Paroxetine Treatment of Episodic Rages Associated With Tourette's Disorder

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Background: Episodic rages have been estimated to occur in as many as 30% of patients with Tourette's syndrome (Tourette's disorder), but their treatment has never been systematically investigated. We report on the results of an open-label pilot study using paroxetine for the treatment of Tourette's disorder–associated rage episodes.

Method: Forty-five Tourette's/rage patients (DSM-IV) were treated with paroxetine, specifically to control their rages. Other symptoms such as tics, attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) were not targeted by this study. Treatment was deemed to be therapeutic when rage symptoms were diminished by 75% or more by patient report and were diminished in frequency by at least 1 point on a 4-point scale devised by the authors.

Results: After 8 weeks on paroxetine treatment, 29 patients (76% of those who completed the study) reported that rages were significantly diminished or completely absent. Nine patients reported no significant change in rages. Seven patients did not complete the study (3 because of side effects and 4 whose rage frequency increased). The mean dose of paroxetine was 33 mg/day; minimum effective dose was 15 mg/day.

Conclusion: We were unable to determine any factors that significantly altered the efficacy of paroxetine for treatment of Tourette's disorder–associated rage episodes. The great majority (87%) of the patients had both ADHD and OCD in addition to Tourette's disorder. The age, sex, and concomitant use of other medications revealed no significant differences in treatment outcome. The results suggest that paroxetine may have an important role in the clinical treatment of episodic rages in Tourette's disorder patients.

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Over the past decade there has been increasing interest in the neurobehavioral problems frequently associated with Tourette's disorder. Obsessive-compulsive disorder (OCD), obsessive-compulsive symptomatology (OCS), other anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and a number of symptoms of impulse and affective dyscontrol have been identified as "associated disorders" in Tourette's disorder studies.[1–4] Episodic rages (commonly termed *rage attacks* by the patients themselves) have been estimated to occur in as many as 30% of Tourette's disorder patients but have not been well characterized.[5,6] These episodic rages are presently a leading cause for psychiatric consultation for Tourette's disorder patients at our center.

In an attempt to better characterize rage attacks, we did a pilot study of 12 children with Tourette's disorder and rage symptoms to examine the comorbidity of associated disorders in this population.[7]

More recently, we have also completed a study of children with Tourette's disorder, with and without rage symptoms, to compare the comorbidity of associated disorders in both populations. Twenty-four children with Tourette's disorder plus rage attacks were compared with 31 children who had Tourette's disorder without rage attacks (C. L. Budman, M.D.; R. D. Bruun, M.D.; K. S. Park, unpublished data, 1997). The results of these two studies suggest that the presence of the comorbid conditions of ADHD, OCD, and mood disorders are correlated with an increased incidence of rage attacks in children with Tourette's disorder.

For purposes of this study, Tourette's disorder–associated rage attacks were defined by use of a screen based on a modification of the DSM-IV diagnostic criteria for intermittent explosive disorder (IED). The only change made in the DSM-IV definition of IED was that Criterion C: "The aggressive episodes are not better accounted for by another mental disorder . . ."[8(p612)] was modified so that the disorders of Tourette's disorder, OCD, ADHD, and conduct disorder were not considered to be exclusionary criteria. As in the DSM-IV definition of IED, Tourette's disorder–associated rage attacks are characterized by

> discrete episodes of failure to resist aggressive impulses resulting in serious assaultive acts or destruction of property (Criterion A). The degree of aggressiveness expressed during an episode is grossly out of proportion to any provocation or

> precipitating psychosocial stressor (Criterion B). . . . The aggressive episodes are not due to the direct physiological effects of a substance . . . or a general medical condition . . . (Criterion C). The individual may describe the aggressive episodes as "spells" or "attacks" in which the explosive behavior is preceded by a sense of tension or arousal and is followed immediately by a sense of relief. Later the individual may feel upset, remorseful, regretful, or embarrassed about the aggressive behavior.[8(pp609–610)]

The rage attacks observed in our Tourette's disorder patients typically have an explosive, uncontrollable quality; are uncharacteristic of the individual's baseline character; and occur in the absence of major depression, character disorder, or psychosis. Tourette's/rage patients and family members that we have studied typically report that once a rage has begun it is impossible to abort until it has "run its course." As in the DSM-IV IED description, these rages "may result in job loss, school suspension, divorce, difficulties with interpersonal relationships, [and] accidents."[8(p610)] Although we have not, as yet, conducted the same comprehensive studies on adults with Tourette's disorder–associated rages, we have evaluated and treated many such adults during the past few years. While some have developed strategies to delay or avert rage attacks, the episodes continue to present a major problem in their lives. It is our impression that adults with Tourette's disorder and rages share the same comorbidities that we have identified in children.

Because of the severity and destructiveness of Tourette's disorder–associated rage attacks, patients typically present with an urgent need for effective treatment. Over the past few years we have explored a wide variety of pharmacologic and nonpharmacologic treatments. It has been our experience that, while behavioral methods are important, it is almost always necessary to employ pharmacologic treatment as well.

The pharmacotherapy of aggressive behavior has been the subject of a large number of investigations. A number of different classes of medications have been found to have some efficacy: neuroleptics, benzodiazepines, antidepressants, psychostimulants, β-blockers, anticonvulsants, and mood stabilizers.[9–18] Our experience with mood stabilizers, β-blockers, and neuroleptics (with the possible exception of risperidone) for Tourette's disorder–associated rages has been disappointing. Many of our patients were taking neuroleptics at the time rage symptoms presented or had been taking them in the past for treatment of tics without any benefit for rages. While benzodiazepine treatment was sometimes effective in emergencies, the effects were not sustained. Based on our findings of a high incidence of ADHD and OCD/OCS in Tourette's disorder children with rages, one might expect that medications affecting noradrenergic and/or serotonergic pathways would be effective. However, few patients responded well to treatment with psychostimulant medications or tricyclic antidepressants alone. Our experience with selective and nonselective serotonin reuptake inhibitor (SSRI/SRI) medications was more positive, and it appeared that paroxetine was the most effective of these medications in controlling the rages. This observation led us to conduct an open-label pilot study using paroxetine for the treatment of Tourette's disorder–associated rage attacks.

METHOD

Tourette's disorder patients with rages were identified by clinical examination, DSM-IV diagnostic criteria for Tourette's disorder, and our revised criteria for IED. Patients with other disorders that are known to be associated with rages (e.g., psychosis, head injury, mental retardation, pervasive developmental disorder, or personality disorder) were excluded from the study. Forty-five Tourette's disorder/rage patients who met our inclusion criteria were then treated with paroxetine, specifically to control their rages. The patients were contacted weekly and were all reevaluated in person after completing an 8-week trial of paroxetine. Other symptoms such as tics, ADHD, and OCD were not targeted by this study.

Patients ranged in age from 6 to 55 (mean = 16) years. Seven patients (16%) were female and 38 (84%) were male. In addition to Tourette's disorder, 39 patients (87%) were diagnosed with OCD and ADHD, 2 (4%) with OCD alone, and 4 (9%) with ADHD alone (by use of DSM-IV criteria, Yale-Brown Obsessive Compulsive Scale [Y-BOCS][19] and Conners[20] scales). Three sibling pairs (2 pairs = fraternal twins) were included in the study.

Thirty-two patients (71%) were taking medications used specifically for tics or ADHD when they entered the study: 9 were taking risperidone; 7, pimozide; 2, haloperidol; 2, fluphenazine; 4, clonazepam; 5, clonidine; 5, methylphenidate; and 1, guanfacine (3 were taking combinations of these medications). They continued taking these medications, without any alterations, throughout the study. Seven patients had previously been treated with other SSRI medications, but all had discontinued them for at least 4 weeks prior to entering the study.

Rages were reported to us by the patients and/or their family members. Since the rages were rarely witnessed by the investigators, we did not attempt to rate them by severity. We felt that patient and/or family reports were not objective enough so that we could rate the severity by them. We were, however, able to rate them by frequency on a 4-point scale: 0 = no rages in a month; 1 = 1 to 3 per month; 2 = 1 to 3 per week; 3 = 1 or more per day. On entering the study, 23 patients (51%) had a rating of 3 and 22 (49%) had a rating of 2. We also asked the patients/families to estimate the global percentage of improvement taking both frequency and severity into consideration.

Table 1. Change in Frequency Rating Before and After Paroxetine

	Frequency Rating									
	0		1		2		3		Total	
Group	N	%	N	%	N	%	N	%	N	%
Before paroxetine	0	0	0	0	20	52.63	18	47.37	38	100.00
After paroxetine[a]										
Number originally in group 2	6	15.79	10	26.32	4	10.53	0	0.00	20	52.63
Number originally in group 3	2	5.26	6	15.79	5	13.16	5	13.16	18	47.37
Number of all patients	8	21.05	16	42.11	9	23.68	5	13.16	38	100.00

[a]Percentage based on total N.

Paroxetine was initiated at a dose of 5 to 10 mg/day and increased by 5 to 10 mg/day increments every week, as tolerated, until satisfactory control of rages or a total daily dosage of 60 mg/day was attained, or until intolerable side effects necessitated cessation. Dosage was deemed to be therapeutic when rage symptoms were diminished (by patients' or their families' estimation) by 75% and were decreased by at least 1 point on the frequency scale. Response rates were estimated using standard methods for proportions and associated 95% confidence intervals (CI). Response rates were compared between sexes and diagnostic groups using the Fisher exact test. Results were considered significant if $p < .05$.

RESULTS

Thirty-eight patients completed the 8-week study. Six (16%) were females and 32 (84%) were males. Ages ranged from 6 to 53 (mean of 16) years. Seventy-six percent (95% CI = 0.62 to 0.90) reported their rage intensity to be diminished in frequency by at least 1 point on the 4-point scale. Twenty-one percent reported rage episodes to be completely absent for more than a month (Table 1).

While, as stated above, we did not attempt to rate the severity of the rages on a scale, we did inquire about them. All but 1 of the patients (or their families) who had improved reported that the global percentage of severity and frequency of rages had lessened by at least 75% (rages were less frequent, shorter in duration, and less destructive).

The response rates were 5/6 (83%) for patients with Tourette's disorder plus either OCD or ADHD alone and 24/32 (75%) for Tourette's disorder plus ADHD and OCD patients. The rates were not significantly different although the sample size was too small to be conclusive.

Of the 7 patients who did not complete the study (16% of the original 45), 3 discontinued paroxetine because of side effects: a 9-year-old boy (also taking haloperidol) had an acute dystonic reaction; a 9-year-old boy taking no other medication exhibited severely regressed behavior; a 21-year-old man experienced a hypomanic episode (no previous history of hypomania). Four patients experienced exacerbation of rage attacks which they attributed to paroxetine. It was not clear to us, however, whether the increase in rage was attributable to paroxetine.

The mean dose of paroxetine was 33.3 mg/day (maximum of 60 mg/day; minimum effective dose of 15 mg/day). Other side effects reported included sedation, agitation, diminished libido, and increased severity of tics.

The 9 patients who were taking risperidone concurrently seemed to have better responses to paroxetine than those taking other concurrent medications (all improved, and 5/9 improved by at least 2 frequency scale points. However, the sample size was too small to do a meaningful subgroup analysis of the patients who were taking other concomitant medications.

DISCUSSION

The results of this open-label study suggest that paroxetine may be particularly helpful in controlling episodic rage attacks associated with Tourette's disorder. Although it is our clinical impression that paroxetine is more effective than other SSRI medications now available, double-blind studies will be needed to confirm this impression. There is a suggestion that patients who were also on the novel neuroleptic, risperidone, may have improved more than others, but a larger study would be required to draw such a conclusion.

The presence of associated disorders was high (as is common in our experience with Tourette's/rage patients). No patients had Tourette's disorder without any associated disorders. The numbers of Tourette's disorder plus ADHD and OCD versus Tourette's disorder plus OCD alone and Tourette's disorder plus ADHD alone were too small to derive any significant differential. We did not rate the patients on a depression scale and recognize this as an omission. However, it was our clinical impression that, although consistently distressed by their outbursts, the patients were not clinically depressed prior to the medication trial. We also observed that 6 of the 7 patients who had been taking other SSRI medications prior to the study did not improve on these but did improve on paroxetine therapy.

Quantifying the amount of improvement in rage attacks was difficult because the rages cannot be systematically observed by the investigators and we were forced to rely on patient or family reports. The estimates of improvement in intensity may have been skewed by a number of

factors but were very similar to the ratings on the frequency scale that we devised. More accurate ways to rate improvement would be desirable and should be sought in future studies.

A number of investigations have provided evidence that serotonin plays an important part in the modulation of aggressive impulses. Decreased cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) concentrations have been correlated with increased aggression and impulsive aggressivity in adults with personality disorders and alcoholism as well as in hyperactive children.[21–23] An inverse relationship has also been demonstrated between CSF 5-HIAA and overt aggression in nonhuman primates.[24,25]

Platelet central serotonergic (5-HT) transporter sites have been demonstrated to be associated with life history of aggression in adults with personality disorder.[26] Blood 5-HT concentrations have been found to have significant negative correlations with aggressive behavior scores in children and adolescents with OCD and comorbid ADHD or oppositional defiant disorder.[27] However, blood 5-HT levels in children with ADHD have been reported as low or, more often, normal.[28–32]

Recent clinical studies have reported the efficacy of other serotonergic agents, such as fluoxetine and clomipramine, for targeting rage symptoms in patients with major depressive disorder.[18,33] While the underlying pathophysiology of episodic rages associated with Tourette's disorder may be distinct from other populations, this open-label study suggests that the SSRIs, and paroxetine in particular, may have an important role in the clinical management of rages in Tourette's disorder patients.

Drug names: clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), fluoxetine (Prozac), fluphenazine (Prolixin and others), guanfacine (Tenex and others), haloperidol (Haldol and others), methlyphenidate (Ritalin), paroxetine (Paxil), pimozide (Orap), risperidone (Risperdal).

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