A Double-Blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Patients With Intermittent Explosive Disorder

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Background: Intermittent explosive disorder (IED) is a disorder of impulsive aggression that affects as many as 7.3% of the U.S. population during some period of life. Since central serotonergic (5-HT) system dysfunction is related to impulsive aggressive behavior, pharmacologic enhancement of 5-HT activity should reduce impulsive aggressive behavior in individuals with IED.

Method: A double-blind, randomized, placebo-controlled trial of the selective 5-HT uptake inhibitor fluoxetine was conducted in 100 individuals with IED (research diagnostic criteria) and current histories of impulsive aggressive behavior. The primary efficacy measure was the aggression score from the Overt Aggression Scale-Modified (OAS-M) for Outpatient Use. Secondary efficacy measures included the irritability score from the OAS-M and the Clinical Global Impressions-Improvement scale (CGI-I) score. The study took place between July 1990 and July 1999.

Results: Fluoxetine treatment resulted in a sustained reduction in OAS-M aggression, and OAS-M irritability scores, apparent as early as week 2 ($p < .01$ for aggression and $p < .001$ for irritability at endpoint). Fluoxetine was also superior to placebo in the proportion of responders on the CGI-I ($p < .001$). Closer examination of the data revealed that full or partial remission of impulsive aggressive behaviors, as reflected by the A criteria for IED, occurred in 46% of fluoxetine-treated subjects. Fluoxetine did not exert an antidepressant or antianxiety effect, and its effects on impulsive aggression were not influenced by presence of current symptoms of depression or anxiety.

Conclusion: Fluoxetine treatment has a clear antiaggressive effect in impulsive aggressive individuals with IED. However, while fluoxetine's antiaggressive effects appear robust, they lead to full or partial remission of IED in less than 50% of subjects treated with fluoxetine.

J Clin Psychiatry 2009;70(5):653–662

Received Feb. 19, 2008; accepted July 1, 2008. From the Clinical Neuroscience & Psychopharmacology Research Unit, Section on Translational and Molecular Neuroscience, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Illinois.

This project was supported in part by National Institute of Mental Health grants RO1MH47495 and KO2MH00951 (Dr. Coccaro) and by a grant from the Eli Lilly Research Laboratories. Eli Lilly also provided the study drug and placebo.

Fluoxetine plasma level assessments were performed under the supervision of Thomas B. Cooper, M.A., Analytic Psychopharmacology Laboratory, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y. Mr. Cooper reports no financial affiliations or other relationships relevant to the subject of this article.

Dr. Coccaro has been a consultant to Azevan. Dr. Kavoussi is an employee of GlaxoSmithKline. Dr. Lee reports no additional financial or other relationship relevant to the subject of this article.

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Intermittent explosive disorder (IED), in DSM-IV,[1] is characterized by recurrent episodes of serious aggressive outbursts that are out of proportion to psychosocial stressors/provocation and that are not better accounted for by another mental disorder, comorbid medical conditions, or the physiologic effects of a pharmacologic agent. Over the past several years, efforts to refine the DSM-IV IED criteria have resulted in IED research criteria that operationalize the type and frequency of aggression and the degree to which the aggressive behavior impacts on psychosocial function.[2,3] Current IED research criteria require the frequency of aggressive behavior to be at least 3 episodes of serious assault (or destruction of property) in a 1-year period, or at least 2 outbursts per week, for no less than 1 month, involving verbal aggression or aggression against objects.[3] These IED research criteria also require criteria-meeting aggressive episodes to be impulsive, as opposed to premeditated, in nature and require the aggressive behavior to be associated with significant psychosocial impairment and/or distress.

Using either DSM-IV or IED research criteria, recent epidemiologic data suggest that as many as 7.3% of the general population in the United States have IED over the course of their lifetime.[3,4] The most recent study[4] examined IED using broad (3 episodes over the lifetime) and narrow (3 episodes in a year) criteria and reports that individuals meeting narrow criteria (which are similar to the research criteria) for IED make up 5.4% of the population, lifetime, and display, on average, more than 27 aggressive outbursts per year. While DSM-IV does not formally

define relevant aggressive outbursts as impulsive, this epidemiologic study required the criterion aggressive acts to occur "all of a sudden" and, thus, be impulsive in nature.

Given that aggression, if not impulsive aggression, is the core feature of IED, pharmacologic treatment options should target the most likely biological target underlying aggression. Over the past 2 decades, multiple studies have replicated the finding that central serotonergic (5-HT) system dysfunction is related to aggression in both humans and in animal models of aggression.[5] In addition, treatment with selective serotonin reuptake inhibitors (SSRIs) can reduce impulsive aggression in human subjects with prominent histories of impulsive aggressive behavior. To date, at least 6 open-label[6–11] and 3 double-blind, placebo-controlled studies[12–14] show that SSRIs reduce aspects of impulsive aggressive behavior in selected psychiatric patients.

The present study reports on the results of a large (N = 100) double-blind, placebo-controlled, clinical trial designed to evaluate the antiaggressive efficacy of the SSRI, fluoxetine, in a group of nondepressed personality disordered individuals with prominent histories of impulsive aggression as defined by research criteria for IED.[15] We hypothesized that fluoxetine, compared with placebo, would reduce impulsive aggressive behavior in subjects with IED. We also hypothesized that fluoxetine treatment would be less likely to be associated with increases in aggression, over time, in individual subjects and that fluoxetine would be effective in producing remission of IED symptoms.

METHOD

Subjects

Male and female subjects with lifetime histories of problematic impulsive aggressive behavior were recruited either by outpatient referral or by self-referral in responses to public service announcements for clinical trials. To focus efforts on a defined clinical group, only subjects meeting DSM-IV criteria for personality disorder and defined histories of impulsive aggressive behavior were eligible for the study. Subjects with a lifetime history of mania or hypomania, schizophrenia, or delusional disorder; subjects with current major depression; or subjects currently dependent on alcohol or other drugs of abuse were excluded from study.

Written informed consent, using an institutional review board–approved consent document, was obtained from all subjects after all procedures were fully explained. Subjects fulfilling all entrance criteria (see Specific Study Entry Procedures) underwent a general physical/laboratory medical examination and a comprehensive psychiatric evaluation and, if eligible, continued on in the protocol (N = 100, see Specific Treatment Protocol). The study took place between July 1990 and July 1999.

Diagnostic and Medical Evaluation

Axis I and Axis II personality disorder diagnoses were made according to DSM-IV criteria. Diagnoses of alcoholism were made by modified research diagnostic criteria as previously described[16]; diagnoses of IED were made by IED research diagnostic criteria.[15] Semistructured interviews for the evaluation of Axis I and II disorders were conducted by experienced master's- or doctorate-level clinicians trained and supervised by research clinicians highly experienced in the administration of these assessments. Diagnoses were made using information from the following: (1) for Axis I disorders, semistructured interviews using the Schedule for Affective Disorders and Schizophrenia (SADS)[17] (modified to include modules for the diagnosis of DSM Axis I disorders not covered by the original SADS) or the Structured Clinical Interview for DSM-IV[18] Axis I disorders and, for Axis II disorders, the Structured Clinical Interview for DSM-IV Personality Disorders[19]; (2) clinical interview by a research psychiatrist; and (3) review of all other available clinical data. The semistructured interviews were conducted by experienced master's- or doctorate-level clinicians trained and supervised by research clinicians highly experienced in the administration of these assessments. Final diagnoses were assigned by team best-estimate consensus procedures[20,21] involving at least 2 research psychiatrists and 3 clinical psychologists as previously described.[14] This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone.[22]

General Study Design

This study was a 14-week, double-blind, randomized, placebo-controlled trial to evaluate the safety and antiaggressive efficacy of fluoxetine (20 to 60 mg p.o.) in personality disordered subjects with clinically significant histories of impulsive aggression. Eligible subjects, after screening, entered a 2-week placebo lead-in phase, after which subjects either were randomly assigned to fluoxetine or placebo or were discontinued from the study. Scores on the behavioral assessments obtained during this period served as a 2-week placebo-control baseline for these assessments. Randomly assigned subjects continued on in the protocol and received up to a 12-week course with fluoxetine (20 to 60 mg p.o. q.d.) or placebo (1 to 3 capsules p.o. q.d.) while undergoing the following behavioral assessments each week.

Assessment of Current and Lifetime History of Impulsive Aggressive Behavior, Clinical Response to Treatment, and Current History of Depressive and Anxiety Symptoms

Current history of impulsive aggression was assessed by weekly interview assessments for overt aggression and irritability (Overt Aggression Scale-Modified for

Outpatient Use [OAS-M]).[23,24] OAS-M aggression scores represent a weighted assessment of the frequency and severity of overt aggressive behavior for the past week (on a scale of 0 to > 999). OAS-M irritability scores represent the sum of subjective and overt irritability assessments (both on a scale of 0–5). Lifetime history of impulsive aggressive behaviors was assessed using the aggression score from the Lifetime History of Aggression[25] interview assessment (scale 0–25). Clinical response to treatment was also assessed with the research psychiatrist–rated Clinical Global Impressions-Improvement scale (CGI-I). This measure assesses improvement on a 7-point scale from "very much improved" to "no improvement" to "very much worse." Primary assessment of depressive and anxiety symptoms were assessed with the 21-item Hamilton Rating Scale for Depression[26] (HAM-D-21) and with the 14-item Hamilton Rating Scale for Anxiety[26] (HAM-A-14).

Specific Study Entry Procedures

This article reports on 2 similar sets of subjects studied by the same team at the same study site. Data from the first set of subjects, published previously,[14] included 40 men and women. For this group, screening criteria required a sufficiently elevated score on at least 2 subscales of a self-report questionnaire reflecting one's lifetime tendency toward aggression (Anger, Irritability, and Aggression Questionnaire [AIAQ][14,23]). Randomization criteria required sufficiently elevated mean scores on a state measure of overt aggressive behavior (OAS-M aggression score ≥ 15 and OAS-M irritability score ≥ 6) during a 2-week, single-blind, placebo lead-in phase following screening. OAS-M aggression scores ≥ 15 represent weekly behavior ranging from 15 verbal outbursts directed at others, 8 physical outbursts directed at objects, or 2 physical assaults against others. OAS-M irritability scores ≥ 6 represent at least a moderate degree of subjective (e.g., "often feeling angry") and overt irritability (e.g., "losing control of temper"). Interrater reliability for OAS-M aggression scores (intraclass correlation coefficient [ICC] > .90[14,23,24]) and for OAS-M irritability scores (ICC > .90[14,23]) is quite high.

Interim analysis of the data from the first 40 randomly assigned subjects revealed that these randomization criteria led to the dismissal of 24 (e.g., nearly 40%) otherwise qualified (i.e., AIAQ screen-positive) subjects who differed little from the randomized group with regard to a number of relevant variables (e.g., screening OAS-M aggression scores; physiologic responses to 5-HT agent [d-fenfluramine] challenge). This suggested that modification of entry criteria could allow for a greater number of appropriate subjects entering the clinical trial, increasing generalizability. The original screening criteria (i.e., elevated scores on the AIAQ) and randomization criteria (i.e., mean OAS-M aggression/irritability ≥ 15/6 during placebo lead-in phase) were replaced with a lifetime diagnosis of intermittent explosive disorder (IED by research criteria[15]) and a screening OAS-M aggression score ≥ 15, both determined on the subject's first visit. After meeting these criteria, the next 60 such eligible subjects entered an identical single-blind placebo lead-in phase to generate a 2-week placebo-control baseline for all measures but continued in the study regardless of their lead-in phase OAS-M scores. At the end of the study, analysis of the 2 study sets revealed no significant differences in basic demographic or diagnostic features and, most importantly, no significant differences in the treatment response to fluoxetine (i.e., examination of the full intent-to-treat data set at endpoint, as a function of study set ["first 40" vs. "second 60" subjects] and gender [male vs. female], using baseline scores as a covariate, revealed significant effects of fluoxetine on OAS-M aggression [ANCOVA $F = 7.86$, $df = 1,91$; $p = .006$] and irritability [ANCOVA $F = 9.86$, $df = 1,91$; $p = .002$] scores without significant drug–study-set interaction [ANCOVA $F = 0.02$, $df = 1,91$; $p = .881$ for OAS-M aggression; ANCOVA $F = 0.35$, $df = 1,91$; $p = .554$ for OAS-M irritability] or significant drug-gender interaction [ANCOVA $F = 0.25$, $df = 1,91$; $p = .621$ for OAS-M aggression; ANCOVA $F = 0.01$, $df = 1,91$; $p = .915$ for OAS-M irritability]; similar examination of responders revealed nearly identical fluoxetine and placebo response rates in the first 40 subjects [66.7% vs. 23.1%] and second 60 subjects [65.8% vs. 31.8%; Fisher exact test $p = .017$ and .016, respectively]) Accordingly, these samples were combined and all 100 subjects are included in the analyses below.

Specific Treatment Protocol

Including the first 40 subjects, a total of 100 subjects were randomly assigned to a 12-week treatment study with fluoxetine or placebo (intent-to-treat sample). Subjects were assigned to drug or placebo at a 2:1 ratio. Behavioral assessments, performed weekly, included the OAS-M aggression and OAS-M irritability scales; CGI-I, HAM-D-21, and HAM-A-14 rating scales were performed for assessment of current depressive and anxiety symptoms. All assessments were made blind to study assignment. OAS-M scores were determined by a trained behavioral assessor; all other assessments were performed by the research psychiatrist (R.J.K.). Plasma fluoxetine (and norfluoxetine) levels were assessed at weeks 4, 8, and 12 and assayed by liquid chromatographic method and fluorescence detection.[27] Plasma fluoxetine levels for at least one of these time points were available in 45 of 65 subjects randomly assigned to fluoxetine (69%). For the first 4 weeks of the double-blind treatment phase, the fluoxetine dose was set at 20 mg p.o. q.d. At the end of week 4 (or later), fluoxetine (or placebo) could be raised to 40 mg (2 placebo capsules) if the patient's average OAS-M aggression score for the previous 2 weeks had not decreased to

< 25% of the patient's average OAS-M aggression score during the placebo lead-in phase. Fluoxetine could be increased to a maximum of 60 mg q.d. (3 placebo capsules) again after week 8 if the average OAS-M aggression score for the previous 2 weeks still had not dropped to < 25% of the average OAS-M aggression score at randomization.

Statistical Analysis

The primary outcome variable for impulsive aggressive behavior in this trial was the mean OAS-M aggression score over successive 2-week windows (i.e., postrandomization weeks 1–2, 3–4, 5–6, 7–8, 9–10, and 11–12). Two-week windows were used because of the high intra-individual variability of OAS-M aggression scores. Since OAS-M aggression scores were not normally distributed, all scores were log-transformed. Secondary outcome variables included the mean OAS-M irritability score over similar 2-week windows and the physician-rated CGI-I at weeks 2, 4, 6, 8, 10, and 12. OAS-M irritability scores were also not normally distributed and were log-transformed. Response was defined as a CGI-I score of "much improved" or "very much improved" during the week in question. Tertiary outcome variables included HAM-D-21 and HAM-A-14 scores at weeks 2, 4, 6, 8, 10, and 12; both sets of scores were not normally distributed and were also log-transformed. The primary statistical procedure used was factorial analysis of covariance (ANCOVA) using the baseline score of the specific variable in question as covariate, with all available subjects at weeks 1–2, 3–4, 5–6, 7–8, 9–10, and 11–12. Endpoint (i.e., last observation carried forward) for all subjects and completer analyses were also performed. Other statistical procedures included t test (with correction for unequal variances where appropriate[28]), Pearson correlation, and χ^2 and Fisher exact test, where appropriate. Probability values were set at a 2-tailed α level of .05.

RESULTS

Demographic, behavioral, and diagnostic characteristics of the subject group as a whole (N = 100) and of those randomly assigned to fluoxetine (n = 65) and placebo (n = 35) are displayed in Table 1. There were no significant differences in any of these characteristics among fluoxetine or placebo subjects except for modestly higher HAM-D-21 and HAM-A-14 scores among placebo subjects, both in the low range of symptom severity. Despite modest baseline differences between the groups in HAM-D-21 and HAM-A-14 scores, neither score correlated with OAS-M aggression or OAS-M irritability scores at baseline or at endpoint.

Antiaggressive Effect of Fluoxetine

Fluoxetine treatment was associated with a lower OAS-M aggression score at each time point, with drug-placebo differences at, or trending toward, statistical significance: week 1–2 (F = 3.10, df = 1,97; p = .081), week 3–4 (F = 16.61, df = 1,85; p = .001), week 5–6 (F = 4.45, df = 1,77; p = .038), week 7–8 (F = 2.93, df = 1,67; p = .092), week 9–10 (F = 4.53, df = 1,58; p = .038), week 11–12 (F = 6.28, df = 1,52; p = .015), and at endpoint (F = 8.05, df = 1,97; p = .006) (Figure 1). Post hoc analyses revealed that fluoxetine's effect was present specifically for OAS-M "verbal aggression" (ANCOVA F for endpoint: F = 8.18, df = 1,97; p = .005) and "aggression against objects" (ANCOVA F for endpoint: F = 4.91, df = 1,97; p = .029) but not for "aggression against persons" (ANCOVA F for endpoint: F = 0.266, df = 1,97; p = .607). The scores for OAS-M "aggression against self," prior to and during the trial, were too low to analyze in the same manner.

Fluoxetine treatment was also associated with a significantly lower OAS-M irritability score at each time point: week 1–2 (F = 7.32, df = 1,97; p = .008), week 3–4 (F = 15.46, df = 1,85; p = .001), week 5–6 (F = 7.03, df = 1,77; p = .010), week 7–8 (F = 5.99, df = 1,67; p = .017), week 9–10 (F = 10.90, df = 1,58; p = .002), week 11–12 (F = 9.61, df = 1,52; p = .003), and at endpoint (F = 12.44, df = 1,97; p = .001), compared with placebo (Figure 2).

Effect of Fluoxetine on CGI-I Ratings: Responder Analysis

Using Fisher exact test, the proportion of visitwise responders among fluoxetine-treated subjects was greater than that for placebo-treated subjects at each time point, with drug-placebo differences at, or trending toward, statistical significance at week 4 (49.1% vs. 22.6%, p = .021), week 6 (66.0% vs. 40.7%, p = .053), week 8 (79.5% vs. 33.3%, p = .001), week 10 (83.3% vs. 42.9%, p = .003), week 12 (80.0% vs. 35.0%, p = .001), and at endpoint (66.2% vs. 28.6%, p < .001) (Figure 3).

Effect on Diagnosis of Intermittent Explosive Disorder

Despite large reductions in impulsive aggressive behavior in the trial, especially in fluoxetine responders (n = 43), less than half of the fluoxetine responders could be considered fully remitted with respect to the A criteria for IED at study completion or exit from study. Specifically, 44% of fluoxetine responders (19/43) reported no significant aggressive outbursts (e.g., verbal argument, temper tantrum, or assault on objects, others, or self) at time of study completion or exit; 26% (11/43) reported 1 significant aggressive outburst, and 33% (14/43) reported 2 or more significant aggressive outbursts at study completion or exit. Including all subjects treated with fluoxetine, the full remission rate in this study was 29% (19/65), and the full plus partial remission rate was 46% (30/65).

Table 1. Demographic, Behavioral, and Diagnostic Characteristics of Patients With Intermittent Explosive Disorder: All Subjects and as a Function of Randomization to Fluoxetine or Placebo[a]

Characteristic	All Subjects (N = 100)	Fluoxetine (N = 65)	Placebo (N = 35)	p Value[b]
Men, %	77	75	80	.80
Race, %				.51
White	85	86	83	
African American	13	12	11	
Other	3	2	6	
Age, mean ± SD, y	36.8 ± 8.7	37.7 ± 8.9	35.5 ± 8.1	.18
Function score (GAF), mean ± SD	56.2 ± 6.7	54.7 ± 7.5	57.1 ± 5.1	.35
LHA aggression score, mean ± SD	18.0 ± 5.2	17.7 ± 5.4	18.7 ± 5.0	.41
OAS-M aggression score (raw score), mean ± SD	47.5 ± 76.1	49.6 ± 90.0	43.6 ± 40.0	.56[c]
OAS-M irritability score (raw score), mean ± SD	6.1 ± 1.3	6.1 ± 1.3	6.0 ± 1.4	.58[c]
HAM-D-21 score (raw score), mean ± SD	4.9 ± 3.5	4.4 ± 3.4	5.7 ± 3.5	.04[c]
HAM-A-14 score (raw score), mean ± SD	4.4 ± 3.4	3.9 ± 3.2	5.2 ± 3.6	.06[c]
Current history of mood disorder	27 (27)	17 (26)	10 (29)	.82
Major depressive disorder	0 (0)	NA	NA	NA
Dysthymic disorder	12 (12)	6 (9)	6 (17)	.33
Depressive disorder-NOS	15 (15)	11 (17)	4 (11)	.57
Current history of anxiety disorder	17 (17)	13 (20)	4 (11)	.40
Lifetime history of mood disorder	58 (58)	37 (57)	21 (60)	.83
Major depressive disorder	24 (24)	15 (23)	9 (26)	.81
Dysthymic disorder	14 (14)	8 (12)	6 (17)	.55
Depressive disorder-NOS	24 (24)	16 (25)	8 (23)	.99
Lifetime history of anxiety disorder	25 (25)	19 (29)	6 (17)	.23
Lifetime history of alcoholism	35 (35)	22 (34)	13 (37)	.83
Lifetime history of drug dependence	27 (27)	15 (23)	12 (34)	.25
Axis II diagnosis				
Dramatic cluster	35 (35)	23 (35)	12 (34)	.99
Borderline	20 (20)	15 (23)	5 (14)	.43
Narcissistic	15 (15)	9 (14)	6 (17)	.77
Antisocial	12 (12)	8 (12)	4 (11)	.99
Histrionic	4 (4)	2 (3)	2 (6)	.61
Anxious cluster	28 (28)	19 (29)	9 (26)	.82
Obsessive-compulsive	26 (26)	17 (26)	9 (26)	.99
Avoidant	5 (5)	4 (6)	1 (3)	.66
Dependent	0 (0)	0 (0)	0 (0)	NA
Eccentric cluster	25 (25)	15 (23)	10 (29)	.63
Paranoid	24 (24)	14 (22)	10 (29)	.47
Schizoid	2 (2)	2 (3)	0 (0)	.54
Schizotypal	1 (1)	1 (2)	0 (0)	.99

[a]Values expressed as N (%) unless otherwise noted.
[b]p Value for the difference between fluoxetine- and placebo-treated subjects.
[c]Statistical testing performed with log-transformed values (see text).
Abbreviations: GAF = Global Assessment of Functioning, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, HAM-A-14 = 14-item Hamilton Rating Scale for Anxiety, LHA = Lifetime History of Aggression scale, NA = not applicable, NOS = not otherwise specified, OAS-M = Overt Aggression Scale-Modified for Outpatient Use.

Effect of Personality Disorder Diagnosis on Responses to Fluoxetine

Fluoxetine was effective in reducing OAS-M aggression scores in subjects without any interaction with personality disorder diagnosis (e.g., drug × personality disorder cluster interaction for endpoint OAS-M aggression score, cluster A: ANCOVA F = .00, df = 1,95; p = .99; cluster B: ANCOVA F = 0.27, df = 1,95; p = .61; cluster C: ANCOVA F =1.37, df = 1,95; p = .25).

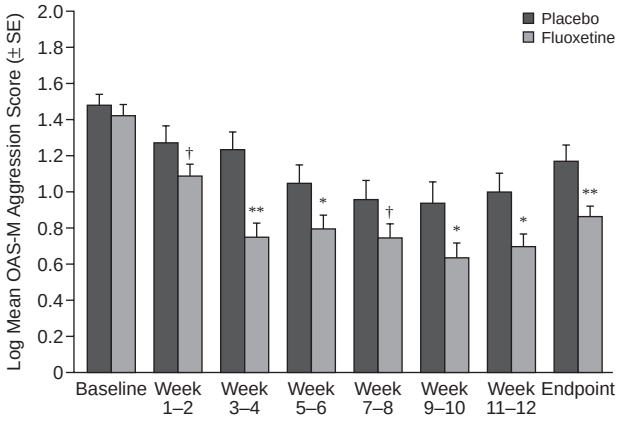
Effect of Fluoxetine on Current Levels of Depression and Anxiety

Fluoxetine had no effect on HAM-D-21 scores (ANCOVA F = 2.00, df = 1,97; p = .160 at endpoint; F = 1.59, df = 1,52; p = .213 for completers) or HAM-A-14 scores (ANCOVA F = 0.79, df = 1,97; p = .377 at endpoint; F = 1.75, df = 1,52; p = .191 for completers). ANCOVA analysis of OAS-M aggression and OAS-M irritability scores with both HAM-D-21 and HAM-A-14 scores as covariates continued to demonstrate fluoxetine superior to placebo at endpoint (ANCOVA F = 5.36, df = 1,95; p = .023 for OAS-M aggression; F = 8.05, df = 1,95; p = .006 for OAS-M irritability) and in completers (ANCOVA F = 4.42, df = 1,50; p = .041 for OAS-M aggression; F = 6.28, df = 1,50; p = .015 for OAS-M irritability).

Changes in Aggression in Individuals During Trial

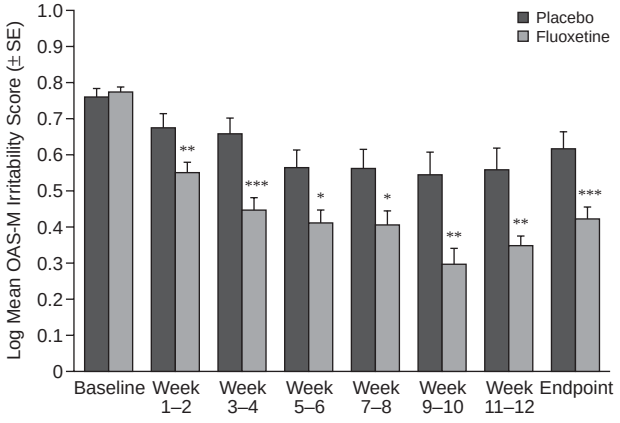
Up to about half (46 of 100: 46.0%) of subjects experienced some increase (i.e., any increase above baseline) in

Figure 1. Visitwise and Endpoint OAS-M Aggression Scores in Fluoxetine- and Placebo-Treated Subjects With Intermittent Explosive Disorder



†p < .10.
*p < .05.
**p < .01.
Abbreviation: OAS-M = Overt Aggression Scale-Modified for Outpatient Use.

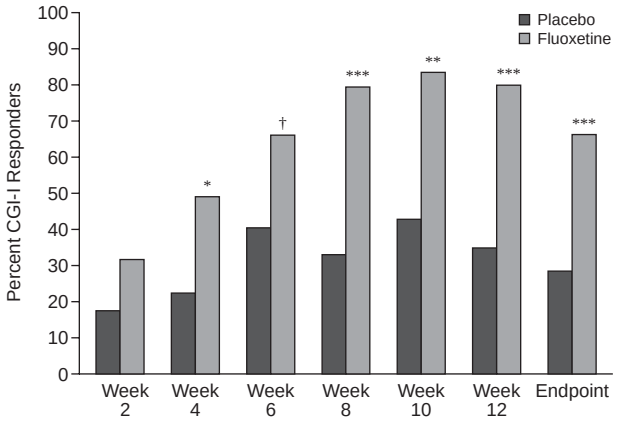
Figure 2. Visitwise and Endpoint OAS-M Irritability Scores in Fluoxetine- and Placebo-Treated Subjects With Intermittent Explosive Disorder



*p < .05.
**p < .01.
***p < .001.
Abbreviation: OAS-M = Overt Aggression Scale-Modified for Outpatient Use.

OAS-M aggression scores after beginning the fluoxetine or placebo arm of the trial. Increases in OAS-M aggression scores occurred more often in placebo-treated compared with fluoxetine-treated subjects (68.6% vs. 33.8%; Fisher exact test p = .001). The magnitude of these changes were also greater in the placebo-treated compared with fluoxetine-treated subjects (i.e., log OAS-M aggression change scores: 1.26 ± 0.56 vs. 0.92 ± 0.45, respectively, t = 2.24, df = 44, p = .03; n.b., raw OAS-M aggression change scores were 34.5 ± 40.0 and 13.5 ± 13.8, respectively). Increases in OAS-M aggression scores occurred most frequently at week 2 (21 of 46: 46%) regardless of treatment group (placebo: 10 of 24, 42% vs. fluoxetine: 11 of 22, 50%) and occurred less frequently as the trial progressed (week 4: 6 of 46, 13%; week 6: 6 of 46, 13%; week 8: 5 of 46, 11%; week 10: 5 of 46, 11%; week 12: 3 of 46, 7%). Despite increases in OAS-M aggression scores, the highest OAS-M aggression score occurred on a final visit in only a third of cases (8 of 24, 33% for placebo; 7 of 22, 32% for fluoxetine).

Figure 3. Visitwise and Endpoint Percent CGI-I Responder Status in Fluoxetine- and Placebo-Treated Subjects With Intermittent Explosive Disorder



†p < .10.
*p < .05.
**p < .01.
***p < .001.
Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

Fluoxetine Dosing and Plasma Levels of Fluoxetine and Norfluoxetine

Fluoxetine-treated subjects were assigned fewer study capsules than placebo-treated subjects at each of the 2 dosage-decision points (week 5: 1.3 ± 0.5 vs. 1.6 ± 0.5; t = 2.48, df = 78, p = .015; week 9: 1.7 ± 0.8 vs. 2.2 ± 0.8; t = 2.28, df = 59, p = .026) and at endpoint (1.5 ± 0.7 vs. 1.9 ± 0.9; t = 2.55, df = 98, p = .012). Mean total plasma levels of fluoxetine (including norfluoxetine) in subjects randomly assigned to fluoxetine were 169.2 ± 64.0 ng/mL at week 4 (n = 34); 293.4 ± 155.7 ng/mL at week 8 (n = 39); 354.2 ± 224.1 ng/mL at week 12 (n = 29); and 332.6 ± 219.3 ng/mL at endpoint (n = 45). Total fluoxetine plasma levels did not correlate with percent improvement in endpoint OAS-M measures either for the total group (r = 0.11, n = 45, p = .46 for OAS-M aggression; r = 0.08, n = 45, p = .60 for OAS-M irritability) or for fluoxetine responders (r = 0.16, n = 34, p = .38 for

Table 2. Frequency of Adverse Events During the Trial

Adverse Event	Fluoxetine (N = 65), N (%)	Placebo (N = 35), N (%)	p Value[a]
Any adverse event	38 (59)	17 (49)	.402
Specific adverse event[b]			
Sexual dysfunction	17 (26)	2 (6)	.015
Sleep disturbance	14 (22)	1 (3)	.017
Nausea/vomiting	14 (22)	1 (3)	.017
Jitteriness/restlessness	14 (22)	2 (6)	.047
Appetite disturbance	14 (22)	3 (9)	.161
Diarrhea	10 (15)	3 (9)	.534
Rash	5 (8)	0 (0)	.159
Dry mouth	1 (2)	0 (0)	.999
Indigestion	4 (6)	3 (9)	.693
Fatigue	13 (20)	8 (23)	.799
Headache	13 (20)	8 (23)	.799

[a]By Fisher exact test.
[b]In order of largest to smallest drug-placebo difference.

OAS-M aggression; r = 0.13, n = 34, p = .48 for OAS-M irritability).

Adverse Events

As shown in Table 2, a non-significantly greater frequency of any adverse event was reported by fluoxetine-treated compared with placebo-treated subjects (38 of 65, 59% for fluoxetine vs. 17 of 35, 49% for placebo; Fisher exact test p = .184). Further examination of specific adverse events revealed significantly greater frequencies of sexual dysfunction, sleep disturbance, nausea/vomiting, and jitteriness/restlessness among fluoxetine-treated subjects (Table 2). Overall, adverse events were of mild to moderate severity and specifically led to withdrawal from the study in only 4 cases, all fluoxetine-treated subjects. No fluoxetine-treated subjects reported an increase in suicidal ideation.

Study Retention and Reasons for Study Withdrawal

Study retention as a function of treatment condition was similar throughout the trial (fluoxetine/placebo after week 2: 88%/97%; week 4: 82%/89%; week 6: 77%/77%; week 8: 68%/66%; week 10: 55%/60%; and week 12: 54%/57%). Four subjects withdrew due to adverse events (all fluoxetine), 3 were withdrawn due to noncompliance with the protocol (fluoxetine: n = 1; placebo: n = 2), 11 withdrew due to lack of efficacy (fluoxetine: n = 3; placebo: n = 8), and 27 discontinued participation without further explanation and were subsequently lost to follow-up (fluoxetine: n = 22; placebo: n = 5). Subjects lost to follow-up (n = 27) did not differ significantly from study completers (n = 55) with respect to mean baseline log OAS-M aggression scores at randomization (lost to follow-up: 1.49 ± 0.53 vs. completers: 1.39 ± 0.37; t = 1.00, df = 80, p = .324), gender (% Male: 77.8% vs. 81.8%, Fisher exact test p = .769), or drug condition (% fluoxetine: 81.5% vs. 63.6%, Fisher exact test p = .128).

Differences Between Responders and Nonresponders Treated With Fluoxetine

Fluoxetine responders were similar to fluoxetine nonresponders in most respects except that responders remained in the trial longer than nonresponders (9.9 ± 3.3 weeks vs. 6.5 ± 4.7 weeks, t = 3.44, df = 32,41; p = .004) and tended to have lower total plasma fluoxetine levels than nonresponders (e.g., at endpoint: 296.8 ± 184.0 ng/mL vs. 443.1 ± 286.4 ng/mL; t = 1.98, df = 43, p = .053). Despite the trend toward lower total fluoxetine plasma levels among responders, daily fluoxetine dosage among the groups was virtually the same (i.e., fluoxetine dosage at endpoint: 29.8 ± 12.6 mg p.o. q.d. for responders vs. 32.7 ± 15.8 mg p.o. q.d. for nonresponders; t = 0.82, df = 63, p = .415). Notably, overall adverse events were non-significantly more frequent among responders than among nonresponders in the fluoxetine group (28 of 43: 65% vs. 10 of 22: 46%; p = .184).

DISCUSSION

The primary finding in this study is that treatment with fluoxetine, compared with placebo, is associated with a statistically significant reduction in impulsive aggressive behavior in personality disordered individuals with intermittent explosive disorder. This effect was present across 3 assessment measures: number and severity of impulsive aggressive events (OAS-M aggression), global severity of impulsive aggressive behavior (OAS-M irritability), and global response to treatment (CGI-I). Fluoxetine's antiaggressive effect was present regardless of type of comorbid personality disorder and occurred in the absence of any effect of fluoxetine on the relatively low levels of state depression or anxiety during the trial; baseline levels of state depression or anxiety also did not impact fluoxetine's efficacy on impulsive aggressive behavior in this trial.

Fluoxetine's effect on impulsive aggressive behavior in these subjects was most pronounced on measures of verbal aggression and aggression against objects. A significant effect was not seen on aggression against others or self, but these kinds of behaviors were much less frequent in these subjects over the course of this trial. Regardless, verbal aggression and aggression against objects are correlated with, and are typically precursors to, aggression against others. Accordingly, reductions in these forms of aggression may well reduce the risk of aggression against others, even if not observed in the context of this short clinical trial. Finally, efficacy of fluoxetine in the treatment of verbal aggression and aggression against objects (especially "nondestructive" aggression against objects in which objects are not damaged) also provides treatment-response validity for including these forms of aggression in the diagnosis of IED for DSM-V.

Fluoxetine responders differed little from nonresponders in most respects except that responders remained

in the study nearly three and a half weeks longer than nonresponders and that they tended to have lower fluoxetine levels than nonresponders. Since fluoxetine levels did not demonstrate any correlation with OAS-M scores, the most important difference between fluoxetine responders and nonresponders may be length of time in the study. Despite this, it is unknown whether efforts to keep subjects in treatment would have been associated with a greater response rate to fluoxetine. The observation that nonresponders, compared with responders, tended to have higher fluoxetine levels is important because it indicates that nonresponse was not due to insufficient fluoxetine exposure and that higher doses of fluoxetine are not likely to affect response and probably are not indicated in the clinical setting. It is possible, however, that higher fluoxetine levels may have led to greater side effects leading to early study discontinuation. While only 6% of fluoxetine-treated subjects discontinued the study explicitly due to adverse events, several others may have chosen to exit the study due to "unstated" physical discomfort while on fluoxetine treatment; note that nearly three quarters of all fluoxetine dropouts (22 of 30) left the study without any stated reason.

The magnitude of fluoxetine's antiaggressive effect on number and frequency, and global severity, of impulsive aggressive events in this study was of at least moderate size, at endpoint, ranging from 0.51 (OAS-M aggression) to 0.66 (OAS-M irritability) standard deviations. Accordingly, fluoxetine treatment is associated with a clinically meaningful antiaggressive effect as has been suggested by previous studies.[12,13] However, closer examination of other clinically meaningful variables suggests that fluoxetine's antiaggressive effect may be more modest and variable than apparent from symptom severity scores alone. Most importantly, only 44% of fluoxetine responders had reached a point of full remission from IED (i.e., no aggressive outbursts) at endpoint, with an additional 23% being in partial remission (i.e., only 1 aggressive outburst) at endpoint. Considering all fluoxetine-treated subjects in the study, only 29% had reached a full remission and only 46% had reached a full or partial remission from IED by endpoint. While the overall results are encouraging, fluoxetine should not be considered a "magic-bullet" for the treatment of impulsive aggression in IED. Other agents and modalities will be needed for the successful treatment of most individuals with IED or with problematic histories of impulsive aggression. Other possible agents include mood stabilizers[29,30] and atypical neuroleptics[31,32]; other modalities include cognitive-behavioral therapies tailored for the treatment of recurrent, problematic, impulsive aggression or IED.[33]

Contrary to the concern raised by some anecdotal reports,[34] fluoxetine treatment was not associated with a greater increase of aggression beyond what would be seen with placebo. Increases of aggression, in this study, were most likely seen in the first 2 weeks after randomization and were twice as often observed in placebo-treated subjects compared to fluoxetine-treated subjects. The magnitude of the OAS-M increase was also about twice as large in placebo-treated subjects. Accordingly, these data do not support the idea that an SSRI will increase impulsive aggression, even in subjects with substantial histories of this behavior. These data do suggest that an increase in impulsive aggressive behavior may be observed in impulsive aggressive subjects soon after any type of antiaggressive treatment is begun, and so one must always be alert to an increase in this behavior, even when the treatment might ultimately be effective in reducing this behavior.

Overall, these data are consistent with other placebo-controlled studies using fluoxetine to treat impulsive aggressive behavior in a variety of similar types of patients, such as those with borderline personality disorder[13] or major depression with anger attacks.[11] One recent study using fluvoxamine in the treatment of borderline personality disorder, however, did not note a drug-placebo effect on aggression,[35] although the study measure used in that study was not comparable to the outcome measure in the present study. The present data are also consistent with clinical psychobiological data suggesting an inverse relationship between impulsive aggression and serotonin system function and with animal data demonstrating that fluoxetine treatment reduces aggressive responding in animal models of aggression, presumably through behavioral inhibition.[5] Consistent with these data is a recent study that demonstrated a fluoxetine-associated increase in relative metabolic activity in the prefrontal cortex of individuals with impulsive aggression who met the criteria for IED as did the subjects in this study.[36] If so, increasing neuronal activity in this brain region, long associated with behavioral inhibition, may underlie the increased inhibition of observed aggressive responding in individuals with IED.

As with many psychopharmacologic trials in these types of subjects, these results should be interpreted with some caution. First, while the number of subjects in this study is the greatest for any antiaggression study utilizing an SSRI to date, the results would need to be replicated in this specific type of clinical population before a formal indication for fluoxetine as an antiaggressive agent in IED could be considered. Second, only somewhat more than half of fluoxetine-treated subjects completed the trial, and this further reduces the sample size upon which to generalize the results. However, an equal number of subjects treated with placebo also dropped out of the study, suggesting that attrition in this trial was more likely due to the unstable interpersonal natures of the subjects, characteristics that make them a particularly difficult population to treat clinically in general. Third, the recruitment of IED subjects from the community, as described, may limit the generalizability of these findings to IED subjects that

come forward for treatment. However, most individuals with IED do not seek clinical treatment for this disorder at this time, and most clinicians do not focus their treatment on IED even when it is present.[4,37] In addition, since all IED subjects in this study also had a personality disorder, it is unknown how IED subjects without a personality disorder would respond to fluoxetine. This may be less of a limitation, however, given that most IED subjects meet at least general criteria for a personality disorder. Finally, the change in entry criteria, after interim analysis, may have affected these results. The changes in entry criteria were largely made to make this trial consistent with most other psychopharmacologic trials in which entry depends on a diagnosis and a beginning level of severity. All subjects in the first-40 group met criteria for IED and met the initial severity threshold for OAS-M aggression score. The only significant change in entry criteria, then, allowed all subjects to be randomly assigned even if their OAS-M aggression score dropped below the initial threshold score (i.e., < 15) at the end of the placebo lead-in period. Examination of all subjects, however, demonstrated no difference in drug-placebo responses on the basis of how subjects entered the study, indicating that the change in this entry criterion had little effect on the outcome of this trial.

In summary, fluoxetine treatment has a clear antiaggressive effect in impulsive aggressive individuals with IED. The effect is not due to any potential effect on mood or anxiety. Importantly, fluoxetine does not appear to increase aggressive behaviors relative to placebo. The drug is reasonably well tolerated, compared with placebo, although there are some SSRI-class effects appearing in excess in fluoxetine-treated subjects. Overall, fluoxetine's antiaggressive effects appear robust, although they may lead to full, or partial, remission of IED in less than 50% of subjects treated with fluoxetine. Additional strategies for treating impulsive aggressive behavior in individuals with IED, including the use of other agents and other nondrug modalities, are warranted.

Drug names: fluoxetine (Prozac and others), fluvoxamine (Luvox and others).

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