Depression and Dysphoria in Adult and Adolescent Patients With Tourette's Disorder Treated With Risperidone

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Background: Depression is a common comorbid condition in patients with Tourette's disorder. While risperidone is not usually known to induce dysphoria or depression in patients treated for other psychiatric disorders, previous short-term 4- to 12-week trials of risperidone for Tourette's disorder have reported a 2.6% to 30.8% incidence of depression.

Method: A retrospective study was carried out in 58 adult and adolescent patients with Tourette's disorder (Tourette Syndrome Classification Study Group diagnosis) who received risperidone between Jan. 1, 1993, and Dec. 31, 2000, at the Allan Memorial Institute, McGill University Health Centre, Montreal, Quebec, Canada. Charts of all patients were examined for evidence of, and risk factors for, DSM-IV–defined major depressive disorder (MDD) or dysphoria.

Results: Seventeen (29.3%) of 58 patients developed MDD, including 1 patient who later committed suicide and 13 patients (22.4%) who became dysphoric while taking risperidone. Nine of the 17 patients who developed MDD were relapses, i.e., patients with a history of depression prior to taking risperidone, while the remainder were new cases, i.e., patients with no previous history of depression. A positive personal history of MDD was the only factor to significantly ($p < .001$) predict the development of depression while taking risperidone. Seventy percent of those who developed MDD or dysphoria and discontinued risperidone did so specifically as a result of this adverse event.

Conclusion: MDD and dysphoria commonly occurred in this cohort of adult and adolescent Tourette's disorder patients treated with risperidone, particularly in patients with a previous history of depression. Depression and dysphoria were frequent reasons for risperidone discontinuation.

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Tourette's disorder is a chronic familial neuropsychiatric disorder that typically begins in childhood. Tourette's disorder is characterized primarily by motor and vocal tics and is commonly associated with comorbid psychiatric conditions including attention-deficit/hyperactivity disorder, obsessive-compulsive disorder (OCD), behavioral problems, and learning disabilities.[1] Depression is also common in patients with Tourette's disorder. Among 246 Tourette's disorder patients, Comings and Comings[2] found that 22.9% had lifetime evidence of depression as measured by the National Institute of Mental Health Diagnostic Interview Schedule. Current evidence of depression, as measured by a modified Beck depression scale, was found in 20.9% of these same patients, especially in those with, as compared to without, comorbid attention-deficit disorder (23.7% vs. 9.7%).[2] Robertson et al.[3] observed that Beck Depression Inventory scores of 22 Tourette's disorder subjects (mean ± SD = 12.1 ± 10.1) were higher than controls (N = 21, 2.7 ± 3.4) but lower than subjects with major depression (N = 19, 25.3 ± 6.4). The actual number of Tourette's disorder patients who had major depression (score ≥ 13) was not provided. Finally, Pitman et al.[4] found that 7/16 patients with Tourette's disorder, 11/16 with OCD, but only 1/16 controls had a lifetime occurrence of unipolar depression. Whether or not Tourette's disorder and depression are genetically linked is not yet determined as some studies have reported evidence in favor of such an association,[5] while others have not.[6]

Although the etiology of Tourette's disorder is unknown, the mainstay of treatment is antipsychotic medications that block the dopamine-2 (D_2) receptor, as excessive amounts of dopamine and D_2-receptor hypersensitivity are believed to play a central role.[7] There is growing evidence that dysfunction in the central monoaminergic systems involves serotonin (5-HT) and that 5-HT_2 receptors may also play a role.[8–10]

Risperidone is a benzisoxazole derivative with both serotonin 5-HT_{2A}-receptor and dopamine D_2-receptor blocking properties. Risperidone has been tried in several open-label studies,[11–15] 1 double-blind parallel-group comparative study versus pimozide,[16] and 1 double-blind placebo-controlled study for patients with Tourette's disorder.[17] While the overall effect of risperidone for Tourette's disorder in these studies was positive, depression emerged as a possible side effect in these patients. Van der Linden et al.[11] found that 9/11 patients aged 19 to 52 years (mean age = 30.0 years) improved significantly while taking 2 to 6 mg/day of risperidone over 4 weeks, although 6 complained of drowsiness. Of the 2 patients who withdrew, 1 (9.1%) did so because of depression.[11] Lombroso et al.[12] demonstrated that all 7 children and adolescents had an 18% to 66% improvement in tic severity after 11 weeks of open-label risperidone treatment. Depression was not inquired about systematically, but 4 patients complained of tiredness.[12] Bruun and Budman[13] found that 22 (58%) of 38 patients aged 8 to 53 years (mean age = 24.7 years) improved after 4 weeks of open-label risperidone. One patient (2.6%) complained of depression, while 1 each complained of anxiety, insomnia, and weakness.[13] Sandor and Stephens[15] explored risperidone's efficacy in 28 children with Tourette's disorder and aggressive behavior, with 78.5% demonstrating reduced aggressivity. Depression did not emerge as a side effect, but 7 patients experienced emotional lability.

In a 12-week, multicenter, double-blind comparative study, an almost equivalent efficacy in tic reduction was demonstrated for both pimozide and risperidone treatment groups.[16] The major side effect in both groups was sedation (somnolence or fatigue) with 22/26 (84.6%) risperidone-treated and 19/24 (79.2%) pimozide-treated patients experiencing this side effect. Depression was also equally common in both groups, 8/26 (30.8%) with risperidone and 6/24 (25%) with pimozide.[16]

Finally, Dion et al.[17] reported that 60.8% of patients treated with risperidone versus 26.1% of patients treated with placebo improved after 8 weeks of double-blind therapy for Tourette's disorder. There was a trend for a greater incidence of depression in the risperidone group as compared with the placebo group (26.1% vs. 4.4%, $p = .10$). All 3 patients terminating the study prematurely in the risperidone group did so because of depression.[17]

The trials described above have been of short duration, 4 to 12 weeks. We, therefore, sought to evaluate the incidence of depression and dysphoria in a cohort of adult and adolescent Tourette's disorder patients treated with risperidone for longer periods of time and to examine for possible risk factors associated with the development of depression or dysphoria in this population.

METHOD

Study Procedure

This retrospective study was based on a chart review of all patients attending the Adult Tourette's Syndrome Clinic at the Allan Memorial Institute, McGill University Health Centre, Montreal, Quebec, Canada, between Jan. 1, 1993, and Dec. 31, 2000. One of the authors (Y.D.) is the psychiatrist in charge of the Adult Tourette's Syndrome Clinic. After obtaining Research Ethics Board approval, all charts were examined (H.C.M.). Patients were included in the study if they were prescribed risperidone for any length of time, were aged 13 to 65 years, and had a Tourette Syndrome Classification Study Group diagnosis of Tourette's disorder.[18] Patients with severe-to-profound mental retardation were excluded.

The following information was obtained from the charts: age, gender, personal history of prior major depression, family history of major depression, presence or absence of selective serotonin reuptake inhibitor (SSRI) treatment prior to beginning risperidone, presence or absence of other antipsychotic treatment prior to risperidone, highest prescribed mean daily risperidone dose, number of weeks of risperidone treatment (or prescribed number of weeks if these data were not precise), whether risperidone treatment was ongoing or not as of Dec. 31, 2000, presence or absence of parkinsonism while taking risperidone, use of anticholinergic medications to treat parkinsonism, and, for those who discontinued, reasons for risperidone discontinuation. To assess for the presence of DSM-IV major depressive disorder (MDD) and dysphoria, all clinic visit notes were carefully reviewed. Only those patients whose chart contained the requisite number of DSM-IV symptoms to qualify for a diagnosis of MDD were classified as such. All other patients who had a distinctly sad or depressed mood were classified as dysphoric. Patients with some symptoms of MDD (but not enough to meet DSM-IV criteria) without a sad or depressed mood were classified as not suffering from either depression or dysphoria. After the initial chart review, each chart was reexamined (Y.D.) for accuracy of diagnosis. Independent consensus for diagnosis of MDD, dysphoria, or no diagnosis was achieved on 56/58 charts (κ coefficient = 0.945). On the remaining 2 charts, the diagnosis of the treating psychiatrist (Y.D.) was ultimately chosen.

Statistical Analysis

Statistical analyses were performed using the microcomputer version of SPSS 10.0.[19] Multiple logistic regres-

Table 1. Characteristics of 58 Patients Who Developed MDD, Dysphoria, or No MDD or Dysphoria While Treated With Risperidone[a]

Characteristic	No MDD or Dysphoria (N = 28)	Dysphoria (N = 13)	MDD (N = 17)	Total (N = 58)
Age, mean ± SD, y[b]	27.9 ± 12.2	32.8 ± 9.5	34.6 ± 11.6	31.0 ± 11.7
Gender, N (% male)	24 (85.7)	10 (76.9)	11 (64.7)	45 (77.6)
Highest daily risperidone dose, mean ± SD, mg	3.29 ± 1.94	4.10 ± 1.99	2.68 ± 2.04	3.29 ± 2.01
Duration of risperidone treatment, mean ± SD, wk	94.7 ± 97.2	92.2 ± 97.6	89.4 ± 107.2	92.6 ± 98.6
Still taking risperidone as of Dec 31, 2000,[c] N (%)	10 (45.5)	2 (15.4)	6 (37.5)	18 (35.3)
Discontinued risperidone during follow-up, N (%)	12 (42.9)	11 (84.6)	9 (52.9)	32 (55.2)
Personal history of prior major depression, N (%)	2 (7.1)	3 (23.1)	9 (52.9)[d]	14 (24.1)
Family history of major depression,[e] N (%)	5 (19.2)	4 (30.8)	7 (41.2)	16 (28.6)
SSRI treatment prior to risperidone, N (%)	9 (32.1)	4 (30.8)	4 (23.5)	17 (29.3)
Prior antipsychotic treatment, N (%)	18 (64.3)	9 (69.2)	11 (64.7)	38 (65.5)
Parkinsonism secondary to risperidone, N (%)	14 (50.0)	10 (76.9)	6 (35.3)	30 (51.7)
Anticholinergic used to treat parkinsonism, N (%)	9 (32.1)	9 (69.2)	6 (35.3)	24 (41.4)

[a]Abbreviations: MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.
[b]Age at time risperidone was started.
[c]Six patients from the no MDD/dysphoria group (revised N = 22) and 1 patient from the MDD group (revised N = 16) were excluded from the analysis, as this information was unknown. Total for this parameter based on N = 51.
[d]Group with MDD significantly different from other 2 groups (odds ratio = 8.10 [95% CI = 2.13 to 30.77]).
[e]Two patients from the no MDD/dysphoria group were excluded from the analysis (revised N = 26), as this information was unknown. Total for this parameter based on N = 56.

sion anlaysis with stepwise elimination of variables at $p > .05$ was used to investigate the relationship between the explanatory variables and an ordinal outcome variable coded as the following: 0 = no dysphoria or MDD, 1 = dysphoria, 2 = MDD. Multiple logistic regression analysis with stepwise elimination of variables at $p > .05$ was also used to investigate the relationship between the explanatory variables and a binary outcome variable coded as the following: 0 = no MDD, 1 = MDD. Because binary outcome variable analysis revealed no changes in the outcome measures, the results are not shown.

RESULTS

Between Jan. 1, 1993, and Dec. 31, 2000, a total of 58 patients with Tourette's disorder who attended the adult and adolescent Tourette's disorder clinic received risperidone. Exposure to risperidone ranged from 0.25 to 86 months (median = 14 months). Of these 58 patients, 17 (29.3%) developed DSM-IV MDD while taking risperidone and 13 (22.4%) others became dysphoric for a total of 30/58 patients (51.7%) who developed either MDD or dysphoria (Table 1). The 17 patients with MDD were composed of 9 relapses, i.e., patients who previously had a history of major depression, and 8 new patients, i.e., patients who had no previous history of depression. One patient committed suicide while taking risperidone. Of the variables analyzed, only the presence or absence of a past history of MDD predicted that a patient would develop MDD while taking risperidone for the treatment of Tourette's disorder (multiple logistic regression analysis: $\chi^2 = 12.2$, $p < .001$). The odds ratio for patients with a history of MDD to develop MDD while receiving risperidone was 8.10 (95% CI = 2.13 to 30.77). Age, gender, highest mean daily risperidone dose, mean weeks of risperidone treatment, family history of MDD, SSRI treatment prior to risperidone, prior antipsychotic treatment, or parkinsonism secondary to risperidone were not found to be significant predictors of the development of dysphoria or MDD during risperidone treatment.

Patients with no prior history of MDD who became depressed were analyzed as a separate group to try to identify factors that might predict new cases of MDD. Other than the lower incidence of previous SSRI use in patients who developed their first major depressive episode, no factors significantly predicted MDD in patients who had no prior history of MDD.

Thirty-two patients (55.2%) discontinued risperidone during the follow-up period (Table 2). The most common reason for discontinuing risperidone was depression or dysphoria (N = 14) followed by sedation/tiredness (N = 4). Thus, of the 30 patients who developed MDD or dysphoria, 14 discontinued risperidone specifically because of this adverse effect (Table 3). On the other hand, 9/13 patients who received a concomitant SSRI to treat their depression or dysphoria responded well enough to be able to remain on risperidone therapy.

DISCUSSION

We found a high incidence of MDD and dysphoria in this cohort of adult and adolescent patients with Tourette's disorder treated with risperidone. While depression has been found to be common in Tourette's disorder patients, 51.7% of our cohort developed dysphoria or depression during a period of exposure to risperidone ranging from 0.25 to 86 months (median = 14 months). Of note, 9/13 (69.2%) patients with complaints of dys-

Table 2. Reasons for Discontinuation of Risperidone[a]

Reason for Discontinuation	No MDD or Dysphoria (N = 12)[b] N (%)	Dysphoria/ MDD (N = 20) N (%)	Total (N = 32) N (%)
MDD/dysphoria	0 (0)	14 (70.0)	14 (43.8)
Sedation/tiredness	3 (25.0)	1 (5.0)	4 (12.5)
Lack of efficacy	3 (25.0)	0 (0)	3 (9.4)
Akathisia	2 (16.7)	0 (0)	2 (6.2)
Sexual dysfunction	2 (16.7)	0 (0)	2 (6.2)
Hyperprolactinemia	1 (8.3)	1 (5.0)	2 (6.2)
Psychomotor retardation/ mental dulling	1 (8.3)	1 (5.0)	2 (6.2)
Constipation	1 (8.3)	0 (0)	1 (3.1)
Decreased energy	1 (8.3)	0 (0)	1 (3.1)
Worsening of migraines	1 (8.3)	0 (0)	1 (3.1)
Parental opposition to treatment	0 (0)	1 (5.0)	1 (3.1)
Leaving country	0 (0)	1 (5.0)	1 (3.1)
Unknown	0 (0)	1 (5.0)	1 (3.1)

[a]Abbreviation: MDD = major depressive disorder.
[b]Three patients in this group had 2 primary reasons for discontinuing risperidone.

Table 3. Treatment Summary for Patients With Dysphoria or MDD[a]

Treatment	Dysphoria (N = 13) N (%)	MDD (N = 17) N (%)	Total (N = 30) N (%)
SSRI treatment of MDD/dysphoria while on risperidone treatment	3 (23.1)	10 (58.8)	13 (43.3)
Risperidone discontinued due to MDD/dysphoria	6 (46.2)	8 (47.1)	14 (46.7)
Risperidone discontinued due to other reasons	5 (38.5)	1 (5.9)	6 (20.0)

[a]Abbreviations: MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

phoria either stopped risperidone or had an SSRI added to risperidone. Among the 12 patients who did not develop MDD or dysphoria but discontinued risperidone, 3 did so due to sedation/tiredness and 1 due to decreased energy, symptoms that are commonly linked to depression and dysphoria.

Among the risk factors that we examined, vulnerability to MDD was associated with a past personal history of previous MDD. However, 8/17 patients (47.1%) who became depressed experienced their first major depressive episode while taking risperidone. Nonetheless, we were able to successfully treat depression with the addition of an SSRI in 7/17 of our patients with MDD, and 2/13 of the patients with dysphoria in order to continue risperidone treatment of Tourette's disorder. Interestingly, there was no significant difference in duration of exposure to risperidone between patients who did or did not develop MDD or dysphoria.

Risperidone itself is not known to cause depression when used to treat other psychiatric conditions. In patients with coexisting psychotic and depressive symptoms, risperidone-treated patients showed a reduction in depression and anxiety as measured by the Bech-Rafaelson Melancholia Scale, although those treated with a combination of haloperidol and amitriptyline had a significantly greater reduction in depression.[20] In that study, there was no significant difference in reduction of depression between the 2 treatment groups in patients with schizophrenia or schizoaffective disorder with concomitant depressive symptoms. Case series and case reports have demonstrated that adjunctive risperidone with SSRIs[21,22] or monoamine oxidase inhibitors[23,24] may be effective for treatment-resistant depression. Adjunctive risperidone with doxepin has even led to mania in a patient with psychotic depression and no known personal or family history of bipolar disorder.[25] Finally, risperidone monotherapy has been used to successfully treat 1 patient with psychotic depression[26] and both the depressed and manic phases of 1 patient with bipolar disorder.[27]

Data from this and other studies suggest that Tourette's disorder patients may be more vulnerable than the general population to develop depression.[2–6] Prior to risperidone, haloperidol was the most commonly used antipsychotic for Tourette's disorder. Some authors postulated that dysphoria commonly occurred in Tourette's disorder patients secondary to haloperidol,[28,29] although this may have just reflected the common coexistence of the 2 disorders, or haloperidol-induced akinesia, which can mimic depression.[30] Furthermore, in these studies, the actual incidence of haloperidol-associated depression was not provided.

Limitations of our study include the lack of a control group and the naturalistic study design that permits us to find associations between depression and risperidone treatment but does not speak to cause and effect. However, our findings suggest that it is important for psychiatrists to evaluate Tourette's disorder patients for vulnerability to depression when prescribing risperidone and other antipsychotic drugs.

Drug names: amitriptyline (Elavil and others), doxepin (Sinequan and others), haloperidol (Haldol and others), pimozide (Orap), risperidone (Risperdal).

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