A Preliminary, Randomized Trial of Fluoxetine, Olanzapine, and the Olanzapine-Fluoxetine Combination in Women With Borderline Personality Disorder

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Background: The intent of this study was to compare the efficacy and safety of fluoxetine, olanzapine, or the olanzapine-fluoxetine combination (OFC) in the treatment of women meeting criteria for borderline personality disorder **(**without concurrent major depressive disorder).

Method: We conducted a randomized double-blind study of these agents in female subjects meeting Revised Diagnostic Interview for Borderlines (DIB-R) and DSM-IV criteria for borderline personality disorder. Treatment duration was 8 weeks. Outcome measures were clinician-rated scales measuring depression (the Montgomery-Asberg Depression Rating Scale) and impulsive aggression (the Modified Overt Aggression Scale). Data were collected from August 2001 through March 2003.

Results: Fourteen subjects were randomized to fluoxetine; 16, to olanzapine; and 15, to OFC. Forty-two of these subjects (93.3%) completed all 8 weeks of the trial. Using random-effects regression modeling of panel data of change-from-baseline scores and controlling for time, olanzapine monotherapy and OFC were associated with a significantly greater rate of improvement over time than fluoxetine on both outcome measures. However, it should be noted that fluoxetine treatment led to a substantial reduction in impulsive aggression and severity of depression. Weight gain was relatively modest in all 3 groups but significantly greater in the olanzapine-treated group than in the groups treated with fluoxetine alone or OFC.

Conclusion: All 3 compounds studied appear to be safe and effective agents in the treatment of women with borderline personality disorder, significantly ameliorating the chronic dysphoria and impulsive aggression common among borderline patients. However, olanzapine monotherapy and OFC seem to be superior to fluoxetine monotherapy in treating both of these dimensions of borderline psychopathology.

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Recent reports have documented the high percentage of borderline patients who are prescribed psychotropic medications, detailing high rates of prolonged use of antidepressants, antipsychotics, mood stabilizers, and anxiolytics.[1,2] These same reports have documented the high percentage of borderline patients who are treated with multiple concurrent medications. In a longitudinal study,[3] 40% of borderline patients were found to be taking 3 or more concurrent medications over 6 years of follow-up, 20% were taking 4 or more concurrent medications, and 10% were taking 5 or more.

Despite this heavy use of different classes of medication, no recent studies have assessed the efficacy of one class of psychotropic medication versus another. However, in the late 1980s and early 1990s, 2 major groups of investigators studied the comparative efficacy of antipsychotic agents versus antidepressants.[4–7] Soloff and associates[4] found that a standard neuroleptic (haloperidol) had a broader band of efficacy than a tricyclic antidepressant (amitriptyline). These same investigators[5] later studied the efficacy of haloperidol versus a monoamine oxidase inhibitor (MAOI; phenelzine), finding that phenelzine was superior to haloperidol on measures of depression, anxiety, psychoticism, and general functioning. However, haloperidol was superior to phenelzine in reducing hostility and impulsivity. In a continuation phase of the same study,[6] phenelzine continued to be superior to haloperidol, particularly in the area of depressive symptoms. Cowdry and Gardner[7] also studied the comparative efficacy of a standard neuroleptic and an MAOI. These investigators found that tranylcypromine had a broader range of effectiveness than trifluoperazine.

Thus, earlier research efforts indicate that the relative superiority of one type of medication to another seems to depend on the particular medications being used. In

addition, no reports have ever appeared in the literature, to the best of our knowledge, that compare the efficacy and safety of monotherapy versus polypharmacy among borderline patients.

The current study explores the efficacy and safety of 2 commonly used medications (fluoxetine and olanzapine) and a combination of the 2 (olanzapine-fluoxetine combination [OFC]) in the treatment of borderline women without concurrent major depressive disorder. These subclasses of medication (selective serotonin reuptake inhibitor [SSRI] and atypical antipsychotic) were chosen for study because they are 2 of the most frequently prescribed types of psychotropic medication for borderline patients.[3] These particular medications were chosen for study because each has been shown to be efficacious and safe in a placebo-controlled trial of women with carefully diagnosed borderline personality disorder.[8,9] In the first of these studies, Salzman et al.[8] found that subjects treated with fluoxetine reported significantly greater reductions in anger and depression than those taking placebo. In the second of these studies, Zanarini and Frankenburg[9] found that olanzapine was superior to placebo in reducing symptoms in all 4 core sectors of borderline psychopathology.

METHOD

Patients

Recruitment of women aged 18 to 40 years who were disturbed by moodiness, distrustfulness, impulsivity, and painful and difficult relationships was accomplished primarily through advertisements in Boston, Mass., area newspapers. Subjects who answered the advertisement were screened by telephone to assess whether they met the DSM-IV criteria for borderline personality disorder using the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV).[10] A general medical and psychiatric history was also taken at the time of first telephone contact. Potential subjects were excluded if they had been successfully treated with fluoxetine or olanzapine, were medically ill, had a seizure disorder, were currently being prescribed any psychotropic medication, were actively abusing alcohol or drugs, or were acutely suicidal (i.e., had a clear-cut and pressing intent to commit suicide in the near future). Subjects who were pregnant, breastfeeding, planning to become pregnant, or not using reliable forms of contraception were also excluded.

Subjects were next invited to participate in face-to-face interviews, at which time written informed consent was obtained. Two semistructured diagnostic interviews were then administered to each subject: the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[11] and the Revised Diagnostic Interview for Borderlines (DIB-R).[12] Subjects were included if they met both DIB-R and DSM-IV criteria for borderline personality disorder and did not meet criteria for current major depressive disorder. The latter disorder was an exclusion criterion because we wanted to determine the effect of the agents we were studying on core borderline psychopathology, rather than their efficacy in treating a concurrent major depressive disorder. Subjects were also excluded if they met criteria for current or lifetime schizophrenia, schizoaffective disorder, or bipolar disorder. Subjects then underwent a physical examination and laboratory analyses, including hematologic indices, serum chemistry studies, and a pregnancy test. Two observer-rated psychiatric scales were also administered during this visit: the Modified Overt Aggression Scale (OAS-M)[13] and the Montgomery-Asberg Depression Rating Scale (MADRS).[14] Baseline assessments also included the Global Assessment of Functioning (GAF)[15] and the Hollingshead Two Factor Index of Social Position.[16]

Study duration was 8 weeks. The randomization procedure was designed to assign equal numbers of subjects to the 3 treatment groups. Subjects were seen every week, and both psychiatric rating scales were readministered at each subsequent visit. The study was approved by McLean Hospital Institutional Review Board. Data were collected from August 2001 through March 2003.

Side Effects

Subjects were weighed at baseline and endpoint. In addition, the presence of extrapyramidal side effects and movement disorders was assessed at each follow-up visit using the following 3 scales: the Simpson-Angus Rating Scale,[17] the Barnes Akathisia Scale,[18] and the Abnormal Involuntary Movement Scale (AIMS).[19] Patients were also asked at every postbaseline visit about other side effects using a structured questionnaire developed for this study and available from the authors upon request.

Treatment

At the beginning of the study, subjects received 2 capsules. For those in the fluoxetine group, 1 of these capsules contained 10.0 mg of fluoxetine and the other contained placebo. For those in the olanzapine group, 1 of these capsules contained 2.5 mg of olanzapine and the other contained placebo. For those in the OFC group, 1 capsule contained 10.0 mg of fluoxetine and the other contained 2.5 mg of olanzapine. Dose was adjusted by an unblinded psychiatrist according to perceived response and side effects. Both subjects and raters were blinded to study assignment. The blind was broken after the acquisition of all endpoint data for all subjects.

Data Analysis

Data were analyzed using STATA software (StataCorp LP, College Station, Tex. [version 7]). Between-group baseline demographic, treatment history, and lifetime Axis I variables and baseline outcome values were analyzed

Table 1. Mean Difference Scores for Fluoxetine, Olanzapine, and OFC Groups in Women With Borderline Personality Disorder

		Difference From Baseline						
Score	Baseline	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Fluoxetine Group	(N = 14)	(N = 14)	(N = 14)	(N = 14)	(N = 14)	(N = 14)	(N = 13)	(N = 13)
OAS-M, mean	23.21	–11.71	–16.21	–13.86	–12.64	–12.93	–16.46	–15.38
OAS-M, SD	19.69	15.41	16.03	19.49	22.27	21.36	20.25	21.25
MADRS, mean	14.43	–2.50	–5.21	–7.29	–8.07	–4.79	–8.15	–8.23
MADRS, SD	4.47	4.55	5.16	6.28	5.99	11.82	6.08	7.19
Olanzapine Group	(N = 16)	(N = 16)	(N = 16)	(N = 16)	(N = 16)	(N = 16)	(N = 16)	(N = 16)
OAS-M, mean	27.81	–12.63	–10.94	–19.13	–22.75	–18.75	–19.13	–19.69
OAS-M, SD	22.89	20.33	21.14	19.94	23.64	19.40	20.72	20.83
MADRS, mean	18.81	–8.81	–8.44	–10.31	–12.44	–10.81	–11.69	–13.63
MADRS, SD	7.19	7.52	8.63	8.80	8.70	10.85	8.52	7.23
OFC Group	(N = 15)	(N = 15)	(N = 15)	(N = 15)	(N = 15)	(N = 13)	(N = 13)	(N = 13)
OAS-M, mean	25.00	–12.40	–12.80	–16.33	–17.87	–18.62	–21.31	–20.15
OAS-M, SD	19.42	19.82	20.74	14.58	19.56	22.27	19.24	15.95
MADRS, mean	16.20	–4.73	–6.80	–7.60	–7.67	–9.08	–11.00	–11.85
MADRS, SD	6.32	7.38	8.81	8.34	8.73	8.13	5.76	5.67

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OAS-M = Modified Overt Aggression Scale, OFC = olanzapine-fluoxetine combination.

using logistic regression for categorical variables and multiple regression for continuous variables. Random-effects regression analyses of panel data were used to assess between-group differences on outcome measures over time. Mean difference scores, treatment status, and time were the independent variables in these modeling analyses. Indicator variables identifying the 3 treatment groups were used to define contrasts between the fluoxetine-treated group and the OFC group and between the olanzapine-treated group and the OFC group. These indicator variables were entered into the regression models as binary explanatory factors. Post hoc tests comparing the fluoxetine and olanzapine groups were then conducted to complete these analyses.

The outcomes of interest were mean changes in the total scores of the OAS-M and the MADRS—representing the impulsive aggression and chronic dysphoria common among borderline patients and described by Siever and Davis[20] as being the core dimensions of psychopathology that underlie borderline personality disorder.

Averaged continuous data are reported as means with standard deviations. Statistical significance required 2-tailed $p < .05$.

RESULTS

Forty-five subjects entered the trial and were randomized to fluoxetine (N = 14), olanzapine (N = 16), or OFC (N = 15). Forty-two subjects (93%) completed all 8 weeks of the trial. All subjects randomized to olanzapine completed the trial, 1 fluoxetine subject dropped out after completing week 6, and 2 OFC subjects dropped out after completing week 5 of the trial. The reason for discontinuation in the fluoxetine group was the onset of a number of psychosocial stressors culminating in a suicide gesture that involved ingesting several capsules that were immediately expelled. Reasons for discontinuation in the OFC group were dizziness and headaches in one case and loss to follow-up after time away for the celebration of a holiday in the second case.

There were no significant between-group differences on any demographic, treatment history, or lifetime Axis I variables. Subjects had a mean age of 23 (SD = 5.7) years, a mean socioeconomic background score of 2.6 (SD = 1.3) on a scale where 1 = highest and 5 = lowest,[16] and a mean GAF score[15] in the low end of fair (52.5 [SD = 6.9]). Eighty percent (N = 36) of the subjects were white. In terms of psychiatric treatment, 71.1% (N = 32) had a history of individual therapy, 31.1% (N = 14) had taken psychotropic medications, and 11.1% (N = 5) had a history of psychiatric hospitalization. (However, it should be noted that no subject was in concurrent psychotherapy during the course of the study.) In terms of Axis I disorders, 93.3% (N = 42) had a history of a mood disorder (all unipolar in nature), 51.1% (N = 23) had a history of a substance use disorder, 48.9% (N = 22) had a history of an anxiety disorder, and 44.4% (N = 20) had a history of an eating disorder.

Table 1 shows the study-week–specific summary OAS-M and MADRS data for the 3 study groups. As can be seen, moderate symptom levels were reported by those in all 3 study groups at the time of subjects' entry into the study, and no significant between-group differences in baseline values were found. For each postbaseline assessment, the table shows mean difference scores over time for the study's outcome measures. OFC was associated with a significantly greater degree of improvement over time than fluoxetine on both outcome measures (Table 2). Olanzapine was also associated with a significantly greater degree of improvement over time than fluoxetine on both outcome measures. In addition, olanzapine was found to be superior to OFC in treating the depressive symptoms

Table 2. Random-Effects Regression Modeling of Outcomes for Fluoxetine, Olanzapine, and OFC Groups in Women With Borderline Personality Disorder

Outcome Measure	Statistic	p Value
OAS-M[a,b]		
Fluoxetine vs OFC	z = 3.566	.000
Olanzapine vs OFC	z = 0.666	.505
Time	z = –5.327	.000
Fluoxetine vs olanzapine	χ^2 = 8.7	.0033
MADRS[c,d]		
Fluoxetine vs OFC	z = 2.378	.017
Olanzapine vs OFC	z = –3.693	.000
Time	z = –6.614	.000
Fluoxetine vs olanzapine	χ^2 = 43.7	.0000

[a]Model χ^2 = 43.49, p = .0000.
[b]OFC > fluoxetine; olanzapine > fluoxetine.
[c]Model χ^2 = 88.55, p = .0000.
[d]OFC > fluoxetine; olanzapine > OFC; olanzapine > fluoxetine.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OAS-M = Modified Overt Aggression Scale, OFC = olanzapine-fluoxetine combination.

of borderline personality disorder. Interactions between treatment agent and time were not significant.

The mean dose at endpoint evaluation for fluoxetine-treated subjects was 15.0 mg (SD = 6.5 mg) (range, 10.0–30.0 mg), while the mean dose for olanzapine-treated subjects was 3.3 mg (SD = 1.8 mg) (range, 2.5–7.5 mg). For the OFC group, the mean dose of fluoxetine was 12.7 mg (SD = 5.9 mg) (range, 10.0–30.0 mg) and the mean dose of olanzapine was 3.2 mg (SD = 1.5 mg) (range, 2.5–7.5 mg). There were no significant differences in the doses of fluoxetine and olanzapine for those treated with monotherapy and those treated with OFC.

Mild sedation that ameliorated with time was common in all 3 study groups: fluoxetine (21.4%, N = 3), olanzapine (75.0%, N = 12), and OFC (46.7%, N = 7). However, a significantly higher percentage of those in the olanzapine group than the fluoxetine group (but not the OFC group) reported this side effect (χ^2 = 7.42, p = .0064). Mild akathisia as rated on the Barnes Akathisia Scale[18] was also found to be common (and about equally likely) among those in all 3 study groups: fluoxetine (35.7%, N = 5), olanzapine (25.0%, N = 4), and OFC (33.3%, N = 5). Importantly, no tardive dyskinesia or other serious movement disorders were observed.

In terms of weight, there were no significant between-group differences in baseline weight (or body mass index [BMI]). By the end of their participation, subjects in the fluoxetine group had gained a mean of 0.8 (SD = 5.0) lb (0.4 [SD = 2.3] kg; range, –15.0 to 6.0 lb [–6.8 to 2.7 kg]), subjects in the olanzapine group had gained a mean of 6.4 (SD = 5.8) lb (2.9 [SD = 2.6] kg; range, –1.0 to 16.0 lb [–0.5 to 7.2 kg]), and those in the OFC group had gained a mean of 3.0 (SD = 2.4) lb (1.4 [SD = 1.1] kg; range, 0 to 8.0 lb [0 to 3.6 kg]). Between-group comparisons revealed that those in the olanzapine group gained significantly more weight than those treated with fluoxetine alone (t = 2.83, df = 28, p = .0085) or OFC (t = 2.12, df = 29, p = .0430). Changes in BMI were also analyzed, and the results were similar to the changes in weight.

DISCUSSION

Two main findings have emerged from this study. The first is that olanzapine seems to be more effective than fluoxetine in treating the impulsive aggression and chronic dysphoria common among borderline patients. This finding is in general agreement with the earlier finding of Soloff and associates[4] concerning the greater efficacy of haloperidol versus amitriptyline. In both their study and the present study, an antipsychotic agent performed better than an antidepressant agent. However, it is important to note that the choice of class of antidepressant may be important, as Soloff and colleagues[5,6] and Cowdry and Gardner[7] found greater efficacy of an MAOI antidepressant versus a standard neuroleptic. Taken together, these findings seem to suggest that the heightened efficacy found in these studies for one type of psychotropic medication versus another may lie in the specific medications being studied rather than in the types of medication being compared.

The second finding is that OFC seems to be superior to fluoxetine (but not olanzapine) in both symptom areas studied. This is a new finding and suggests that combining an atypical antipsychotic and an SSRI, or at least this particular combination of medications, may lead to a greater reduction in both chronic dysphoria and impulsive aggression among borderline subjects than an SSRI, or at least fluoxetine, alone. However, the evidence in these data supporting polypharmacy is limited, as olanzapine was as effective as OFC in treating impulsive aggression and more effective than OFC in treating the dysphoria associated with borderline personality disorder.

One factor in making the decision whether to prescribe olanzapine or OFC for borderline patients not suffering from a major depressive episode might be the relative weight gain associated with these 2 compounds. Because subjects taking olanzapine alone gained about 6 lb (3 kg) and those taking OFC gained about 3 lb (1 kg), OFC may be a better choice if a borderline patient is particularly weight conscious. However, it should be noted that the actual weight gain in either case was relatively small. It should also be noted that this was a small-scale, preliminary study and its results may not be replicated by larger, more definitive studies. In addition, this was a relatively short study, and it would be very important to follow weight gain in similar subjects who took these agents for considerably longer periods of time.

One of the strengths of the current study is our high retention rate. We attribute this, in part, to our careful attention to the management of side effects in these particularly sensitive subjects. Our management strategy

involved the careful balancing of dosing for efficacy with the subjects' physical and emotional comfort throughout their participation in the study.

The current study has 2 limitations. The first is that there was no placebo group for comparison, particularly for OFC, which has never been compared with placebo in a study of borderline personality disorder. Second, the study was limited to women with borderline personality disorder, and there is no way of knowing if men with borderline personality disorder would have the same response pattern as the women in this study.

Taken together, the results of the study suggest that all 3 compounds studied appear to be safe and effective agents in the treatment of women with criteria-defined borderline personality disorder, significantly improving the chronic dysphoria and impulsive aggression common among borderline patients. However, olanzapine monotherapy and OFC seem to be superior to fluoxetine monotherapy in treating both of these dimensions of borderline psychopathology.

Drug names: amitriptyline (Elavil and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), phenelzine (Nardil), tranylcypromine (Parnate), trifluoperazine (Stelazine and others).

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