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Aripiprazole in Children and Adolescents with Tourette Disorder with and without Explosive Outbursts

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Abstract

Objective: We conducted a retrospective, observational study of aripiprazole for the treatment of tics and/or co-morbid explosive outbursts in 37 children and adolescents with Tourette disorder (TD).
Method: Thirty seven children and adolescents with TD, with and without explosive outbursts, and refractory to previous treatment were treated at one of two university affiliated specialty clinics. All diagnoses were made using *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) criteria. Tic severity was rated using the Clinical Global Impressions Scale for tics (CGI-Tics) and frequency of explosive outbursts was assessed using the CGI-Rage; both measures were obtained at pretreatment baseline and at post-treatment follow up.
Results: High rates of psychiatric co-morbidity were observed in these subjects: 31 of 37 (84%) subjects met criteria for obsessive-compulsive disorder (OCD), and 31 of 37 (84%) met criteria for attention-deficit/hyperactivity disorder (ADHD). Twenty nine of 37 (78%) subjects met criteria for intermittent explosive disorder (IED) minus criterion C; the remaining 8 subjects had TD only. Eight subjects (22%) discontinued treatment before 12 weeks due to inability to tolerate the drug. At follow up, tics reduced at a mean daily dose of 12.3 (7.50) mg in 29 of 29 (100%) subjects who completed the study, and explosive outbursts improved in 24/25 subjects (96%) who completed the study. Aripiprazole was tolerated reasonably well, although 8/37 (22%) subjects discontinued treatment; most common side effects included weight gain, akathisia, and sedation.
Conclusion: Aripiprazole should be investigated further as a treatment option for TD with and without co-morbid explosive outbursts.

Introduction

Tourette disorder (TD) is a neuropsychiatric disorder of childhood onset characterized by multiple motor and vocal tics (American Psychiatric Association 2000). The majority of clinically referred individuals with TD also meet criteria for one or more co-morbid psychiatric disorders, including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), mood disorders and non-OCD anxiety disorders (Coffey et al. 2000b). Although the relationship between TD and associated co-morbid psychiatric disorders has been difficult to untangle, behavioral and emotional symptoms are leading causes of dysfunction and disability in clinically referred samples (Coffey et al. 2000a).

Aggressive symptoms, typically of an impulsive nature, have been reported to occur in 25–70% of clinically referred youths with TD (Comings and Comings 1987; Riddle et al. 1988; Wand et al. 1993; Budman et al. 2003). Explosive outbursts, frequently referred to as "rage attacks," represent discrete, recurrent episodes of severe impulsive verbal and/or physical aggression that occur in response to relatively trivial provocation or frustration. When present, explosive outbursts are leading causes of morbidity in TD, resulting in increased family distress, maladaptive educational and/or occupational functioning, interpersonal conflicts, and increased rates of psychiatric hospitalization (Moldofsky and Brown 1982; Dooley et al. 1999; Budman et al. 2000). However, there are relatively few studies investigating either the phenomenology or treatment of these highly disruptive

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symptoms in TD (Storms 1985; Stokes et al. 1991; Kurlan et al. 1993; Wand et al. 1993; Bruun and Budman 1998; Sukhodolsky et al. 2003; Scahill and Sukholdolsky 2006).

Because abnormalities of cortico-striatal-thalamic-cortical pathways and dysfunction of both dopamine and serotonin are believed to be associated with TD, there is a theoretical basis to assume that at least some aggressive symptoms in TD have an underlying neurobiological etiology (Albin 2004). Pharmacotherapeutic agents, such as the atypical neuroleptic aripiprazole, that can differentially target both serotonin and dopamine receptors in both cortical and subcortical structures, may have a beneficial impact on impulsive aggression in patients with TD.

Presently, the only formal, Food and Drug Administration (FDA)-approved indications for use of aripiprazole in youth are for schizophrenia and bipolar disorder in adolescents ages 13–17. Currently, the only medications formally approved for use in TD are haloperidol and pimozide (Thompson 2007). However, significant side effects, including extrapyramidal symptoms (EPS) such as acute dystonic reactions, Parkinsonism, akathisia, and tardive dyskinesia (Shapiro et al. 1973) prompted the development of the novel atypical neuroleptics. In recent years, the atypical neuroleptics, such as risperidone and olanzapine, have been used to target both aggressive symptoms across several psychiatric disorders and tics. These newer agents have demonstrated efficacy in reducing aggressive symptomatology or disruptive behavior in autism, pervasive developmental disorder (PDD), mood disorders, and conduct disorder (Benedetti et al. 1998; McDougle et al. 1998; Scheier 1998; Findling et al. 2000; Chen et al. 2001; Aman et al. 2002; McDougle et al. 2002; Research Units on Pediatric Psychopharmacology [RUPP] Autism Network 2002). Risperidone is now approved for treatment of aggressive behavior in children with autism. However, in recent years, concerns have been raised about these newer medications too, as reports have emerged demonstrating serious potential side effects, including substantial weight gain (Stigler et al. 2004a), development of abnormal glucose and lipid metabolism, elevated serum prolactin levels, and/or cardiac effects such as prolongation of the QTc interval (Green 2001; Stigler et al. 2004b).

Because both tics and explosive outbursts in children with TD may be associated with significant morbidity, there is an urgent need to explore and study potentially helpful treatments of these symptoms in such children. Preliminary evidence suggests that aripiprazole's benefit-versus-risk profile merits further exploration for use in TD. The aim of the study was to explore the use and tolerability of aripiprazole as a treatment for tics and explosive outbursts in youths with TD. To this end, we undertook a retrospective, observational study of patients treated with aripiprazole to describe estimates of dosing, tolerability, and treatment response in 37 children and adolescents with TD with and without explosive outbursts.

Methods

Subjects

Design of the study was a retrospective chart review of 37 patients who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR)(American Psychiatric Association 2000) criteria for TD with or without intermittent explosive disorder (minus criterion C) in two affiliated academic centers. All subjects were treated with aripiprazole for tics, and those with explosive outbursts were also treated for the outbursts. All subjects were evaluated by one of the two senior investigators who have expertise in the diagnosis and treatment of TD. All subjects had been treated in the past with conventional tic medications, including α-adrenergic agonists and/or typical or atypical neuroleptics; most subjects who had been treated with an atypical neuroleptic had received risperidone.

Subjects ranged in age from 8 to 18 years. Parents provided informed consent for use of aripiprazole, which does not have an approved indication for treatment of tics and/or explosive outbursts in subjects less than 18 years; subjects age 18 provided their own consent. Approval for conducting the retrospective chart review was obtained by the Institutional Review Boards (IRB) at both sites. Subjects were eligible for inclusion in our sample only if they were being treated with aripiprazole because they had failed to respond or had been unable to tolerate previous medication for tics and/or explosive outbursts. Subjects were excluded from our sample if they met criteria for any acute psychotic illness, major medical illness, substance abuse or dependence, or had a history of physical and/or sexual abuse. Concomitant psychotropic medications for co-morbid disorders were allowed if the agent(s) and dose(s) had been stable for at least 1 month prior to treatment and were held constant during the entire period of study observation.

Tic severity and explosive outburst frequency were assessed at pretreatment and at 3-month post-treatment using the Clinical Global Impressions–Tics (CGI-Tics) and the Clinical Global Impressions–Rage (CGI-Rage) scales. Operational definition of CGI-Tics severity was as follows: (1) normal or no tics at all; (2) borderline, tics may or may not be present; (3) mild, observable motor and/or vocal tics that may or may not be noticed, would not call attention to the individual, and are associated with no distress or impairment; (4) moderate, observable motor and/or vocal tics that would always be noticed, would call attention to the individual, and may be associated with some distress or impairment; (5) marked, exaggerated motor and/or vocal tics that are disruptive, would always call attention to the individual, and are always associated with significant distress or impairment; (6) severe, extremely exaggerated motor and/or vocal tics that are disruptive, would always call attention to the individual, and are associated with injury or inability to carry out daily functions. Operational definition of CGI-Rage severity was as follows: (1) normal or no explosive outbursts at all; (2) borderline, occasional verbal and/or physical expression of anger (i.e., explosive outbursts) present in the past month; (3) mild, at least 1 explosive outburst in the past week; (4) moderate, 2–3 explosive outbursts per week; (5) marked, 4–5 explosive outbursts per week; (6) severe, daily explosive outbursts, often occurring multiple times throughout the day.

Aripiprazole was initiated at doses of 1.25–2.5 mg daily in prepubertal children and at 2.5–5 mg in adolescents, and flexibly titrated every 5–7 days as tolerated and clinically indicated. Treatment duration was 6–12 weeks (with dosing generally titrated to therapeutic range within about 4–5 weeks). Potential adverse effects were discussed in detail prior to initiation of treatment with aripiprazole and were closely monitored at each office visit by review of systems and review

Table 1. Demographics and Co-Morbid Diagnoses ($N = 37$)

	n (%)
Males	26 (70.3)
Females	11 (29.7)
Mean age (SD)	13.4 (2.8)
Co-morbid diagnosis	
IED	29 (78)
ADHD	31 (84)
OCD	31 (84)
BP	7 (19)
MDD	1 (3)
Non-OCD Anxiety	2 (5)
MR	1 (3)
PDD spectrum	6 (16)

SD = standard deviation; IED = intermittent explosive disorder (minus C criterion); ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder; BP = bipolar disorder; MDD = major depressive disorder; MR = mental retardation; PDD spectrum = pervasive developmental disorders.

of the most common adverse effects associated with atypical neuroleptics; adverse effects that were reported both at scheduled visits and during any telephone contacts between visits were documented in the charts throughout the treatment period.

Results

Description of sample

Sociodemographic characteristics of the study sample are described in Table 1 and Fig. 1. Subject age range was 8–18 years, with mean age 13.4 years (standard deviation [SD] 2.8). Twenty nine of 37 (78%) subjects met criteria for intermittent explosive disorder (IED) minus criterion C, and were designated as TD subjects with explosive outbursts. Psychiatric co-morbid disorders were present in the vast majority of subjects: 31 of 37 (84%) subjects met criteria for OCD; 31 of 37 (84%) met criteria for ADHD; 7 of 37 (19%) for bipolar disorder; 2 of 37 (5%) for non-OCD anxiety disorders; 1 of 37 (3%) for major depressive disorder (MDD); and 6 of 37 (16%) met criteria for PDD spectrum disorders. Twenty eight of 37 (76%) subjects were taking other psychotropic medication for comorbid psychiatric disorders (see Table 1 and Fig. 1).

Eight of 37 subjects (22%) discontinued aripiprazole before 12 weeks. Of those 8 subjects, 6 were adolescents and 2 were prepubertal children; 5 had tics and explosive outbursts, and 3 had tics only. The mean age of the 8 dropouts was 13.75 (1.98) and 7 of the 8 (88%) were male. Of the psychiatric co-morbid disorders, 7 of 8 (88%) met criteria for OCD; 5 of 8 (63%) met criteria for ADHD; 1 of 8 (13%) met criteria for bipolar disorder; and 1 of 8 (13%) met criteria for separation anxiety disorder.

The dose range for aripiprazole in this sample was 2.5–40 mg daily; mean daily dose for the entire sample was 11.69 mg (SD 7.15). Mean daily dose for the 29 completers was 12.33 (7.49) mg and mean daily dose for the dropouts was 9.375 (5.1) mg.

Tic effects

Mean (SD) pretreatment (baseline) CGI-Tics severity score for the 29 subjects who completed was 4.38 (0.81) (Table 2, Fig. 2). Mean (SD) posttreatment (end point) CGI-Tics severity score was 2.69 (0.88). Reduction in tic severity was defined as reduction by at least one point on the CGI-Tic scale; reduction in tic severity by at least one point occurred in 29 of 29 subjects (100%) at end point.

Explosive outburst effects

Mean (SD) pretreatment (baseline) CGI-Rage score for the 25 subjects with explosive outbursts who completed was 4.96 (1.22) (Table 2; Fig. 2). Mean (SD) post treatment (end point) CGI-Rage frequency score was 2.53 (1.13). Reduction in rage was defined as reduction in at least one point on the CGI-Rage scale. Reduction of explosive outbursts by at least one point occurred in 24/25 subjects (96%) at end point.

Adverse effects

The majority of subjects tolerated aripiprazole well, but 8 (22%) dropped out before 12 weeks. In 7 of the 8 cases, the adverse effects emerged when the dose was increased in an attempt to target symptoms that did not respond to lower dosage. Titrations were always made in 2.5 mg increments only. In 1 subject, agitation and akathisia were noted at the initial dose of 2.5 mg. Among the subjects who discontinued treatment, akathisia (6/37, 16%), increased agitation (3/37, 8%), increased mood lability and/or anxiety (3/37, 8%), and symptoms of drug-induced Parkinsonism, such as bradykinesia, new onset of tremor, and mask-like facies (1/37, 3%) were reported as the primary reason for discontinuation of the medication. One of 37 subjects (3%) complained of extreme daytime sedation requiring discontinuation of the medication.

Mild headaches, dizziness, nausea, and/or sedation occurred in some subjects who continued treatment and were experienced as acceptable transient side effects. Among the 15 subjects for whom weight data were available, weight gain was documented in 13 of 15 subjects (87%) and weight loss was documented in 2 of 15 (13%) subjects. Among the 13 subjects with clinically significant weight gain, there was a mean (SD) increase of 18 pounds (12.3).

Discussion

Preliminary results of this exploratory, retrospective, observational study suggest that aripiprazole appears to have benefit in reducing both tics and explosive outbursts in a case series of children and adolescents with TD who had failed to respond or been unable to tolerate previous treatment.

Table 2. Tic and Rage Effects in TD Subjects with and without Explosive Outbursts ($N = 29$)

Rating	*Baseline*	*End point*
CGI-Tic mean (SD)	4.38 (0.81)	2.69 (0.88)
CGI-Rage mean (SD)	4.96 (1.22)	2.53 (1.13)

TD = Tourette disorder; CGI-Tic = Clinical Global Impressions Scale for tics; CGI-Rage = Clinical Global Impressions Scale for rage.

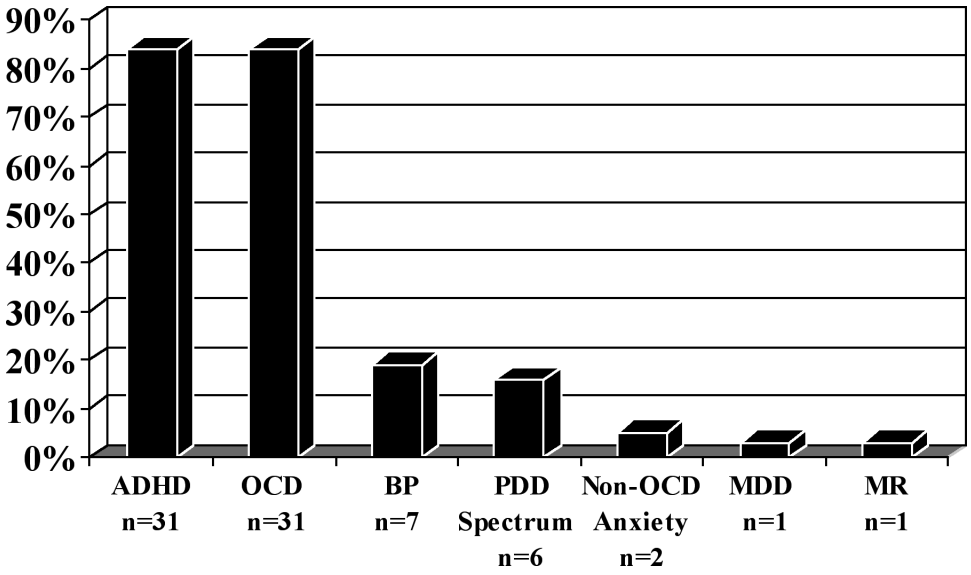

FIG. 1. Results for co-morbidity characteristics (n = 37). A 78% overall sample also met diagnostic criteria for IED (minus criterion C). IED = intermittent explosive disorder.

Mean dose was in the low-to-moderate range when compared to the typical dose range 15–30 mg used to treat schizophrenia and bipolar disorder.

Aggressive symptoms are a particularly troubling phenomenon in clinically referred youth with TD. In an international study of 3,500 outpatients with TD, 37% reported a lifetime history of anger control problems, and 25% experienced current anger control problems (Freeman et al. 2000). In a study of Japanese outpatients with TD from a specialty clinic, 48% of patients reported problems with aggression and impulsivity, and 20% reported self-injurious behaviors (Kano et al. 1998). A community survey of 446 individuals with TD between the ages of 6 and 78 years, conducted by the Tourette Syndrome Foundation of Canada, reported that 21% of children and 15% of adults reported problems with aggression; 30% of children and 19% of adults reported problems with temper (Wand et al. 1993). In a recent study of 58 Swedish children ages 5–15 years with TD, 35% were reported by their teachers to have significant aggressive dyscontrol, including repeated verbal assaults or physical aggression (Kadesjo and Gillberg 2000).

Explosive outbursts in TD are a type of impulsive aggression that occurs commonly in association with specific co-morbid psychiatric disorders, such as ADHD, OCD, and/or mood disorders (Budman et al. 1998; Budman et al. 2000; Budman and Feirman 2001; Budman et al. 2003). This observation has been reported by other investigators, including Stephens and Sandor (1999), who found higher rates of co-morbid ADHD and/or OCD in 33 unmedicated children with TD with aggressive problems, compared with 6 TD-matched controls, and Spencer et al. (1998), who demonstrated that children with co-morbid TD and ADHD scored significantly higher on parental and teacher ratings of aggression, compared with children with TD without

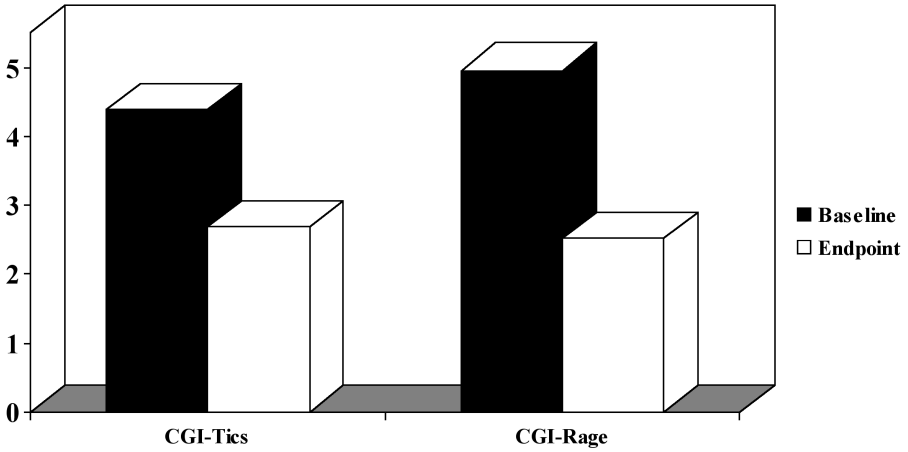

FIG. 2. Results for symptom reduction (n = 29). Scores are based on the Clinical Global Impressions scales (CGI).

ADHD and normal controls. In a study of 113 children with TD ages 7–17 years, the 48 (43%) subjects with explosive outbursts were more likely to meet current DSM-IV criteria for major depression, depression not otherwise specified (NOS), bipolar I disorder, ADHD, oppositional defiant disorder (ODD), and lifetime criteria for OCD and/or ODD than the 65 comparison subjects without explosive outbursts; tic type and/or severity and non-OCD anxiety disorders did not significantly differ between the two groups (Budman et al. 2003).

Treatment of explosive outbursts in youth with TD is challenging. Potential efficacy of the atypical neuroleptics for treating impulsive aggression symptoms in children with TD has been explored through a retrospective review of treatment response that suggested risperidone could be an effective monotherapy for impulsive aggression in these youths (Sandor and Stephens 2000). More recently, Stephens et al. (2004) treated 10 children and adolescents with TD and impulsive aggression with the atypical agent olanzapine for 8 weeks; they reported a reduction in tics and impulsive aggression, but a significant weight gain occurred in most subjects.

There is preliminary evidence that aripiprazole reduced aggression in youths with conduct disorder in low-to-moderate doses (1–10 mg) and was well tolerated when dosages were adjusted for body weight (Findling et al. 2003). A second study reported improvement in maladaptive aggressive behavior in 5 youths (ages 5–18 years) with PDD at mean dose of 12 mg daily (range 10–15 mg) (Stigler et al. 2004a). In addition, there have been several recent small case series describing reduction of tics in youth and young adults with TD with aripiprazole (Kastrup et al. 2005; Murphy et al. 2005; Yoo et al. 2006)

However, in recent years it has been reported that aripiprazole is not without potential for significant adverse effects. There have been a few case reports describing extrapyramidal symptoms, including one report of neuroleptic malignant syndrome and another of acute dystonia (Singh et al. 2007), and sedation associated with aripiprazole in youth (Alessi et al. 2004; Cohen et al. 2005). Of note, in our sample, a significant number of children with TD (22%) discontinued treatment with aripiprazole due to the emergence of intolerable adverse effects including agitation, akathisia, medication-induced symptoms of Parkinsonism, and increased anxiety and/or mood lability. The frequency of extrapyramidal side effects in this sample of children with TD appears to be higher than expected, compared with the frequency of such symptoms reported in studies of adults with schizophrenia (Marder et al. 2003). Given aripiprazole's partial dopamine agonist–antagonist effects, and the likely therapeutic mechanism of action involving D_2 receptor blockade, it is possible that youths with TD, with disinhibition of their cortico-striato-thalamic-cortical tracts, may be particularly vulnerable to extrapyramidal side effects of this medication.

In our series, among the 15 subjects for whom data on weight were available, clinically significant weight gain occurred during treatment with mean increase of 18 pounds. This too was an unexpected finding, because previous studies using aripiprazole monotherapy for treatment of schizophrenia in adults resulted in a modest weight loss over an 8-week study duration (Casey et al. 2003).

Limitations

Several limitations of this study must be taken into account. Regarding our sample, all subjects had failed to respond or had been unable to tolerate previous conventional tic and explosive outburst treatments, so they could be considered to have unique and treatment-refractory symptoms. Furthermore, this was a small sample of TD subjects treated within specialty programs, and thus referral bias is possible; in addition, our rate of OCD was higher than in our previous reports (Coffey et al. 2000c). This may be a function of our high prevalence rate of children with explosive outbursts in this sample. Although recent literature has suggested that TD patients evaluated in specialty clinics have diagnostic profiles similar to patients evaluated in general pediatric psychopharmacology settings (Coffey et al. 2000c), children with TD and explosive outbursts may be a more complex group of patients with higher rates of OCD and/or ADHD than children with TD without explosive outbursts. It is possible that our findings will be generalizable to other clinical settings in which children with TD and explosive outbursts are evaluated and treated; it is also possible that these findings may not be generalizable.

Because the vast majority of our subjects were taking concomitant psychotropic medication for psychiatric co-morbid disorders, we cannot rule out drug interactions as contributing to adverse effects observed, nor can we exclude the possibility that particular concomitant psychotroic medication combinations might be contributing to synergism or additive therapeutic effects.

With regard to methodology, our retrospective, observational design limited our findings; we did not have a comparison group with either placebo or another active drug. Furthermore, we were not blinded to treatment assignment, as this was an open methodology. We did not consistently use standardized rating instruments, such as the Yale Global Tic Severity Scale and the CGI–Improvement scale in all subjects, which would have enabled us to quantify our findings more fully and reliably.

Another noteworthy limitation was that our measurement of explosive outbursts was limited to the domain of frequency, which did not include intensity or duration of the episodes. It should be noted that the research criteria for studying IED in adults, applied by Coccaro et al. (1998), relies only on frequency criteria, quantified as the presence of three or more episodes per week. Our pilot work investigating explosive outbursts in children with TD, which are defined using the DSM-IV diagnostic criteria for IED minus criterion C used this same research criteria. Validated measures, such as the Halperin Scale (Halperin et al. 2002), have been used in previous studies in youths with aggressive behavior and incorporate several domains of severity. However, this was an exploratory study with chart review methodology. Although we were beginning to pilot a new rating scale incorporating intensity and duration as well as frequency during this study, we did not have systematic data on all subjects in domains other than frequency. We have preliminary data (Kano et al. 2008) that suggests frequency, not severity (in terms of intensity or duration of episode), is most highly correlated with clinically significant rage.

In this small pilot study, our aim was to contribute to the growing literature describing aggressive symptomatology, specifically impulsive aggression, in children with TD. It is a limitation that we were not able to rate intensity and duration of episodes as well. Further follow-up studies using more sophisticated rating scales are warranted. Finally, information reported on safety and tolerability was limited to data collected on adverse effects that were considered significant enough to merit discontinuation of aripiprazole. Therefore, milder effects may have been under-recognized and under-reported. Given that this was not a randomized controlled trial, it is not possible to draw conclusions about the subject dropouts.

Conclusions

Despite these limitations, findings in our exploratory study indicate that aripriprazole may be a potentially beneficial and tolerable treatment option for tics and/or explosive outbursts in children and adolescents with TD and merits future, controlled studies.

Disclosures

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