did placebo in the meta-analytic pooling of studies (for minimal therapeutic exposure, response = 58.6% vs. 33.8%, $p < .001$; remission = 39.8% vs. 22.3%, $p < .001$; for intent-to-treat, response = 48.5% vs. 28.0%, $p < .001$; remission = 31.8% vs. 18.5%, $p = .001$). The minimal therapeutic exposure results are shown in Figures 6 and 7.

Treatment-Emergent Adverse Events

Table 2 displays the treatment-emergent adverse events. The following events occurred statistically significantly more among fluoxetine-treated patients than with placebo-treated patients: insomnia, asthenia, somnolence, gastroenteritis, decreased libido, chills, and confusion.

Table 3 presents the activation and sedation subsets of treatment-emergent adverse events. At a dose of 20 mg/day, sedation, but not activation, was a statistically significant treatment-emergent phenomenon.

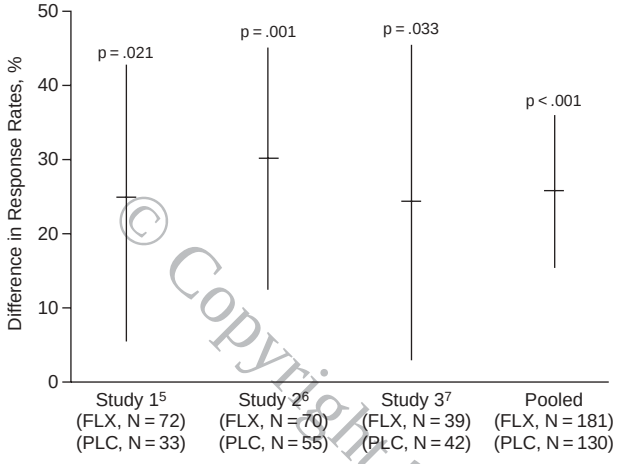
Reasons for Discontinuation

An analysis was conducted to compare reasons for discontinuation (adverse event, lack of efficacy, study completion, or other reasons) between treatment groups (Table 4). The placebo-treated patients had a trend for higher discontinuation due to lack of efficacy, and no statistically significant difference was found between treatment groups in the percentage of patients who discontinued early owing to an adverse event or for other reasons.

Adverse Events Causing Discontinuation

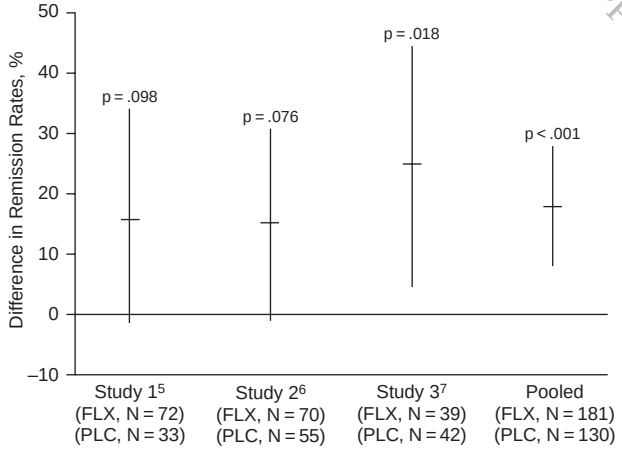
The specific adverse events leading to treatment discontinuation were also examined. In the 2 clinical studies in which discontinuation could be attributed to multiple events,[5,6] no events were found to cause discontinuation significantly more often with fluoxetine. The

Figure 6. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Response Rates in Subjects Receiving Minimal Therapeutic Exposure[a]



[a]Minimal therapeutic exposure defined as more than 3 weeks of treatment. Small horizontal lines represent mean differences between fluoxetine and placebo in response rates; vertical lines depict 95% confidence intervals. All p values result from Pearson chi-square test. Pooled placebo response rate = 33.8%; pooled fluoxetine response rate = 58.6%.

Figure 7. Mean Difference Between Fluoxetine (FLX) and Placebo (PLC): Remission Rates in Subjects Receiving Minimal Therapeutic Exposure[a]



[a]Minimal therapeutic exposure defined as more than 3 weeks of treatment. Small horizontal lines represent mean differences between fluoxetine and placebo in remission rates; vertical lines depict 95% confidence intervals. All p values result from Pearson chi-square test. Pooled placebo remission rate = 22.3%; pooled fluoxetine response rate = 39.8%.

only events causing discontinuation at an incidence of ≥ 2% were found for fluoxetine-treated patients: nausea (2.5%, vs. 0.8% for placebo) and insomnia (2.0%, vs. 1.5% for placebo).

In the one clinical study in which only a primary event causing study discontinuation was collected,[7] there also were no events that caused discontinuation significantly more with fluoxetine. The most common events (incidence ≥ 2%) causing discontinuation were found in the fluoxetine-treated patients: agitation (2.2% [N = 1] vs. 0% for placebo) and convulsion (2.2% [N = 1], vs. 0% for placebo).

Table 2. Percentage of Subjects Who Had Treatment-Emergent Adverse Events[a]

Event	Fluoxetine, 20 mg/d (N = 245)	Placebo (N = 172)
Nausea	18.8	11.0
Headache	17.6	19.2
Rhinitis	12.7	14.0
Anxiety	12.2	10.5
Insomnia	12.2[b]	5.8
Diarrhea	11.4	9.9
Nervousness	10.6	11.6
Dizziness	10.2	5.8
Dry mouth	9.0	8.7
Asthenia	7.8[b]	2.9
Anorexia	7.3	4.7
Somnolence	6.5[b]	2.3
Sweating	6.1	4.1
Infection	5.3	7.0
Gastroenteritis	3.7[b]	0.6
Decreased libido	2.4[b]	0.0
Chills	1.6[b]	0.0
Confusion	1.6[b]	0.0
Sinusitis	0.8	4.7[b]

[a]Occurring in ≥ 5% of patients in the fluoxetine 20-mg/day group or with a statistically significant difference ($p < .05$) between groups.
[b]Statistically significantly greater incidence vs. the other treatment group ($p \leq .05$).

Table 3. Percentage of Subjects Who Had Activation and Sedation Adverse Events

Classification of Event	Fluoxetine (N = 245)	Placebo (N = 172)	p Value
Activating[a]	28.2	25.0	.750[b]
Sedating[c]	13.5	4.7	< .001

[a]Agitation, akathisia, anxiety, central nervous system stimulation, insomnia, and nervousness.
[b]DerSimonian-Laird incidence difference since there was statistically significant heterogeneity across trials.
[c]Apathy, asthenia, central nervous system depression, and somnolence.

Table 4. Treatment Discontinuations (%)

Reason for Discontinuation	Fluoxetine (N = 245)	Placebo (N = 172)	p Value
Adverse event	6.1	5.8	.879
Lack of efficacy	16.7	23.3	.089
Other reasons	13.9	11.6	.530
Study completion	63.3	59.3	.295

DISCUSSION

Endpoint analysis, as well as response- and remission-rate analysis applied to the data from this meta-analytic pooling of studies, continues to support the previously reported efficacy of the 20-mg/day dose of fluoxetine in

the treatment of moderate-to-severe major depression.[5–7] Specifically, the 20-mg/day fluoxetine dose effectively treated major depressive disorder as assessed by group mean changes in HAM-D total score relative to placebo. With respect to specific clusters of symptoms, fluoxetine, 20 mg daily, compared with placebo significantly reduced all HAM-D factor scores except sleep disturbance in this meta-analysis.

The results (see Table 2) of this meta-analysis confirm the previously described adverse event profile of fluoxetine, which includes those events considered typical of serotonin reuptake inhibitors (e.g., the psychomotor activating event of insomnia but conversely also the psychomotor slowing events of somnolence and asthenia).[18] In comparison with previous analyses using combined dosages of fluoxetine (20–80 mg/day),[1–4] the patients in this 20-mg/day meta-analysis, as predicted, had lower frequencies for most adverse events. Some events commonly thought to be associated with fluoxetine treatment did not occur statistically significantly more frequently than with placebo treatment (anxiety, nausea, nervousness, tremor, dizziness, dyspepsia). The enhanced safety and tolerability of the low dose is also supported by the incidence of discontinuations due to adverse events. At a dose of 20 mg/day, fluoxetine-treated and placebo-treated patients had a similar incidence of discontinuation due to an adverse event, 6.1% in the fluoxetine group and 5.8% in the placebo group.

Activation and sedation associated with fluoxetine therapy were assessed using the methodology first described by Beasley et al. in an imipramine-controlled study[19] and subsequently in separate trazodone-controlled[20] and the early placebo-controlled studies.[8] Important results of this 20-mg/day meta-analysis, and differing from the results in the earlier report[8] that included studies of multiple fixed doses of fluoxetine, were the findings that reports of events reflecting sedation but not activation were statistically significantly higher in the 20-mg/day group compared with the placebo group. The results and conclusions reported here can be considered more definitive regarding the activating and sedating effects of fluoxetine at a dose of 20 mg/day than those in the earlier report[8] that was not a formal meta-analysis. In the earlier report, the overall incidence of activation appeared to be relatively flat across the dose range of 5 mg/day to 40 mg/day when combining the earlier studies, and it was concluded that 20 mg/day was more activating than placebo. However, differences between placebo and 20 mg/day of fluoxetine varied considerably across these individual, early, dose-group comparisons. In the one study that compared placebo (N = 78) and fluoxetine 5 (N = 96), 20 (N = 96), and 40 (N = 93) mg/day in patients with moderate-to-severe depression,[8] a significant increase in activating events ($0.01 < p \leq .05$) was found at both 5 and 20 mg/day. However, in the comparison of placebo (N = 107) and fluoxetine 20 (N = 210), 40 (N = 215), and 60 (N = 214) mg/day, data were combined from the 2 studies[5,11] in patients with mild or moderate-to-severe depression, and a significant increase in activating events was observed only with the 40- and 60-mg/day doses, with the largest increase occurring with the 60-mg/day dose. The difference in activation outcomes with the 20-mg/day patients in the studies described above compared with those in this article may be attributable to sample size differences and/or patient population differences (inclusion of mildly depressed patients in the placebo–fluoxetine 20-40-60–mg/day study),[5] as well as the difference in underlying treatment-emergent activation as suggested by the difference in incidence observed with placebo across studies: 18% in the placebo–fluoxetine 5-20-40–mg/day study[6] and 25% in the placebo–fluoxetine 20-40-60–mg/day study.[5]

The only qualification on these findings with respect to activation is with regard to influence specifically on sleep. A statistically significantly greater incidence of insomnia was found with fluoxetine, 20 mg/day, than with placebo. Daytime psychomotor activation as well as combined daytime and nocturnal activation did not differ between fluoxetine, 20 mg/day, and placebo.

With respect to sedation, this meta-analysis is in agreement with a previous report with multiple fixed doses of fluoxetine.[8] Sedation occurred as a statistically significant treatment-emergent phenomenon at 20 mg/day in both the present analysis (13.5% as compared with 4.7% for placebo) and the multiple fixed doses report. Furthermore, discontinuations due to adverse events were statistically no different between placebo and 20 mg daily of fluoxetine in the present analysis, and discontinuations due to activation and sedation events were statistically no different between placebo and 20 mg daily of fluoxetine in the fixed-doses report.

This meta-analysis was designed to address some of the limitations the above studies had in regard to assessing the effects of low-dose fluoxetine on psychomotor activation. First, the studies included in our meta-analysis were placebo controlled and used fixed 20-mg/day doses. Secondly, a more homogeneous population was used in that only nongeriatric patients with moderate-to-severe depression and without significant comorbid medical illness were included. The meta-analysis therefore included those patients who qualified from the fixed-dose studies discussed above,[8] as well as patients from a more recent 20-mg fixed-dose study.[7] The addition of the third study[7] and the use of more formal analytical techniques have led us to expand upon our previous conclusions regarding activation. These data and our meta-analysis strongly suggest that fluoxetine is actually more sedating than activating at a dose of 20 mg/day relative to placebo. This further supports the recommendation of a 20-mg/day dose of fluoxetine for the treatment of depression.

On an individual patient basis, the minimal effective dose of fluoxetine may be less or greater than 20 mg/day. Wernicke[6] reported that 5 mg/day of fluoxetine was similar to 20 mg/day with respect to last-observation-carried-forward mean change in HAM-D score and that the 20-mg/day dose was superior on the basis of secondary endpoints. Conversely, Fava and colleagues[21] reported that once a fluoxetine trial of adequate duration (8 weeks) and standard dosage (20 mg/day) had failed in the treatment of depression, patients benefited from increasing the dosage of fluoxetine to 60–80 mg/day.

Two additional studies of fixed-dose 20-mg/day fluoxetine versus placebo in patients with distinctly different illnesses and/or demographic characteristics but without significant comorbid illness were not included in this meta-analysis in order to maintain homogeneity. In a 6-week trial in moderately to severely depressed outpatients over age 60 years,[11] fluoxetine was significantly more efficacious than placebo in overall rates of response (43.9% vs. 31.6%, $p = .002$) and remission (31.6% vs. 18.6%, $p < .001$). Additionally, early discontinuations due to adverse events were similar between fluoxetine and placebo. In a separate study of patients with mild major depressive disorder (HAM-D score of 14–19),[11] mean changes in treatment measures showed little difference among treatment groups. However, pattern analysis of treatment response showed more patients in the active treatment groups having a persistent or delayed persistent response, the types of response specifically associated with active treatment.

The results of this study also suggest good treatment tolerance on fluoxetine therapy at 20 mg/day, a critical factor for adequate antidepressant therapy.[22] Tolerability, as a contributor to compliance, is especially important in light of data recommending long-term treatment.[23] The low incidence of fluoxetine discontinuation due to adverse events suggests good patient acceptance.

Drug name: fluoxetine (Prozac).

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