Impulsive Aggressive Behavior: Open-Label Treatment With Citalopram

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Background: Results from open-label and placebo-controlled trials suggest that the selective serotonin reuptake inhibitors reduce impulsive aggressive behavior. The objective of this open-label study was to investigate whether citalopram treatment has anti-aggressive effect on impulsive aggressive subjects meeting DSM-IV criteria for a cluster B personality disorder or intermittent explosive disorder.

Method: In this 8-week trial, subjects were initiated on 20 mg/day of citalopram and titrated up to 60 mg/day by the fourth week, if tolerated. The primary outcome measure was the Overt Aggression Scale-Modified (OAS-M), a scale used to quantify verbal and physical aggression, subjective irritability, and overt irritability. Secondary outcome measures included the Barratt Impulsiveness Scale and Buss-Durkee Hostility Inventory.

Results: Of 25 subjects enrolled, 20 completed the study. The mean daily dose was 45.5 mg, and citalopram was generally well tolerated. Statistically significant decreases were found in the OAS-M aggression scores (32.82 ± 19.76 to 4.73 ± 7.57, p = .000), subjective irritability scores (3.50 ± 0.60 to 1.45 ± 1.18, p = .000), and overt irritability scores (3.23 ± 0.81 to 0.91 ± 1.02, p = .000).

Conclusion: These results suggest that citalopram is an effective treatment for reducing impulsive aggressive behavior.

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A large body of literature now exists indicating that disturbances of central serotonin (5-HT) function have an important role in suicidal behavior, aggression, and other personality traits that are characterized by impulsivity. Psychiatric disorders such as obsessive-compulsive disorder, eating disorders, paraphilias, and the unclassified impulse control disorders (intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania) also have common features involving impulse control problems and appear to be associated with serotonergic dysfunction. Research over the past 20 years provides evidence for a strong link between these 2 features. The finding of reduced indices of 5-HT function in individuals who prominently exhibit impulsive behavior has led to the view that behavioral restraint is an important role of the serotonin system.

Depue and Spoont[1] proposed the existence of 2 systems that oppose each other in modulating behavior. The behavioral facilitation system is related to specific behavioral patterns of positive engagement (e.g., incentive reward) with the environment. It involves the mesolimbic dopamine (DA) tracts, which originate in the ventral tegmental area and terminate in the nucleus accumbens (NAc), and inhibits a series of GABA neurons, resulting in releasing the globus pallidus from normal tonic inhibition. The complementary behavioral inhibition system is composed of median raphe 5-HT neurons that terminate on the septohippocampal region. The behavioral inhibition system functions in a "just checking" mode, alert for signals of non-reward, punishment, or uncertainty (affective correlates are frustration, fear, and anxiety). The inhibitory DA pathway to GABA neurons in the NAc is itself inhibited by increased 5-HT, facilitating the GABAergic inhibitory activities as a result. In animals, low 5-HT conditions result in behavior described as hyperirritable, hyperexcitable, and hypersensitive. Lesions of raphe nuclei (where 5-HT neurons originate) are known to produce unusually high aggressiveness and irritability in rats.

Other pharmacologic manipulations have been shown to support this model. Amphetamine-induced locomotion is attenuated by tryptophan, 5-HT, or 5-hydroxytryptophan (5-HTP) and is potentiated by lesions of raphe nuclei, *p*-chlorophenylalanine (PCPA; inhibitor of 5-HT synthesis), or 5-HT antagonists. Lesions of the median raphe are

associated with increased locomotor activity to DA agonists that can be attenuated by direct injection of 5-HT into the NAc. A number of human studies have extended this work. For example, the orbital-prefrontal region inhibits limbic and other subcortical regions involved in the modulation of aggression. Reduced prefrontal cortical activity has been reported in a number of subject groups with impulsive aggression (for review, see Siever et al.[2]). In a recent study,[2] impulsive aggressive subjects showed blunted activation ([^{18}F]fluorodeoxyglucose positron emission tomography [FDG-PET]) of this region compared with controls following fenfluramine challenge, consistent with reduced serotonergic modulation.

TREATMENT STUDIES

Various agents may have efficacy in moderating impulsive and aggressive behavior in humans.[3–6] These include lithium, carbamazepine, selective serotonin reuptake inhibitors (SSRIs), β-blockers, fenfluramine, buspirone, and tryptophan. Other agents without prominent 5-HT actions, such as antipsychotics, other anticonvulsants, and anxiolytics, may have nonspecific effects that also lead to a reduction of impulsive behavior. Most of the more recent work, however, has focused on SSRIs and valproate.

Markovitz et al.[7] studied 22 patients with personality disorders prospectively in an open-label treatment with fluoxetine, titrated to a maximum of 80 mg/day. By week 12, the number of self-destructive physical acts had decreased by 74%. Similarly, Kavoussi et al.[4] conducted an 8-week open-label trial of sertraline in 11 patients with personality disorder and demonstrated that the treatment significantly decreased both irritability and aggression, as measured by the Overt Aggression Scale-Modified (OAS-M), by week 4. This kind of response with the SSRI treatment was also seen in a double-blind, placebo-controlled study. Coccaro and Kavoussi[3] conducted a 12-week study of fluoxetine in 40 patients with personality disorder in a double-blind, placebo-controlled fashion. By the end of the study, patients treated with fluoxetine showed significantly lower scores on the OAS-M aggression and irritability scores than patients treated with placebo.

Positive results have also been reported from recent trials of SSRIs for both pathological gambling[8,9] and compulsive shopping.[10] For example, a placebo-controlled study suggested fluvoxamine to be efficacious in the treatment of pathological gambling, a disorder also characterized by poor impulse control.[8]

Despite the abundant evidence for the relationship of serotonin and impulsivity, the number of clinical trials is limited. Therefore, the present pilot study was designed to examine whether citalopram, an SSRI, could reduce impulsive aggressive behavior in subjects with cluster B personality disorder or intermittent explosive disorder.

METHOD

Subjects

The study was approved by the Human Subjects Subcommittee of the Veterans Affairs Long Beach Healthcare System (Long Beach, Calif.). Subjects were recruited primarily through print advertising in local newspapers. The nature of the advertisement was to target individuals who perceived themselves as having problems with anger control to the point that there was a negative impact on interpersonal and/or occupational functioning. After signing informed consent, subjects were screened for eligibility. To be included in the study, subjects were required to meet DSM-IV criteria for either cluster B personality disorder (borderline, narcissistic, antisocial, or histrionic) or intermittent explosive disorder. Baseline laboratory values were required to be within normal limits or, in the judgment of the investigator, clinically insignificant. All subjects were required to score at least 15 on the aggression subscale of the OAS-M.[11] Subjects were excluded if they had a (1) history of significant cardiovascular, endocrinologic, or neurologic disease; (2) current unstable medical illness or significant abnormal laboratory function; (3) urine drug screen positive for stimulants, phencyclidine hydrochloride (PCP), or opiates; (4) greater than moderate (12 oz/week) use of alcohol; (5) history of psychotic disorder, bipolar disorder, obsessive-compulsive disorder, posttraumatic stress disorder, organic mental disorder, or present major depression; (6) treatment within the past month with antidepressant or antipsychotic medication; or (7) history of serious physical assault. Furthermore, subjects were excluded if they had pending legal actions of any kind.

Baseline Evaluation

All subjects received a medical and psychiatric history evaluation, physical examination, and laboratory studies (chem-20, thyroid function, complete blood cell [CBC] count, urinalysis, urine drug screen) before entering the treatment phase. Rating scales administered at baseline included the OAS-M, Barratt Impulsivity Scale (BIS-11),[12] Buss-Durkee Hostility Inventory (BDHI),[13] and Montgomery-Asberg Depression Rating Scale (MADRS).[14] Psychiatric diagnosis was established through use of the Structured Clinical Interview for DSM-IV (SCID-I and -II).[15]

Treatment

Following the baseline evaluation, subjects were started on 20 mg/day of citalopram given in the morning. Medication was increased weekly, as tolerated, to a maximum dose of 60 mg/day. Since treatment of impulsive aggression is not very well studied, the dose of 60 mg/day was chosen to avoid the possibility of underdosing. In the event that side effects were encoun-

tered, the dose was reduced to the previously tolerated level or not increased at the investigator's discretion. Subjects were evaluated weekly in an outpatient setting for the first 4 weeks of the treatment and every 2 weeks thereafter. All subjects remained on a fixed dose of citalopram for weeks 5 through 8. The OAS-M and MADRS were completed at each visit in addition to inquiry of medication side effects. The BIS-11 was completed at week 4 and at termination; the BDHI was completed at termination.

Statistical Analysis

For all scales, analyses were preformed on subjects who completed at least 4 weeks of dosing (see Results). The intent-to-treat method, with the last observation carried forward, was used for all efficacy analyses. To test the effectiveness of citalopram, dependent-samples t tests were performed on all rating scales. This method was utilized due to the variability in scaling among the subscales, which precluded between-subscale mean comparisons. To further investigate changes in subscale scores, multiple dependent-samples t tests were performed with an α adjusted by the Bonferroni method of correction. The primary outcome measure was the OAS-M rating scale score at study termination.

RESULTS

Twenty-five subjects (17 males and 8 females) with a mean age of 37.9 years were enrolled and included 10 veterans and 15 non-veterans. The most common diagnosis was borderline personality disorder (N = 12), followed by intermittent explosive disorder (N = 8) and personality disorder NOS (N = 4; these subjects all had prominent features of borderline personality disorder). Aggressive behavior was typically mild to moderate and most commonly included verbal outbursts, slamming doors or telephones, punching walls, and hostile gesturing toward others. Less common was physical assault against others. Past psychiatric history was significant in these subjects: 11 with prior substance abuse, 10 with depression, and 7 with histories of either suicide attempts or self-injurious behavior. Moreover, 13 subjects had prior arrest; 8 of whom were incarcerated. Fourteen subjects reported prior psychiatric treatment; 6 of whom had received specific treatment for their anger problems.

Seventeen subjects completed the entire protocol, and an additional 3 subjects completed all but the last visit, creating an evaluable pool of 20 subjects. Five subjects completed less than 4 weeks of the treatment and were excluded from the analysis. Of these 5, 1 discontinued because of medication side effects, and the remainder were lost to follow-up. For these subjects, the reasons for discontinuation were not known. For the 20 evaluable subjects, the mean daily dose of citalopram was 45.5 mg.

Table 1. Mean ± SD Rating Scale Scores in 20 Citalopram-Treated Subjects With Cluster B Personality Disorder or Intermittent Explosive Disorder

	Baseline	Last Observation	p Value
OAS-M			
Aggression	32.82 ± 19.76	4.73 ± 7.57	.000*
Subjective irritability	3.50 ± 0.60	1.45 ± 1.18	.000*
Overt irritability	3.23 ± 0.81	0.91 ± 1.02	.000*
BIS-11			
Total	75.00 ± 12.06	62.70 ± 17.93	.007*
Nonplanning impulsiveness	28.40 ± 6.75	23.90 ± 6.75	.005***
Motor impulsiveness	25.20 ± 4.95	22.00 ± 5.85	.035
Cognitive impulsiveness	21.40 ± 3.98	17.75 ± 4.53	.002***
BDHI			
Total	52.88 ± 9.57	36.82 ± 17.42	.001*
Assault	8.94 ± 9.80	7.11 ± 10.29	.029
Indirect hostility	7.35 ± 1.84	5.29 ± 2.36	.001**
Irritability	9.12 ± 1.58	5.29 ± 3.18	.000**
Negativism	3.12 ± 1.58	2.12 ± 1.83	.027
Resentment	5.12 ± 2.26	2.94 ± 2.44	.001**
Suspicion	5.35 ± 1.90	4.23 ± 2.61	.070
Verbal hostility	10.12 ± 2.32	7.53 ± 3.24	.003**
Guilt	6.00 ± 2.03	4.65 ± 2.74	.030

*Significant at $\alpha = .05$.
**Significant at $\alpha = .006$.
***Significant at $\alpha = .016$.
Abbreviations: BDHI = Buss-Durkee Hostility Inventory, BIS-11 = Barratt Impulsiveness Scale, OAS-M = Overt Aggression Scale-Modified.

A summary of baseline and end-of-treatment rating scale scores is provided in Table 1. The OAS-M rating scale is composed of 3 components: total aggression score, subjective irritability score, and overt irritability score. The α for each analysis was set at .05. As shown in Table 1, reductions were observed in all 3 components. Figures 1 and 2 show the mean scores for total aggression and subjective irritability. As can be appreciated, there was a rapid but sustained decrease in both of these measures.

Similarly, the BDHI total score also showed a significant reduction following the treatment ($t = 4.30$, $df = 16$, $p = .001$). With α set at .006, significant decreases in indirect hostility ($t = 4.15$, $df = 16$, $p = .001$), irritability ($t = 4.75$, $df = 16$, $p = .000$), resentment ($t = 3.91$, $df = 16$, $p = .001$), and verbal hostility ($t = 3.438$, $df = 16$, $p = .003$) were observed, but not in assault ($t = 2.39$, $df = 16$, $p = .029$), negativism ($t = 2.43$, $df = 16$, $p = .027$), suspicion ($t = 1.97$, $df = 16$, $p = .070$), or guilt ($t = 2.38$, $df = 16$, $p = .030$).

A significant decrease in the BIS-11 total score was also observed ($t = 3.02$, $df = 19$, $p = .007$). Further investigation of the subscales with the α set at .016 showed significant decreases in nonplanning impulsiveness ($t = 3.16$, $df = 19$, $p = .005$) and cognitive impulsiveness ($t = 3.65$, $df = 19$, $p = .002$), but not in motor impulsiveness ($t = 2.27$, $df = 19$, $p = .035$).

Although no subjects met criteria for major depression, mild depressive symptoms were not uncommon among these subjects. The mean MADRS score at entry was

Figure 1. Mean ± SD for the Overt Aggression Scale-Modified Total Aggression Score at Corresponding Weeks of Treatment (N = 20)

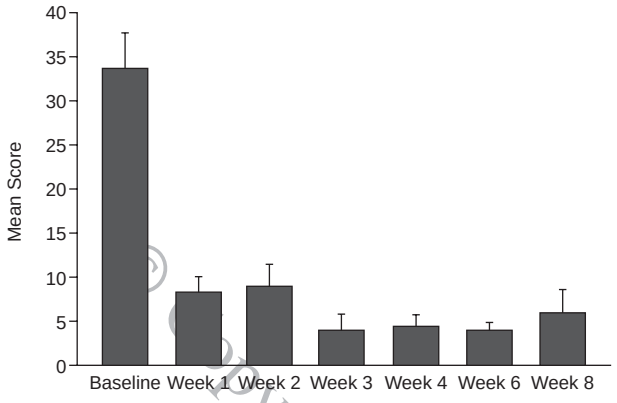
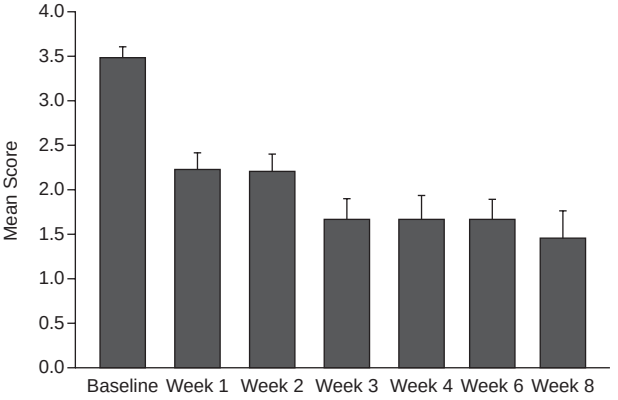


Figure 2. Mean ± SD for the Overt Aggression Scale-Modified Global Subjective Irritability Score at Corresponding Weeks of Treatment (N = 20)



11.86 ± 8.03. This was reduced to 4.27 ± 5.57 at study endpoint (t = 3.47, df = 21, p = .002). There was no relationship between baseline depression and measures of aggression or impulsivity, respectively.

Citalopram was well tolerated in this study. The most common side effect was sexual dysfunction (N = 9, 36% of subjects) followed by gastrointestinal symptoms (N = 6, 24%) and sedation (N = 5, 20%). Sexual side effects occurred more frequently in males (8/17, 47%) compared with females (1/8, 12.5%). The majority of sexual side effects remitted with dose reduction or time but persisted in 4 subjects (16%, 3 males, 1 female). Of note is that for subjects who completed the study, sexual side effects persisted in only 1 subject. An overall mean decrease in weight of 1.9 lb (0.85 kg) was also observed by the end of the study.

DISCUSSION

The present study offers preliminary support for the effectiveness of citalopram for reducing impulsive aggressive behavior in subjects with a diagnosis of borderline personality disorder or intermittent explosive disorder. A rapid decrease in the OAS-M scores was observed by the second week of citalopram treatment, which was sustained throughout the remainder of the study. This pattern of response was also observed in a study by Coccaro and Kavoussi,[3] who treated impulsive aggressive subjects with fluoxetine in a double-blind, placebo-controlled fashion. In their study, a similar early response was noted for both the fluoxetine and placebo groups. The placebo group, however, showed an increase in OAS-M scores after week 4 with significant separation from the treatment group. This finding is suggestive of the presence of a "monitoring effect" in the early phase of the treatment. In addition to improvement on the OAS-M instrument, the total hostility scale of the BDHI and the subscales related to hostility and irritability also showed significant reductions. This observation is consistent with another study in which fluoxetine reduced subjective anger in borderline patients.[16]

Of note were the reductions in the BIS-11 scores, which were believed to reflect trait characteristics of the subjects and, therefore, should have remained stable over time. This may reflect a primary effect of the medication treatment. Alternatively, this may be reflecting a heightened cognitive awareness in the subjects as a consequence of completing weekly behavioral evaluations. This conclusion is supported by the observation that the cognitive impulsivity and nonplanning subscales, but not the motor impulsivity subscale of the BIS-11, showed significant decreases after the treatment.

Of relevance to the conceptualization of impulsive behavior as one mediated by serotonin, it is important to consider the observations of this study as being a consequence of nonspecific antidepressant effects. The decreases in OAS-M measures, however, were of similar magnitude in those patients with and without depressive symptoms, and similar findings (i.e., reduction in aggression by SSRI treatments was independent of changes in depression) were also reported by the previously mentioned studies. Future studies, therefore, should compare the antiaggressive effects of serotonergic antidepressants with those with non-serotonergic mechanisms. In addition, in order to discern monitoring effects from treatment effects, a double-blind, placebo-controlled design is necessary.

Drug names: buspirone (BuSpar and others), carbamazepine (Tegretol and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), sertraline (Zoloft), valproate (Depacon).

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