

Atypical Antipsychotic Treatment of Disruptive Behavior Disorders in Children and Adolescents

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Disruptive behavior disorders, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified, are serious conditions in children and adolescents that include a behavior pattern of violating the basic rights of others and age-appropriate rules or standards and may include aggressive behavior. Although no pharmacotherapy is currently approved for use in this population, evidence suggests that atypical antipsychotic treatment may be useful in patients with these conditions who present with problematic aggression. Currently, research on risperidone shows it to be effective in treating aggressive behavior in this patient population. Limited research is also available on olanzapine, quetiapine, and aripiprazole, but more research is needed on these and other agents. As with any pharmacotherapy, adverse events (including weight gain, headache, and somnolence) should be carefully considered with these medications, especially in children and adolescents, and it is important to properly dose and monitor patients during medication therapy.

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Disruptive behavior disorders, primarily including conduct disorder and oppositional defiant disorder, in children and adolescents are associated with aggression and poor short- and long-term outcomes. Evidence suggests that pharmacologic treatment, despite being currently off-label, may be effective in treating patients with these disorders and problematic aggression.

DISRUPTIVE BEHAVIOR DISORDERS

Disruptive behavior disorders include conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified. Disruptive behavior disorders often include aggression, and problematic aggression usually causes parents or other caregivers to bring these patients to psychiatric professionals for diagnosis and

treatment. While attention-deficit/hyperactivity disorder (ADHD) is estimated to occur in 3% to 5% of school-age children, disruptive behavior disorders are almost as common, with conduct disorder occurring in 1% to 4% of children and adolescents aged 9 to 17 years and oppositional defiant disorder occurring in 1% to 6% of the population.¹

Conduct Disorder

Many of the aggressive children and adolescents who are seen by clinicians for treatment have conduct disorder. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),² people with conduct disorder have a repetitive and persistent pattern of behavior that violates the basic rights of others or violates major age-appropriate societal norms or rules. Conduct disorder is manifested by the presence of at least 3 of the following criteria in the past 12 months, with at least 1 criterion present in the past 6 months: aggression toward people or animals; destruction of property; deceitfulness or theft; and serious violation of rules. The behavioral disturbances must also cause clinically significant impairment in social, academic, or occupational functioning. The aggression present in conduct disorder may include fighting, bullying, use of weapons, and other physical cruelty.²

In addition to the childhood problems brought on by current behavior disturbance, conduct disorder is associated with poor long-term outcomes. Conduct disorder is a risk factor for becoming a victim and/or a perpetrator of violence from or to an adult partner.³ Boys who meet the criteria for conduct disorder are more likely to develop antisocial personality disorder as adults,⁴ and boys with ADHD and comorbid conduct disorder have been shown

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to have a psychophysiological response pattern similar to that found in adults with antisocial personalities.⁵ Children with depression and comorbid conduct disorder may also create high and enduring societal costs as adults in the form of frequent utilization of inpatient and criminal justice services.⁶ The increased likelihood of poor long-term consequences of conduct disorder is an impetus for early and effective intervention for children with conduct disorder.

Subtypes of Aggression

Two subtypes of aggression may be manifested in patients with conduct disorder: predatory and impulsive/affective.⁷ Predatory aggression is goal-oriented, planned, and controlled. Individuals exhibiting this subtype of aggression may hide their aggressive acts and may be able to control their own behavior when they are being aggressive. They are very careful to protect themselves while being aggressive and try to benefit from being aggressive. They plan their aggressive acts and may even be proud of them.

Impulsive/affective aggression is reactive, unplanned, and uncontrolled. Symptoms may include nonprofitable damaging of the individual's own property and a loss of control in front of other people. Individuals exhibiting impulsive/affective aggression may expose themselves to physical harm and fight with stronger children. This subtype of aggression is often unplanned and without clear purpose, and individuals exhibiting it may express remorse afterwards. It appears that it is the impulsive/affective form of aggression, rather than the predatory form of aggression, that may be amenable to pharmacologic intervention.⁸

TREATMENT OPTIONS

Psychological and pharmacologic interventions may be effective in treating disruptive behavior disorders. According to an international consensus statement on ADHD and disruptive behavior disorders,⁹ psychological interventions—including school-based and family-based behavior therapy, group therapies, and individual therapies—are suggested first-line treatment for conduct disorder. In cases of disruptive behavior disorder, especially conduct disorder, in which aggression and/or impulsivity has been persistent and problematic, pharmacologic treatment was recommended.⁹ When using pharmacotherapy for children with conduct disorder, careful titration of dose is important, with full-day coverage as the goal; long-term, regular follow-up is necessary.

Potential pharmacotherapy for conduct disorder with marked aggression includes mood stabilizers, typical antipsychotics, and atypical antipsychotics. Several trials^{10–13} in the early 1980s investigated the use of typical antipsychotics in aggressive children with conduct disorder and

found active treatment superior to placebo. However, typical antipsychotic treatment was associated with problematic sedation with low-potency agents. Difficulties with extrapyramidal side effects were seen with high-potency agents. For these reasons, treatment with typical antipsychotics was problematic in this population. Therefore, atypical antipsychotics became of interest for treating children with aggression and disruptive behavior disorders.

ATYPICAL ANTIPSYCHOTICS

The safety and efficacy of atypical antipsychotics, including risperidone,^{14–22} olanzapine,^{23–25} quetiapine,^{26–28} and aripiprazole,²⁹ in treating aggression in children with conduct disorder and other disruptive behavior disorders have been examined by multiple studies in the last decade. Atypical antipsychotics have generally been significantly more efficacious than placebo in treating aggression, but they have varying side-effect profiles.

Risperidone

To date, risperidone is the most extensively studied atypical antipsychotic for disruptive behavior disorders; studies^{14–22,30} have shown that risperidone is beneficial in treating children and adolescents with conduct disorder and other disruptive behavior disorders and tends to be well tolerated.

For example, Aman and colleagues¹⁷ conducted a 6-week, multicenter, double-blind, parallel-group trial of risperidone in 118 children aged 5 to 12 years with disruptive behavior disorders and subaverage intelligence (with an inclusive IQ of 36–84). In order to be included in the study, participants had to have a score of ≥ 24 on the conduct problem subscale of the Nisonger Child Behavior Rating Form (NCBRF).³¹ Study participants also had a DSM-IV diagnosis of severe disruptive behavior disorder and a Vineland Adaptive Behavior Scales³² score of ≤ 84 . They were randomly assigned to receive risperidone at a weight-adjusted dose of 0.02 to 0.06 mg/kg per day or placebo. Those who received active treatment took, on average, 1.16 mg/day of risperidone.

As early as week 1 of double-blind treatment, a significantly greater reduction in symptom severity occurred with risperidone versus placebo, as measured by mean change from baseline in NCBRF conduct problem subscale scores ($p \leq .01$), and this difference was maintained throughout the study.¹⁷ Improvement was also measured by the Clinical Global Impressions (CGI) scale change score, with a significantly larger group of patients improving with active treatment in a clinically observable fashion when compared with those who were treated with placebo ($p < .001$).

It is important to pay close attention to dosing in this population, especially since atypical antipsychotics are associated with substantial adverse events, in hopes of

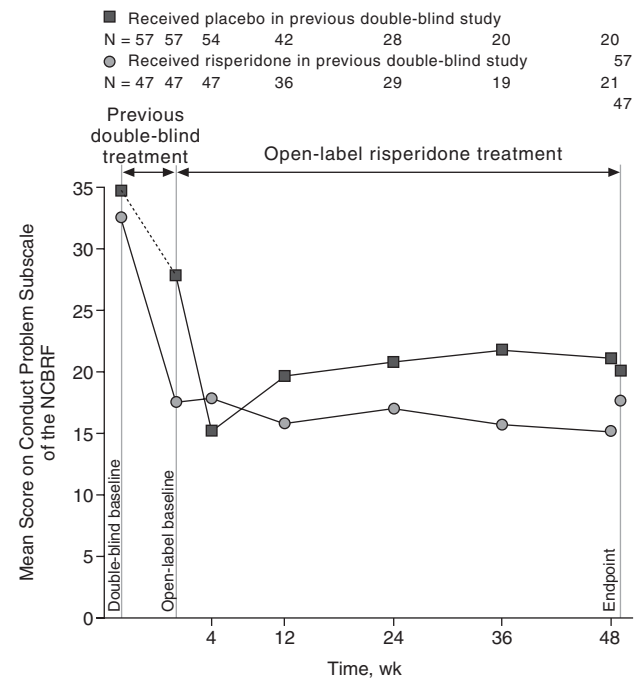
minimizing risk. Ninety-eight percent of participants taking risperidone in this trial¹⁷ experienced some kind of adverse event, while 70% of subjects taking placebo experienced adverse events. The most common adverse events with risperidone and placebo were somnolence (experienced by 51% of the risperidone group and 10% of the placebo group) and headache (experienced by 29% of the risperidone group and 14% of the placebo group). However, somnolence did not seem to be the cause of the symptom amelioration. In fact, not experiencing sedation was associated with better outcomes in the active treatment group. Other side effects included vomiting, dyspepsia, weight gain, prolactin elevation, increased appetite, and rhinitis. Weight gain was experienced by 15% of participants taking risperidone, compared with 2% of participants taking placebo, and the mean weight increase was significantly greater with risperidone (2.2 kg) than with placebo (0.9 kg; $p < .001$).

In an open-label, 48-week extension¹⁸ of this trial conducted in 107 children, Findling and colleagues found that symptom reduction, measured by a lowering of NCBRF conduct problem subscale scores, was maintained over time with a mean risperidone dose of 1.51 mg/day. Patients taking placebo during the earlier double-blind phase of the trial were switched to risperidone at baseline of the open-label phase and eventually achieved symptom reduction comparable to those patients who had been taking risperidone during the double-blind phase (Figure 1). The most common side effects with risperidone were somnolence, headache, rhinitis, and weight gain.

Another large open-label trial³³ of risperidone treatment for disruptive behavior disorders and subaverage IQ (range, 36–84) examined 504 children aged 5 to 14 years (with a mean age of 9.7 years). Participants had an NCBRF conduct problem subscale score of 24 or greater and a Vineland Adaptive Behavior Scales score of 84 or less. Taking a median dose of risperidone of 1.5 mg/day, participants experienced a substantial decrease in conduct problems on the NCBRF ($p < .001$). Symptom amelioration was generally reached by week 3 or 4 of active treatment and was maintained over the course of the 52-week study.

Risperidone treatment of disruptive behavior disorders with comorbid ADHD. It has been observed for quite some time that children and adolescents with disruptive behavior disorders often have comorbid ADHD. Many of these patients are already receiving psychostimulant treatment for their ADHD prior to the initiation of antipsychotic treatment for a disruptive behavior disorder. Aman and colleagues³⁴ pooled data from 2 identically designed, 6-week, double-blind, placebo-controlled studies of risperidone in children with disruptive behavior disorders and subaverage IQ who also had comorbid ADHD. Ongoing psychostimulant treatment, including methylphenidate, dextroamphetamine, and pemoline, was found in

Figure 1. Scores on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (NCBRF) of Children With Severe Disruptive Behaviors and Low IQ Taking Risperidone in a 48-Week Open-Label Extension Study^a



^aReprinted with permission from Findling et al.¹⁸ Lower scores indicate better condition.

about half (47.1%) of the 155 children (aged 5 to 12 years). Therefore, the 4 treatment groups were those receiving placebo and stimulant, those receiving placebo and no stimulant, those receiving risperidone and stimulant, and those receiving risperidone and no stimulant. Both risperidone treatment groups showed significant improvement in conduct, hyperactivity, and irritability compared with the placebo groups when measured by the NCBRF and the Aberrant Behavior Checklist (ABC), regardless of whether or not the patient was receiving stimulant treatment.

Researchers hoped concomitant stimulant treatment would mediate the weight gain that is often associated with atypical antipsychotic treatment. However, the side effect profiles, including weight gain, across the treatments were not significantly affected by the presence or absence of a stimulant.³⁴ The most common adverse events were somnolence and headache. Weight gain was experienced by none of the participants taking placebo (with or without a stimulant), 14.3% of participants taking risperidone and a stimulant, and 7.0% of participants taking risperidone and no stimulant.

Relapse prevention of disruptive behavior disorders with risperidone. Disruptive behavior disorders, including conduct disorder, are chronic conditions that require maintenance therapy. Reyes and colleagues²¹ conducted a

double-blind, maintenance study of children and adolescents 5 to 17 years of age with disruptive behavior disorders. Subjects (N = 335) who had responded acutely to 6 weeks of open-label risperidone and in whom response had continued for 6 additional weeks of single-blind treatment were randomly assigned to receive 6 months of maintenance treatment at their previously effective dosage of risperidone or 6 months of placebo as part of a discontinuation paradigm. Inclusion in the study required that participants have NCBRF Parent Version conduct problem subscale scores of ≥ 24 at screening and initiation of treatment. The majority of subjects had an IQ score within the normal range, and two thirds of subjects had comorbid ADHD. Mean risperidone dosage in the maintenance phase was 0.02 mg/kg per day.

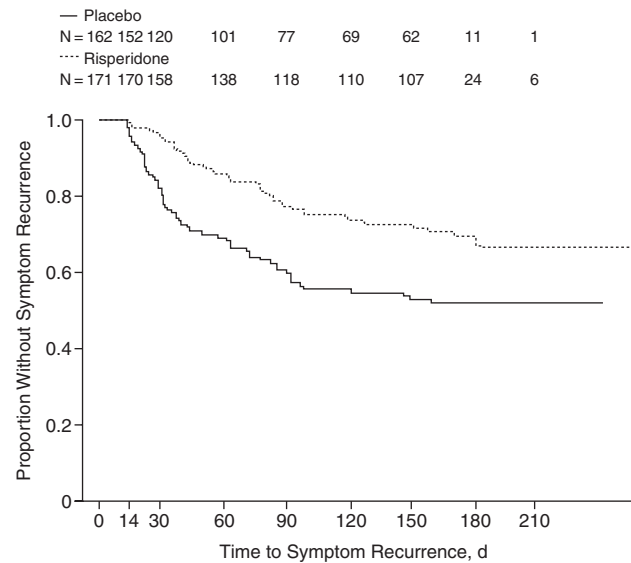
The primary outcome measure was time to symptom recurrence after randomization; recurrence was defined as a sustained deterioration according to CGI-Severity scale rating and NCBRF conduct problem subscale scores.²¹ Risperidone was effective for relapse prevention; the rate of relapse was significantly higher in the placebo group (42%) than in the risperidone group (27%). The time until 25% of patients experienced symptom recurrence was 119 days in the group receiving risperidone treatment and 37 days in the group taking placebo (Figure 2). Although ongoing active treatment proved superior to placebo for relapse prevention, it is important to point out that a substantial number of subjects taking placebo did not relapse.

Long-term safety of risperidone. When considering long-term treatment of disruptive behavior disorders with atypical antipsychotics, it is important to also consider long-term safety. As with efficacy, more data exist about long-term safety with risperidone than with other atypical antipsychotics. Risperidone does not appear to be associated with adverse changes in height or pubertal development, which are important considerations when administering pharmacotherapy to children and adolescents.

Dunbar and colleagues³⁵ compared the observed versus expected outcomes for height and sexual maturation in pooled data from 5 studies that included 700 children and adolescents, aged 5 to 15 years, with disruptive behavior disorders. Subjects treated with risperidone up to 12 months had an average increase in height that was 1.2 cm greater than the reference population. No delay in sexual maturation occurred, measured according to Tanner staging, in risperidone-treated subjects. The temporarily elevated levels of prolactin that have been associated with risperidone treatment were not correlated with any abnormal growth or sexual maturation.

In another analysis of pooled data from 5 trials, Findling and colleagues³⁶ specifically investigated the possible correlation between adverse events and the elevated prolactin levels found in patients treated with risperidone over the long-term. Although an initial increase

Figure 2. Relapse Prevention of Disruptive Behavior Disorders With Risperidone: Time to Relapse Among Children and Adolescents^a



^aReprinted with permission from Reyes et al.²¹

in prolactin levels occurred in children treated with risperidone, particularly during the first 2 months of treatment, prolactin levels gradually decreased over the course of 1 year of treatment. At least 1 side effect hypothetically attributable to prolactin elevation was reported in 2.2% of children, but no direct correlation between hyperprolactinemia and these side effects was found.

Olanzapine

Fewer data are available on treatment of aggression in disruptive behavior disorders with other atypical antipsychotics, but a few studies²³⁻²⁵ have been conducted with olanzapine. Although these studies showed benefit for olanzapine treatment, side effects, especially weight gain, were problematic in all of them.

Handen and Hardan²⁴ conducted an open-label, prospective trial of olanzapine in 16 adolescents (aged 13-17 years) with disruptive behavior disorders and subaverage intelligence (IQ 36-79). Significant improvement was found on the irritability and hyperactivity subscales of the ABC and Conners Parent Rating Scale Hyperactivity Index after 8 weeks of olanzapine treatment (average dose 13.7 mg/day; $p < .002$). Four subjects had been discontinued prematurely due to worsening of symptoms or side effects. Weight gain was the most common side effect, with a mean weight gain of 12.7 lb and 10 patients gaining 10 lb or more.

Masi and colleagues²⁵ explored the efficacy and tolerability of olanzapine in a retrospective study (review of clinical records) of 23 adolescents with conduct disorder.

These patients had not satisfactorily responded to adequate trials of mood stabilizers and nonpharmacologic interventions. In addition to receiving olanzapine treatment (average dose 8 mg/day), all subjects participated in some type of psychological treatment, including psychotherapy, family therapy, and day-hospital group treatments. Follow-up lasted 6 to 12 months. Based on 2 outcome measures (a 50% improvement on the Modified Overt Aggression Scale and a CGI-Improvement scale score of 1 or 2), 60.9% of subjects were responders. Mean weight gain by the end of follow-up was 4.6 kg, and sedation was another common side effect.

Quetiapine

Research about quetiapine for aggression has begun, and the drug seems to have benefit in conduct disorder. Findling and colleagues²⁶ conducted an 8-week pilot study of the effectiveness, safety, and pharmacokinetics of quetiapine in 17 moderately aggressive children (aged 6–12 years) with conduct disorder, with subjects taking a median dose of 150 mg/day (mean 4.4 mg/kg/day). Fifty percent of the 12 completers had a CGI-I scale score of 1 or 2 at endpoint. Fatigue was the most common side effect, and the median weight gain was 2.3 kg. There were no extrapyramidal side effects or changes in prolactin levels. In the 26-week open-label extension study, Findling and colleagues²⁷ examined the long-term effectiveness and safety of quetiapine in 9 subjects and found that benefit was generally sustained at similar doses. Quetiapine was also reasonably well tolerated with adjunctive stimulants. Median increase in weight was 2.3 kg at endpoint.

Kronenberger and colleagues²⁸ conducted a study of adjunctive quetiapine in moderately aggressive adolescents (aged 12–16 years) with disruptive behavior disorders and comorbid ADHD who had not adequately responded to methylphenidate monotherapy. Subjects received 3 weeks of OROS methylphenidate monotherapy titrated to 54 mg/day (N = 30) and then received 9 weeks of adjunctive quetiapine (given b.i.d., with a maximum dose of 600 mg/day) for those subjects who remained symptomatic (N = 24). At study endpoint, 42% met all criteria for clinically significant improvement, and 79% had minimal aggression. Sedation was the most common side effect. A mean weight loss of 0.9 kg occurred during methylphenidate monotherapy, but a mean weight gain of 1.2 kg occurred during combination treatment.

Aripiprazole

Few data exist on the treatment of disruptive behavior disorders with aripiprazole, but one study done by Findling and colleagues²⁹ found approximately 52% of study participants (N = 23) with conduct disorder to be responders after 2 weeks of treatment, according to CGI scale criteria. This study was part of a dose-finding study, so subjects were initially treated with approximately 0.1–0.2

mg/kg/day of aripiprazole, which led to some tolerability problems, mostly vomiting and somnolence. Dosage was then cut approximately in half, which readily addressed these side effects. This finding is a reminder that it is important not only to test pharmacotherapy but to test it at a proper dose.

CONCLUSION

Conduct disorder and other disruptive behavior disorders are serious conditions. Nonpharmacologic therapy is important in children and adolescents with these disorders, but evidence suggests that pharmacotherapy may be effective in some patients, especially those experiencing problematic aggression. Impulsive/affective aggression seems to be a key treatment target. Although much research on risperidone has been conducted, more research, particularly long-term study, is needed on other agents, including those discussed in this article and other atypical antipsychotics that have not been studied systematically in these conditions in order to provide more rational and scientifically rigorous approaches for the treatment of this population with this class of drug.

Drug names: aripiprazole (Abilify), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Ritalin, Concerta, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, dextroamphetamine, methylphenidate, olanzapine, quetiapine, and risperidone are not approved by the U.S. Food and Drug Administration for use in youths with disruptive behavior disorders.

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