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Fluvoxamine and Sulpiride in Comorbid Obsessive–Compulsive Disorder and Gilles de la Tourette Syndrome

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Recently interest has arisen concerning the genetic, pharmacologic and phenomenologic links between Gilles de la Tourette Syndrome (GTS) and Obsessive–Compulsive Disorder (OCD). Some theorize the two disorders may be phenotypic variations of the same neurobiologic defect. Previous studies have demonstrated serotonin (5HT) abnormalities in OCD patients and dopamine dysfunction in patients with tics and GTS. We probed the relationship between 5HT and dopamine in these disorders with a 14-week, double-blind, placebo-controlled crossover trial of fluvoxamine (a specific 5HT reuptake inhibitor) versus sulpiride (a dopamine (D2) antagonist) followed by single-blind combined therapy (4 weeks) in 11 subjects with comorbid OCD and GTS.

Sulpiride monotherapy significantly reduced tics and non-significantly improved OC symptoms. Fluvoxamine, either alone or combined with sulpiride, non-significantly ameliorated tics and reduced OCD symptoms. Additionally, tics and OC symptoms covaried. These results are consistent with a possible coupling of dopaminergic and 5HT systems in comorbid OCD/GTS subjects.

KEY WORDS—OCD, obsessive-compulsive, Tourette Syndrome, dopamine, serotonin, fluvoxamine, sulpiride.

INTRODUCTION

Links between obsessive–compulsive disorder (OCD) and Gilles de la Tourette Syndrome (GTS) have recently attracted interest (Pitman *et al.*, 1987). Twin studies examining the development of these two disorders have shown a high concordance for both GTS (Wasman *et al.*, 1978) and OCD (Rasmussen and Tsuang, 1986) among monozygotic twins, and for GTS in triplets (Segal *et al.*, 1990). Family studies have shown that in patients who have either OCD or GTS there is a marked increase of family members who have the other disorder (Pauls and Leckman, 1986). Pauls *et al.* (1986) have suggested that there may be a common gene that has as phenotypes either OCD or GTS. In addition, many patients with GTS have obsessive–compulsive symptoms (Frankel *et al.*, 1986; Caine and Polinsky, 1979; Robertson *et al.*, 1988), while OCD patients frequently have tics (Pitman *et al.*, 1987). Thus, these two disorders often run in the same families, and sometimes occur within the same person. Some have referred to OCD, OCD with tics, and GTS as an 'OCD spectrum' of disorders (Baxter, 1990; George 1992a,b).

These data suggest an intricate relationship between OCD and GTS, although this link is criticized by some (Shapiro and Shapiro, 1982; Shapiro *et al.*, 1987). GTS may prove to be an important neurobiological model to explore the pathogenesis of OCD. Further, patients with GTS often suffer more from their associated OCD than from the tics themselves.

GTS is usually treated by dopamine antagonists such as pimozide, haloperidol (Shapiro *et al.*, 1989) and sulpiride (Robertson *et al.*, 1990). These agents have been thought to have little to no effect in classical obsessive–compulsive disorder, although studies are few and poorly documented (Ananth, 1976). Recently there have been advances in the treatment of obsessive–compulsive disorder involving serotonin (5HT) reuptake blockers such as fluoxetine (Turner *et al.*, 1985), fluvoxamine (Price *et al.*, 1987) and clomipramine (Montgomery, 1980). These drugs work well in OCD but are not thought to be of value in treating tics. No double-blind studies have been performed to assess their efficacy in OCD when it occurs in GTS, although open-labelled studies show some efficacy of fluoxetine (Como and Kurlan, 1991; Riddle *et al.*, 1988, 1990).

In order to pharmacologically dissect the dopa-

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mine and serotonin systems in OCD and GTS, we studied 11 subjects with comorbid OCD and GTS in a 14-week prospective, randomized, double-blind crossover trial of fluvoxamine (a 5HT reuptake inhibitor) versus sulpiride (a selective dopamine D2 antagonist) followed by 4 weeks of single-blind combined treatment with the two agents.

MATERIALS AND METHODS

Twenty subjects were screened and 11 subjects with comorbid OCD and GTS were enrolled into the study (Table 1). All gave informed consent prior to starting, were evaluated by the authors and met

Table 1. Subject data

	Fluvoxamine first	Sulpiride first
Sex	5M/1F	3M/2F
Initial YBOC	26·8 ± 5·6	21·4 ± 4·4
Initial TSS	80·3 ± 14	67·8 ± 14
Initial NIMH OC	10 ± 1·3	9·2 ± 1·9
Mean age	28·3 ± 3·2	29·6 ± 2·9

Means, ± standard deviation.

DSM III-R criteria for GTS and OCD. Additional screening measures included a neurologic examination, EEG, SPECT scan, and serologic tests to exclude secondary causes of GTS or OCD. Exclusionary criteria included hepatic, renal or cardiac disease, pregnancy, seizure disorder, mental retardation, inability to tolerate the placebo phases of the trial, or the presence of depression or severe psychiatric illnesses other than OCD and GTS at the time of entering the trial. Six of the 11 subjects were medication-free at the start of the trial. The other five were tapered off medications (primarily dopamine-blocking agents or antidepressants, or both) and were medication-free for 4 weeks prior to entry.

Subjects were randomized into two groups, one group taking sulpiride first for 6 weeks and the other fluvoxamine for 6 weeks (see Figure 1 and Table 1. Sulpiride was started at 200 milligrams (mg) daily and increased as tolerated by side-effects to a limit of 1 gram (g) (Robertson *et al.*, 1990) (490·4 mg average dose). Fluvoxamine was started at 50 mg nightly, increasing to a maximum of 300 mg as tolerated (Price *et al.*, 1987) (122·7 mg average dose). Subjects were given active drug and placebo in differing tablets (a double-dummy design). Both pills were scheduled as coupled and increased in concert from one each at night for the first week, to one twice a day for one week, to one each morning and two at night for two weeks, to four daily, up to a maximum of six daily.

Patients were assessed in person every two weeks by a neurologist and psychiatrist (MSG), blinded to the patient's medication status. Tics were assessed by the Yale Global Tic Severity Scale (TSS) (Leckman *et al.*, 1989). Obsessive--compulsive symptoms were assessed by the Yale-Brown Obsessional Scales (YBOC) (Goodman *et al.*, 1989b) and the NIMH OC scale (Rapoport *et al.*, 1980). After completion of one 6-week trial, subjects were given blinded placebo for two weeks and then crossed-over in a blinded fashion to the other medication phase of the trial. At completion of the second 6-week trial, whichever medication they were not taking was added to their existing regimen in a single-blind fashion. They were then monitored for another 4 weeks (thus 6 weeks sulpiride or fluvoxamine, 2 weeks placebo, 6 weeks of whichever medication they did not receive initially, 4 weeks combined therapy = 18 weeks total).

Data analysis

Five of the 11 subjects (45 per cent) fully completed all three stages of the study. Because of the high drop-out rate in some stages, and in order to more fully analyse the effect of medication in all subjects, end-point analysis was used for subjects receiving medication for at least two weeks in any given stage. (A repeated measures analysis for the five subjects who completed all aspects of the study yielded similar results. However, in the authors' opinions, this analysis failed to capture the true impact of the medications on the symptoms in the wider group of patients.)

A 2 × 4 repeated measures analysis of variance (ANOVA) with order as a factor was used to test for an order effect for each measure (NIMH OC, YBOC, TSS), and to compare the relative efficacy of fluvoxamine versus sulpiride. Two-tailed paired Student's *t*-tests and end-point analysis were used to compare each stage (e.g. response to sulpiride, fluvoxamine, combined) with baseline. Paired Student's *t*-test values are expressed as two-tailed.

A simple regression analysis was performed comparing weekly rating scale means for OCD and tic symptoms to assess whether these responses covaried.

Table 2. Rating scale means and significant changes by week*

Week	(*n*)	YBOC (SD) *p*-value	TSS (SD) *p*-value
0 Baseline	*(10)*	*19·9 (10·1)*	*70·5 (16·6)*
2 Sulpiride phase	(11)	17·9 (9·7)	66·4 (19·8)
4	(10)	19·6 (11·5)	60·4 (25·4)
6	(7)	15·1 (8·1)	50·1 (20·7)
End-point analysis	(11)	17·5 (11·5) **0·27**	58 (24·9) **0·01**
0 Baseline	*(11)*	*21·3 (9·5)*	*70·6 (19·7)*
2 Fluvoxamine phase	(11)	21·2 (10·8)	69·6 (20·7)
4	(10)	18·5 (11·9)	66·7 (18·9)
6	(9)	16·6 (12·5)	65 (17·9)
End-point analysis	(10)	16·7 (11·7) **0·20**	63·1 (17·9) **0·21**
Beginning of combined phase	*(6)*	*18·5 (13·8)*	*62·6 (12·6)*
2 Combined phase	(6)	17·8 (12·0)	50·5 (22·5)
4	(5)	13·5 (13·5)	48 (29·2)
End-point analysis	(6)	15·5 (11·7) **N.S.**	48·5 (22·7) **N.S.**

*Paired Student's *t*-tests, two-tailed, compared with baseline at the start of each phase of the trial, using end-point analysis for all who received at least 2 weeks of a medication.
N·S· = Not significant.

RESULTS

Results are presented in Table 2 and Figure 1. Figure 1 demonstrates mean ratings depending on the order of receiving either fluvoxamine or sulpiride. There was no significant order effect for either medication. Additionally, neither medication was statistically superior to the other for any of the measures, although the power for this analysis in this study is limited.

Sulpiride monotherapy significantly reduced tics (mean TSS starting 70·5, reduced by 18 per cent to 58, *df* 8, $p = 0{\cdot}01$, two-tailed) compared with baseline at the start of the treatment phase. This drug also decreased obsessions, although not significantly (starting YBOC 20, improved by 12 per cent to 17·5, *df* 9, $p = 0{\cdot}27$, two-tailed). These data are complicated by four subjects who were unable to fully complete their sulpiride monotherapy phase due to side-effects (listed below).

Fluvoxamine was an effective, although not statistically significant, anti-obsessional agent even in this small study with limited statistical power (starting YBOC 21·3 reduced by 25 per cent to 16, *df* 9, $p = 0{\cdot}20$). Interestingly, fluvoxamine monotherapy also reduced tics although not significantly (starting TSS 71, reduced by 11 per cent to 63 after 6 weeks, *df* 9, $p = 0{\cdot}21$).

The tic and OC response to the medications changed in concert and covaried (*R*-squared 0·527, $p = 0{\cdot}01$).

Combination therapy with both agents improved both tic and OC symptoms compared with the beginning of the combined phase, but because of the small numbers this is not statistically significant.

SIDE-EFFECTS

There were three complete withdrawals from the trial; two on sulpiride due to severe depression and one during the placebo washout because of uncontrollable tics. One subject was advanced through the sulpiride portion secondary to severe worsening of OCD symptoms (unable to get out of bed secondary to complex rituals) and another because of galactorrhoea and oculogyric crises. That is, rather than dropping completely out of the study, these two subjects were moved in a blinded fashion to the placebo cross-over phase and then on to receive fluvoxamine. Other reversible side-effects included: on sulpiride monotherapy—mild to moderate depression (3/11 subjects) and akathisia treated with propanolol (10–20 mg) (2/11 subjects); on fluvoxamine monotherapy—mild transient nausea limited to the first two weeks (4/11), mild apathy (2/11), dystonia (1), akathisia (2), and mild hypomania (1). These symptoms did not break the blind.

DISCUSSION

OCD is a common neuropsychiatric disorder with an estimated prevalence of 2–3 per cent (Robins *et al.*, 1984). GTS is less common, with estimates

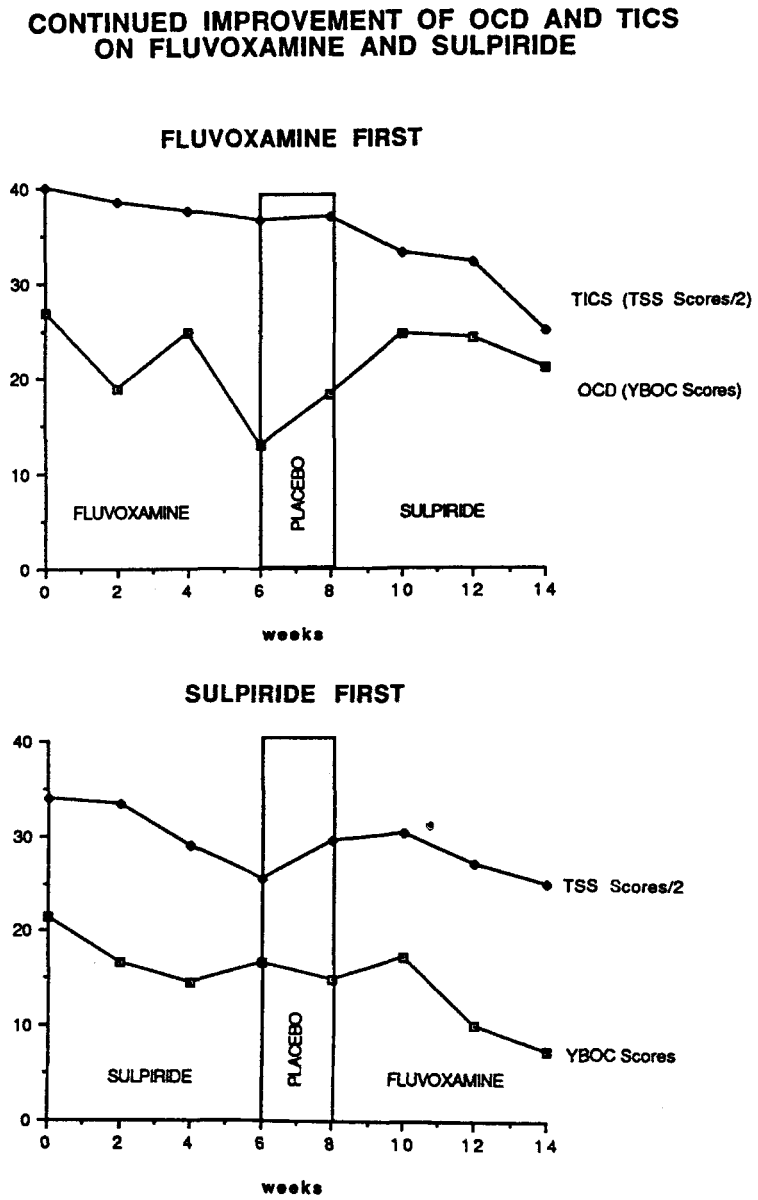

Figure 1. Split figure demonstrating the actual temporal order and showing the mean ratings of those who received fluvoxamine first (top) or sulpiride first (bottom). Note that OCD symptoms worsened during the placebo phase after fluvoxamine was discontinued (top) and tic symptoms worsened after sulpiride was stopped (bottom). The bottom graph illustrates the significant covariation of tic and OC symptoms seen throughout the study

ranging from 1 in 500 to 1 in 2000 (Shapiro *et al.*, 1987). Even more rare are patients who meet DSM III-R criteria for both OCD and GTS, and who are both ill enough to require medications yet can tolerate a 4-week initial washout and a 2-week crossover placebo period. Nevertheless this unique comorbid population can serve as an interesting model of both OCD and GTS and can yield meaningful clinical and theoretical information.

There are limitations of the present study. Because of the uncommon nature of the comorbid study group the number of subjects in the study

has limited statistical power. Dropouts reduced the numbers in the final combined treatment phase. Yet despite these problems, several significant findings have emerged.

This study brings into focus the difficult and sometimes controversial problem of distinguishing between a complex motor tic and a compulsion. For the purposes of this study a tic was defined as a repeated, largely involuntary, *rapid* movement or noise which, when resisted, caused mounting tension and anxiety. A compulsion was defined as a more complex behaviour, largely voluntary, involving thought and coordinated muscle groups in a complex behaviour. Thus, for example, touching an object would be defined as a compulsion.

Many of these patients (5/11) developed depression on sulpiride monotherapy. In 3/11 the depression cleared when they were advanced to fluvoxamine monotherapy or when the sulpiride was discontinued. Interestingly, two of the five were able to tolerate sulpiride when combined with fluvoxamine without developing a recurrent depression. For three subjects, this was their first ever episode of depression. Sulpiride has been proven effective in the treatment of GTS (Robertson *et al.*, 1990) and even displays antidepressant effects at low doses (Serra *et al.*, 1990). Thus, from this small sample, sulpiride-induced depression appears to be dose-related. Additionally, there may be something particular to this comorbid OCD/GTS population that renders them especially vulnerable to sulpiride's depressant side-effect. Other dopamine blocking agents have been reported to cause depression or dysphoria in GTS patients (Caine and Polinsky, 1979; Bruun, 1982).

Theoretical links

The two study medications were chosen for their pharmacologic specificity. Fluvoxamine is a potent 5HT reuptake inhibitor with no known direct dopamine activity. Other 5HT reuptake inhibitors used to treat OCD such as fluoxetine and clomipramine display some dopamine blocking activity (Austin *et al.*, 1991; Meltzer *et al.*, 1979). Sulpiride is a potent dopamine blocker with most of its activity occurring at the D2 receptor site (Spano *et al.*, 1979). It is not known to have direct action at 5HT receptors.

It is possible, although unlikely, that the anti-obsessional activity of sulpiride, the anti-tic activity of fluvoxamine, or their combined synergy are due to direct effects of the medications at receptor sites not usually associated with the therapeutic action of these drugs.

Another possible interpretation for these findings is that the dopamine and 5HT systems might directly influence each other. In support of this explanation, recent animal experiments have revealed important 5HT and dopamine interactions (Wozniak *et al.*, 1990). Blandina *et al.* (1989) demonstrated that 5HT3 receptors in rat striatum modulate the release of dopamine. Administration of a 5HT3 antagonist to rats attenuates drug-induced dopamine release in the nucleus accumbens (Imperato and Angelucci, 1989). These studies provide a potential mechanism by which fluvoxamine (5HT3 antagonist) could reduce tics, the latter possibly caused by excessive dopamine. Whatever the underlying mechanism, evidence from CSF studies in man show that 5HT and dopamine metabolites are linked and covary (Bowers *et al.*, 1969).

Clinical implications

This study confirms previous studies showing fluvoxamine's ability to reduce OC symptoms in OCD and sulpiride's ability to decrease tics in GTS. This is the first controlled study showing their efficacy in comorbid OCD/GTS.

At least four double-blind placebo-controlled studies have shown fluvoxamine's effectiveness in reducing OC symptoms in OCD (Perse *et al.*, 1987; Goodman *et al.*, 1989a; Cottraux *et al.*, 1990; Marks, 1987). In the present study, surprisingly, fluvoxamine monotherapy also non-significantly decreased tics. Clinically, patients often got worse initially followed by a gradual reduction in tics. One subject on fluvoxamine monotherapy developed a dose-dependent dystonic reaction in her jaw similar to that seen with dopamine blocking medications (George and Trimble, 1993). Recently, Ratzoni *et al.* (1990) described an OCD/GTS patient whose tics responded to treatment with clomipramine.

Sulpiride monotherapy slightly reduced OC symptoms, although this change was not significant and was complicated by the high rate of depression. There are few reports of the direct effects of dopamine blockade as monotherapy in patients with OCD. Robertson *et al.* (1988) demonstrated that GTS subjects taking neuroleptic medications had less OC symptoms than others. Two studies (Jellife, 1927; Joffe *et al.*, 1991) have shown that oral dex-

troamphetamine (and not methylphenidate) can transiently reduce obsessions in OCD subjects. Combining fluvoxamine and sulpiride produced synergistic reductions in both OC and tic symptoms, although the small numbers in this single-blind phase of the trial limit the statistical power for analysing the improvement over monotherapy with either agent. These results confirm reports by McDougle *et al.* (1990) where the addition of pimozide in a single-blind fashion improved refractory OCD subjects taking fluvoxamine and Delgado *et al.* (1990) where concurrent pimozide and fluvoxamine reduced OCD symptoms in a comorbid OCD/GTS patient.

The current study demonstrates that combining a 5HT reuptake blocker with a D2 blocking agent may be beneficial in comorbid GTS/OCD patients. Further studies are needed to determine whether this effect would also occur in OCD subjects with or without tics and to expand our knowledge concerning the neuropharmacology of OCD and GTS (Maclean, 1990; George, 1992b).

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