A Randomized Controlled Trial of Risperidone in the Treatment of Aggression in Hospitalized Adolescents With Subaverage Cognitive Abilities

Jan K. Buitelaar, M.D., Ph.D.; Rutger Jan van der Gaag, M.D., Ph.D.; Peggy Cohen-Kettenis, Ph.D; and Caroline T. M. Melman, M.Sc.

Background: Risperidone is an atypical antipsychotic drug that blocks dopamine as well as serotonin receptor systems. The present study was designed to examine the efficacy and safety of risperidone in a 6-week double-blind, randomized, parallel-group design in the treatment of aggression in adolescents with a primary diagnosis of DSM-IV disruptive behavior disorders and with subaverage intelligence.

Method: We randomly assigned 38 adolescents (33 boys; 10 subjects with slightly subaverage IQ, 14 with borderline IQ, and 14 with mild mental retardation), who were hospitalized for treatment of psychiatric disorders associated with severe aggression, to receive risperidone or placebo. The main efficacy measures were the Clinical Global Impressions-Severity of Illness scale (CGI-S), the modified Overt Aggression Scale (OAS-M), and the Aberrant Behavior Checklist (ABC). Side effects were measured using the Extrapyramidal Symptom Rating Scale (ESRS).

Results: The mean daily dose of risperidone at the end of treatment was 2.9 mg (range, 1.5–4 mg). Risperidone, compared with placebo, was associated with significant improvements on the CGI-S ($p < .001$) and the at-school ABC overall and hyperactivity scales ($p < .05$). During a 2-week washout following the 6-week trial, a statistically significant worsening was found in the risperidone group on the CGI-S scale, the OAS-M, and the ABC. Extrapyramidal symptoms were absent or very mild during risperidone treatment. Transient tiredness was present in 11 (58%) of 19 drug-treated subjects. Other untoward effects included sialorrhea, nausea, and slight weight gain (mean = 3.5% of body weight in the risperidone group). No clinically relevant changes were found in laboratory parameters, electrocardiogram, heart rate, or blood pressure.

Conclusion: These results suggest that risperidone may be effective for severe aggression in adolescents with disruptive behavior disorders and subaverage intelligence, and these results are consistent with reports suggesting its effectiveness for treating severe aggression in adolescents in general.

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Reprint requests to: Jan K. Buitelaar, M.D., Ph.D., Department of Child Psychiatry, B.01.324, P.O. Box 85500, 3508 GA Utrecht, the Netherlands (e-mail: J.K.Buitelaar@psych.azu.nl).

To date, no medication has received approval by the U.S. Food and Drug Administration or similar agencies in other countries to be used specifically for the treatment of aggression for either the adult or the pediatric population. In spite of this, in clinical practice, medication is often used in the management of aggression in children and adolescents, either as an adjunct in a comprehensive treatment approach, in the case of treatable comorbid conditions, when behavior therapy interventions are insufficient, or when aggression may lead to immediate danger.

Although a variety of medications have been tried in the management of aggression, such as lithium, clonidine, carbamazepine, stimulants, β-blockers, serotonin reuptake inhibitors, and classical neuroleptics,[1–3] consistently effective and safe pharmacotherapies have not been established. For example, 1 small controlled study[4] and 2 larger double-blind placebo-controlled studies[5,6] reported lithium to be significantly more effective than placebo in the treatment of aggressive behavior in hospitalized school-aged children, but another controlled study[7] in outpatient children and a controlled study[8] in hospitalized adolescents, although lasting only 2 weeks, could not establish superiority of lithium over placebo. Initial promising effects of carbamazepine in treating aggression in 10 children with conduct disorder in an open trial[9] could not be confirmed in a double-blind placebo-controlled follow-up study in 22 children.[10] Clonidine was shown to reduce aggression[11] and irritability and explosiveness[12] in small studies. Further, even though stimulants have been shown to reduce aggression in children with attention-deficit/hyperactivity disorder (ADHD) (for review, see Weller et al.[3]), the evidence

that stimulants affect destructive and antisocial behavior was inconsistent.[13,14] In a recent placebo-controlled trial, however, methylphenidate had positive effects on antisocial behavior in 84 children with conduct disorder. These effects were independent of the initial severity of comorbid ADHD symptoms and of stimulant-induced changes in ADHD symptoms.[15] The selective serotonin reuptake inhibitor (SSRI) fluoxetine was superior to placebo in the treatment of impulsive aggressive behavior of adults with personality disorders.[16] This result supports the evidence of an inverse relationship between central serotonergic system functioning and impulsive aggressive behavior.[17] Controlled studies with SSRIs in children and adolescents with aggression have not yet been performed. Open-label studies have described favorable effects of trazodone in the treatment of aggressive behavior in pediatric inpatients.[18,19]

Conventional neuroleptic agents have been the most commonly prescribed drugs for children and adolescents with aggressive behavior.[20] The effects of neuroleptics have been investigated in a number of older controlled studies and include a reduction of aggression, hostility, unresponsiveness, and hyperactivity.[5,21–23] However, concerns about side effects limit the use of classical neuroleptics. Worrisome untoward effects particularly include extrapyramidal symptoms, the risk of tardive dyskinesia and neuroleptic malignant syndrome, excessive sedation, and cognitive blunting.[24]

Risperidone is the first of a new class of neuroleptic agents that block dopamine-2 (D_2) as well as serotonin-2 ($5\text{-}HT_{2A}$) receptors.[25] It has been found effective in treating the positive and negative symptoms of schizophrenia and is reported to have a much lower potential than conventional neuroleptics to induce extrapyramidal side effects and, presumably, tardive dyskinesia.[26] In clinical trials of psychotic patients, treatment with risperidone was further associated with a marked decrease of hostility and aggression.[27] Explorative studies in psychogeriatric patients and subjects with mental retardation showed that risperidone has beneficial effects on disruptive behavior problems, whereas it induced only few extrapyramidal side effects.[28,29]

The experience with risperidone in a pediatric population is still limited. Uncontrolled observations point to beneficial effects of risperidone in children and adolescents with developmental disorders,[30–36] schizophrenia,[36,37] aggression,[38,39] and chronic tic disorders.[40] A recent controlled study,[41] using a 10-week treatment period and a parallel-group design (N = 20), reported that risperidone was superior to placebo in ameliorating aggression in children between 6 and 14 years old who had conduct disorder and intellectual skills in the normal range.

The present randomized, double-blind, placebo-controlled study was designed to examine the clinical effectiveness and safety of risperidone in the treatment of aggression of adolescent inpatients with subaverage cognitive skills.

METHOD

Subjects

The subjects included in the study were institutionalized because of a chronic pattern of repetitive aggressive behavior that had been found to be refractory to treatment approaches delivered on an outpatient basis, although not all had received prior drug treatments. They were hospitalized in the Beele or in Groot Emaus, which are tertiary referral centers in Voorst and in Ermelo (the Netherlands), respectively, for adolescents with severe aggressive behavior and borderline intelligence or mild mental retardation. Subjects typically stay in the Beele or Groot Emaus for about 2 years. Problem behaviors included severe verbal aggression and threatening behavior, property destruction, and physical violence. The subjects underwent an extensive psychiatric, psychological, and medical examination, and diagnostic and laboratory assessment was completed with information on prior treatment and developmental history.

Subjects could be included in the study if (1) their overt aggressive behavior persisted during hospitalization, as reflected in a score of at least 1 on the modified Overt Aggression Scale (OAS-M)[42] rated by nurses in the ward at the end of the baseline phase; (2) their aggressive behavior failed to respond to behavioral treatment approaches (typically, these behavioral treatments involve contingency management and social skills training delivered on an individual basis for at least 2 months); (3) there was a clinical indication for drug treatment; (4) they were between 12 and 18 years old; (5) they had a principal diagnosis of conduct disorder, oppositional defiant disorder, or attention-deficit/hyperactivity disorder (ADHD) according to DSM-IV; and (6) they had a full-scale IQ between 60 and 90 on the Wechsler Intelligence Scale for Children-Revised.

Subjects were excluded if (1) they were suffering from neurologic, cardiac, pulmonary, or hepatic diseases; (2) they were suffering from primary mood disorders, schizophrenia or other active psychosis, or suicidality; (3) they had a comorbid substance abuse disorder according to DSM-IV; (4) if female, they were pregnant or used inadequate contraception; (5) a major change in treatment strategy (such as transition to another ward) was expected in the near future; or (6) it was not considered feasible to discontinue current psychotropic medication. The study was approved by the Institutional Review Board committees of the Beele, Groot Emaus, and the University Medical Center Utrecht (the Netherlands). All participants and their caregivers gave informed consent.

Trial Design

We employed a double-blind, placebo-controlled, parallel-group design that included a 2-week baseline period, a 6-week double-blind treatment period, and a 2-week

washout period. Since the participants continued taking previous psychotropic medication, if any, during the baseline period, this was an observation period with continuation of prior treatments. The subjects who had been taking psychotropic medication entered the trial because of dissatisfaction with the current medication due to side effects or lack of efficacy. At the end of the baseline period, current medication was discontinued and subjects were randomly assigned to matching risperidone, 1 mg/day, or placebo tablets. This procedure was chosen for the following reasons: it mimics clinical practice most in that one medication is substituted by another without a medication-free interval, change and washout of prior medication took place under double-blind conditions, and subjects with and without prior medications had a change in treatment once and at the same time, i.e., at the start of the double-blind period. The randomization code had been generated by computer in blocks of 4 numbers. The double-blind treatment period consisted of a 2-week dose-rising phase and a 4-week fixed-dose phase. Titration started with 0.5 mg twice daily (8:00 a.m. and 6:00 p.m.). The daily dose could be increased by 1 mg daily to a maximum of 5 mg twice daily. The dosage was adjusted by the responsible psychiatrist (J.K.B. or R.J.v.d.G.), who was blind to the treatment, on the basis of clinical response, which was based on the reports of the child and the nurse on the ward and on the psychiatrist's own clinical global impression (see below) and on the basis of adverse effects (see below). During the fixed-dose phase, dosages remained as fixed as possible at the dosage level attained during the dose-rising phase. The dose could be lowered in case of adverse effects. The use of concomitant psychotropic medication was not allowed during the double-blind period, except for biperiden and oxazepam, respectively, for subjects developing extrapyramidal symptoms and for subjects requiring additional sedation. Concomitant medication for acute or chronic somatic illnesses was allowed during the trial, at the discretion of the clinician in charge. At the end of the double-blind period, all trial medication was stopped for a 2-week washout period.

Compliance was checked in 3 ways. First, the subjects took the trial medication while under supervision of the ward personnel. Second, all unused medication was collected and stored, and tablets were counted by the trial monitor. Third, at the end of the double-blind period, plasma concentrations of risperidone were determined.

Measures

Efficacy. The primary efficacy measure was the overall severity of the subject's condition, as assessed by the psychiatrist and as reflected on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[43] This 7-point scale is scored as follows: no symptoms = 1, borderline = 2, mild = 3, moderate = 4, marked = 5, severe = 6, and very severe = 7. Secondary efficacy measures were the OAS-M[42] and the Aberrant Behavior Checklist (ABC).[44] The OAS-M and the ABC were completed by both the ward personnel and the teachers. The OAS-M measures the severity of 4 types of aggression (verbal aggression, destruction of property, aggression to self, and physical violence). Each type of aggression is rated on a 4-point scale with prespecified anchors. The sum score ranges from 0 to 16, with higher scores reflecting greater severity of aggression.[42] The ABC has been specially developed for studies in subjects with developmental disabilities and mental retardation.[44] The ABC consists of 58 items that are rated on a 4-point scale and are distributed across 5 subscales: irritability, social withdrawal, stereotypy, hyperactivity, and inappropriate speech. The CGI-S,[43] the OAS-M,[42] and the ABC[44] have all been shown to be sensitive to the effects of psychotropic medication. The efficacy measures were taken at selection, at the end of the baseline period, following the start of the double-blind period at 2, 4, and 6 weeks (endpoint), and at the end of the washout period. All efficacy measures thus captured observations over a 2-week period. Prior to the study, the ward personnel and the teachers were familiarized with the OAS-M and ABC checklists and instructed about the completion thereof. It was planned that a single teacher and the same 2 nurses on the ward would complete the checklists for a participant.

Safety. Extrapyramidal side effects were measured on the Extrapyramidal Symptom Rating Scale (ESRS).[45,46] The ESRS includes 6 clusters: general questionnaire, parkinsonism, dystonia, dyskinetic movements, clinical global impression of severity of dyskinesia, and clinical global impression of severity of parkinsonism. The ESRS was completed by the psychiatrist at the end of the baseline period, at the end of the double-blind period, and at the end of the washout period. At each clinical visit, the subjects were prompted to communicate the presence of any adverse experience by being asked "Have you experienced any discomfort since the last visit?" At each clinical visit, blood pressure and heart rate were recorded in sitting position, and the subject was weighed. Blood samples were obtained by means of venipuncture at selection and at the end of the double-blind period to determine plasma levels of risperidone and to perform laboratory tests for clinical hematology and biochemistry. An electrocardiogram (ECG) was recorded at selection and at the end of the double-blind period. Cognitive function was evaluated at baseline, at the end of the double-blind period, and at the end of the washout period to determine the influence of risperidone on this domain. These results will be reported separately.

Data Analyses

At the start of this trial, insufficient data were available regarding the influence of risperidone on aggressive behavior of adolescents. Therefore, it was impossible to calculate a priori the required sample size. We decided that

this trial would be an exploratory parallel trial with 40 participants. This would give 80% power to find an effect size of 0.7 with $\alpha = .05$ and nonparametric testing.[47]

Because the data were not normally distributed, they were analyzed with nonparametric statistics using an intent-to-treat approach. We used the Fisher exact test for categorical measures. Within-subject changes from baseline to endpoint and from endpoint to the end of washout were analyzed with the Wilcoxon signed rank test. Differences between treatment groups in the changes from baseline to endpoint (i.e., treatment effects) and from endpoint to the end of washout (i.e., washout effects) were evaluated with the Wilcoxon 2-sample test. The end of the 6-week double-blind period served as endpoint. If patients did not have a visit following 6 weeks of double-blind treatment, the data from the last visit in the treatment period were used for endpoint analysis (last observation carried forward). All statistical tests were interpreted at a 5% 2-tailed level of significance.

RESULTS

Demographics

All subjects who were hospitalized in the Beele between October 1, 1994, and October 1, 1996, were screened for meeting the inclusion and exclusion criteria. In a similar way, subjects hospitalized in Groot Emaus between October 1, 1995, and October 1, 1996, were screened. Of a consecutive series of 145 subjects screened, 48 were found eligible and asked to participate in the study. Ten children and their parents or caregivers declined participation on grounds of negative attitudes toward the prescription of psychotropic medication. As a result, 38 participants (the Beele, N = 28; Groot Emaus, N = 10) were recruited and enrolled into the study.

Table 1 summarizes the clinical features of the subjects, including age, sex, intelligence test scores, principal diagnosis and comorbid disorders, onset of symptoms, details of hospitalizations, severity of psychosocial stressors (Axis IV of DSM-IV), and Global Assessment of Functioning scores (Axis V). Fourteen subjects (risperidone, N = 7; placebo, N = 7) had a full-scale IQ in the borderline intellectual range, and 14 subjects (risperidone, N = 6; placebo, N = 8) had mild mental retardation. The risperidone and placebo groups appeared not to differ in clinical features, except for greater severity of psychosocial stressors in the risperidone group (Wilcoxon 2-sample test, p = .01) and a trend that the subjects in the risperidone group had a higher number of prior hospitalizations. During the initial observation period, 6 subjects in the risperidone group were taking medication (3 taking neuroleptic monotherapy; 2 taking 2 neuroleptics, thioridazine and zuclopenthixol; 1 taking a neuroleptic and oxazepam; and 1 taking a neuroleptic and an antiparkinsonian agent). Similarly, 6 subjects in the placebo group were taking medication at entry (5 taking neuroleptic monotherapy and 1 taking methylphenidate). In the risperidone group, 5 subjects had an unsuccessful trial with a conventional neuroleptic (all had 1 trial) before they were selected for the present study. Similarly, in the placebo group, 5 subjects had prior trials with a conventional neuroleptic (4 subjects had 1 trial, 1 subject had 2 trials). Eighteen subjects had a history of prior unsuccessful treatment with psychostimulants for ADHD.

Table 1. Sample Characteristics[a]

Variable	Risperidone (N = 19)	Placebo (N = 19)	p Value[b]
Age, y, mean ± SD	14.0 ± 1.5	13.7 ± 2.0	NS
Sex, M:F	17:2	16:3	NS
WISC-R IQ, mean ± SD			
Full-scale	76.0 ± 9.9	73.3 ± 10.1	NS
Verbal	74.5 ± 11.0	71.2 ± 6.9	NS
Performance	84.4 ± 9.8	81.2 ± 15.9	NS
Principal diagnosis, N			
Conduct disorder	14	16	NS
Oppositional defiant disorder	4	2	NS
Disruptive behavior disorder NOS	1	1	NS
Comorbid diagnosis, N			
ADHD	14	12	NS
Anxiety disorder	0	3	NS
Use of psychotropic medications at entry, N	6	6	NS
Age at onset of symptoms, y, mean ± SD	4.8 ± 3.1	4.5 ± 2.9	NS
No. of prior hospitalizations, mean ± SD	3.1 ± 1.3	2.5 ± 2.0	.06
Age at current hospitalization, y, mean ± SD	13.1 ± 1.5	12.8 ± 1.4	NS
Length of current hospitalization, d, mean ± SD	276 ± 237	377 ± 500	NS
Severity of psychosocial stressors, N[c]			
Moderate	1	4	
Severe	13	5	
Extreme	3	2	.01
GAF score, mean ± SD (range, 30–70)	50.0 ± 9.6	52.9 ± 10.5	NS

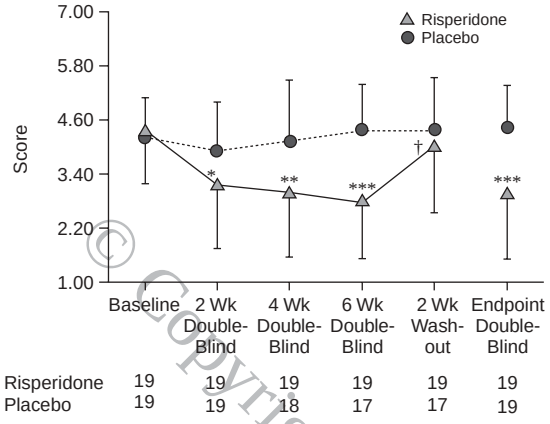
[a]Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAF = Global Assessment of Functioning, NS = not significant, WISC-R = Wechsler Intelligence Scale for Children-Revised.
[b]Wilcoxon 2-sample test or chi-square test, as appropriate.
[c]According to Axis IV of DSM-IV.

The subjects from the Beele had worse scores on CGI-S and OAS-M as rated at the ward than the subjects from Groot Emaus. No systematic differences in treatment effects were found between the subjects of these 2 centers.

Premature Trial Termination, Compliance, and Dose

Two subjects in the placebo group stopped treatment during the double-blind period because of lack of therapeutic effects and uncontrollable aggressive behavior.

Figure 1. CGI-Severity Scores (mean and SD) for Risperidone and Placebo as Rated by the Investigator[a]



[a]Abbreviation: CGI-Severity = Clinical Global Impressions-Severity of Illness scale. Asterisks reflect a significant treatment effect, i.e., larger change from baseline for the subjects on risperidone compared with those on placebo (*$p < .05$, **$p < .01$, ***$p < .001$) on Wilcoxon matched pairs test. The dagger (†) indicates a significant withdrawal effect ($p < .01$) for risperidone compared with placebo. The analysis at endpoint uses last observation carried forward.

One patient in the risperidone group terminated the study following 1 week of washout because of unmanageable aggression. The treatment compliance appeared to be very good. At endpoint, no risperidone was detected in the plasma of the subjects treated with placebo. In one subject from the risperidone group, the plasma sample had by mistake been taken 14 days after the last intake of medication. In the plasma of all other subjects in the risperidone group, measurable amounts of risperidone were found (mean ± SD concentration = 18 ± 24 ng/mL).

At endpoint, none of the risperidone-treated subjects took a daily dose higher than 4 tablets (4 mg), while 1 placebo-treated subject took 5 tablets and 2 took 6 tablets. The most frequently (63% of the subjects) used end dose of risperidone was 3 mg/day. The mean daily dose of risperidone at endpoint was 2.9 mg (range, 1.5–4 mg). This was equivalent to 0.044 mg/kg (range, 0.019–0.080 mg/kg). The dose had been reduced because of adverse experiences in 5 subjects (risperidone, N = 4; placebo, N = 1). The main reason for dose reduction in the risperidone group was tiredness, which disappeared after dose reduction. One patient in the risperidone group stopped treatment temporarily because of an adverse experience (nausea).

Efficacy

The distribution of the scores on the CGI-S is shown in Figure 1. At selection, 15 subjects (79%) in each treatment group were rated on the CGI-S as "markedly," "severely," or "extremely severely" disturbed. After treatment with risperidone for 6 weeks, only 4 subjects (21%) were considered to be "markedly" or "severely" disturbed. In contrast, 16 subjects (84%) of the placebo group were still "markedly" to "extremely severely" disturbed at endpoint. With respect to the changes in the CGI-S scores, risperidone was statistically superior to placebo after 2 weeks of treatment (Wilcoxon 2-sample test, $p = .013$) and throughout the whole treatment period thereafter (mean ± SD CGI-S score in risperidone group = 4.3 ± 1.4 at baseline and 2.7 ± 1.2 at endpoint; in placebo group, 4.2 ± 0.9 at baseline and 4.4 ± 1.0 at endpoint; treatment effect, $p < .001$). In terms of changes in CGI-S score on an individual level, at endpoint 9 subjects in the risperidone group had improved by 2 points and 4 by 3 points, whereas none of the subjects deteriorated by 2 points or more. In the placebo group, none of the patients improved by 2 points and only 1 by 3 points, and 2 patients deteriorated by 2 points. During the washout period, the subjects in the risperidone group showed a significantly greater deterioration than the subjects treated with placebo (CGI-S score at washout 4.0 ± 1.6 for risperidone vs. 4.4 ± 1.2 for placebo; washout effect, $p < .01$).

The OAS-M and ABC data rated by the ward personnel and the teachers have been summarized in Table 2. Ward treatment with risperidone was associated with a significant reduction of the overall OAS-M scores (Wilcoxon signed rank test, $p < .01$) and of the OAS-M scores for physical aggression ($p < .001$) and aggression to property ($p < .01$) obtained at endpoint compared with scores at baseline. Among the subjects treated with placebo, no significant changes of OAS-M scores on the ward were observed. However, the difference in changes between the treatment groups failed to reach the 5% level of statistical significance. At the end of the washout, overall OAS-M scores ($p < .05$) and scores for physical aggression ($p < .01$) deteriorated significantly within the risperidone group. This washout effect was significantly greater for risperidone than for placebo for both measures ($p = .05$ and $p < .01$, respectively). On the OAS-M scores rated by the teacher at school, no significant changes were found within or between the treatment groups.

Within the risperidone group, overall ABC scores (Wilcoxon signed rank test, $p < .05$) and scores on the subscales of irritability ($p < .05$), hyperactivity ($p < .01$) and inappropriate speech ($p < .01$) improved significantly at endpoint compared with baseline. Significant deteriorations during washout were detected on the overall ($p < .05$) and hyperactivity ($p < .01$) scores of the risperidone group. Such significant changes were absent within the placebo group. When the changes between the treatment with risperidone and placebo were compared, tendencies toward differences were found for the overall ABC score (Wilcoxon 2-sample test, $p = .06$) and for hyperactivity and inappropriate speech ($p < .10$).

The ABC scores obtained from the teachers showed similar changes and similar intergroup differences as the

Table 2. Ratings (mean ± SD) by Ward Personnel and Teachers at Baseline and Endpoint and Following Washout[a]

	Risperidone			Placebo		
Measure	Baseline	Endpoint	Washout	Baseline	Endpoint	Washout
OAS-M						
At the ward						
Overall score	11.5 ± 8.2	6.7 ± 6.3**	10.4 ± 7.9* †	9.0 ± 7.4	8.1 ± 6.9	8.0 ± 6.8
Verbal aggression	1.7 ± 0.9	1.6 ± 0.9	1.8 ± 1.0	1.5 ± 1.0	1.4 ± 1.0	1.5 ± 1.1
Aggression against property	1.6 ± 1.0	0.9 ± 0.9**	1.3 ± 1.0	1.3 ± 1.2	1.2 ± 1.1	1.2 ± 1.2
Physical aggression	1.4 ± 1.0	0.7 ± 0.8***	1.4 ± 1.0** ††	1.2 ± 0.8	1.1 ± 0.9	1.0 ± 0.9
Autoaggression	1.2 ± 0.9	0.7 ± 1.1	0.7 ± 1.0	0.7 ± 0.9	0.6 ± 0.7	0.6 ± 1.1
At school						
Overall score	7.5 ± 6.2	5.6 ± 6.8	6.4 ± 6.7	7.2 ± 5.5	6.7 ± 7.1	5.6 ± 7.2
Verbal aggression	1.5 ± 0.9	1.1 ± 1.2	1.4 ± 1.2	1.5 ± 0.9	1.3 ± 1.1	1.0 ± 1.1
Aggression against property	1.1 ± 1.0	0.8 ± 1.1	1.0 ± 1.1	1.0 ± 0.8	0.8 ± 0.9	0.5 ± 0.9
Physical aggression	1.1 ± 0.7	0.8 ± 0.8	0.9 ± 0.8	1.0 ± 0.7	1.1 ± 1.0	0.9 ± 0.9
Autoaggression	0.9 ± 0.8	0.8 ± 1.0	1.0 ± 1.2	0.6 ± 0.6	1.0 ± 0.7	1.0 ± 0.8
ABC						
At the ward						
Overall score	55.4 ± 21.2	37.8 ± 19.9*	49.4 ± 17.5*	51.7 ± 15.7	46.5 ± 21.8	46.0 ± 27.9
Irritability	15.5 ± 8.1	11.2 ± 6.8*	14.3 ± 7.2	14.3 ± 5.8	12.6 ± 6.2	13.2 ± 8.7
Lethargy	9.7 ± 8.1	7.0 ± 5.7	7.7 ± 6.2	9.9 ± 6.4	8.0 ± 7.3	7.1 ± 7.5
Stereotypies	2.8 ± 3.4	2.3 ± 3.6	3.5 ± 4.1	3.4 ± 3.5	3.3 ± 5.7	3.3 ± 5.7
Hyperactivity	24.0 ± 8.9	15.8 ± 8.6**	22.0 ± 7.1**	21.4 ± 7.8	19.8 ± 7.5	19.7 ± 8.7
Inappropriate speech	3.6 ± 2.8	1.6 ± 1.6**	2.1 ± 2.0	3.8 ± 2.6	3.7 ± 3.2	3.2 ± 3.5
At school						
Overall score	43.8 ± 20.7	28.9 ± 21.0** †	36.2 ± 30.0* †	36.3 ± 22.4	32.6 ± 29.6	31.5 ± 30.3
Irritability	10.9 ± 8.4	7.6 ± 9.0*	10.3 ± 10.6** †	8.9 ± 7.0	7.2 ± 8.0	7.9 ± 8.1
Lethargy	9.0 ± 5.9	7.6 ± 5.9	5.1 ± 5.8	7.4 ± 9.7	6.3 ± 9.9	5.5 ± 10.8
Stereotypies	2.4 ± 3.0	1.3 ± 2.0*	2.2 ± 3.6	2.4 ± 3.2	3.2 ± 5.6	3.4 ± 5.7
Hyperactivity	19.1 ± 9.7	10.7 ± 8.7** †	16.4 ± 12.6** ††	15.6 ± 8.4	14.4 ± 11.6	13.3 ± 11.4
Inappropriate speech	2.9 ± 2.1	1.9 ± 2.1**	2.3 ± 2.8	2.5 ± 2.2	2.1 ± 3.1	2.1 ± 3.2

[a]Abbreviations: ABC = Aberrant Behavior Checklist, OAS-M = modified Overt Aggression Scale.
*p < .05, **p < .01, ***p < .001; within-group changes between endpoint and baseline or between end of washout and endpoint.
†p < .05, ††p < .01; differences in changes between risperidone and placebo (i.e., treatment effects).

ABC scores at the ward. Within the risperidone group, but not within the placebo group, overall ABC scores (Wilcoxon signed rank test, p < .01) and ABC scores for irritability (p < .05), hyperactivity (p < .01), stereotypy (p < .05), and inappropriate speech (p < .01) improved significantly at endpoint and deteriorated at the end of the washout. In the comparison between risperidone and placebo, significant group differences were observed for the overall score (Wilcoxon 2-sample test, p < .05) and hyperactivity score (p < .05) at endpoint and for the overall score (p < .05) and irritability (p < .05) and hyperactivity (p < .01) scores at the end of the washout.

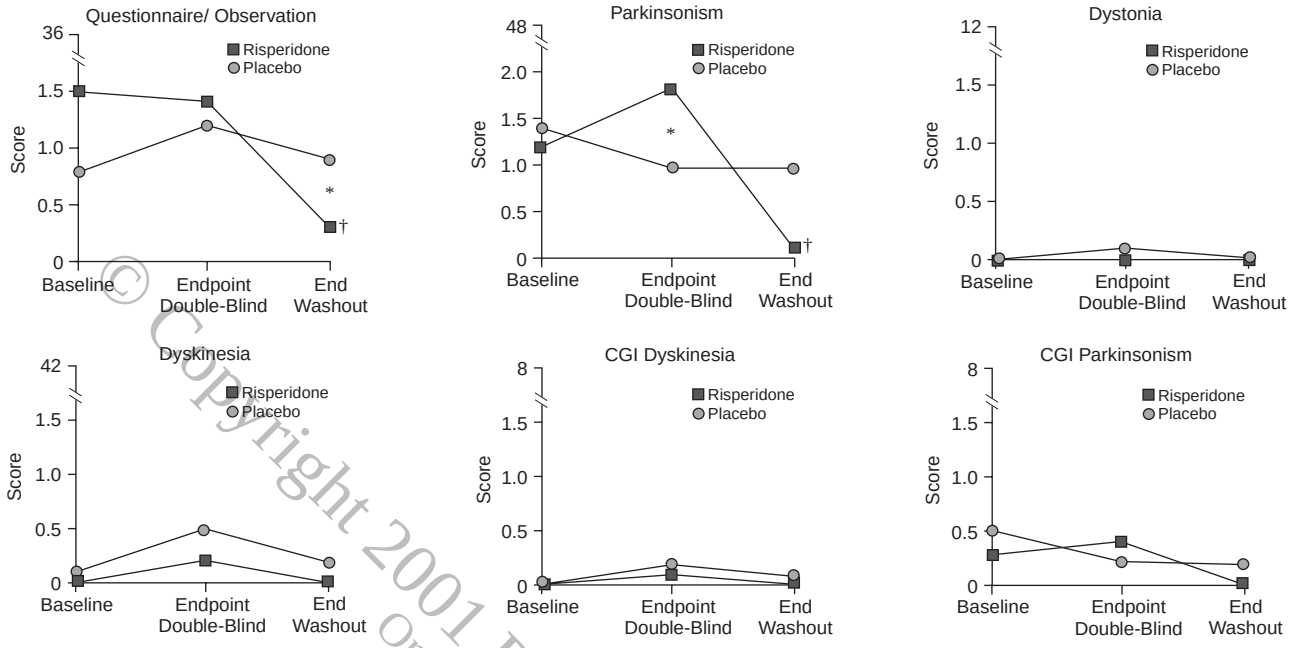
Inspection of the data revealed that the changes on the CGI-S and the ABC at school in the risperidone group during the placebo-controlled treatment period were rather similar over 3 IQ strata (60–69, 70–79, and 80–90), as were the corresponding changes in the placebo group over these IQ strata. A larger study, however, is necessary to decide whether IQ is related to treatment results. Similarly, inspection of the data showed the results on the CGI-S and the ABC at school to be independent of the use of prior medication.

Safety

Significant adverse events occurred in 3 subjects. One subject in the placebo group ran away from the treatment center during the double-blind treatment and was hospitalized elsewhere for some days because of alcohol intoxication. Two subjects in the risperidone group had a strong relapse of aggressive behavior following the double-blind treatment period. For 1 subject, the washout period had to be shortened from 2 weeks to 1 week. Adverse experiences that started during the double-blind treatment period were mentioned by 17 (89%) of 19 subjects in the risperidone group and by 11 (58%) of 19 subjects in the placebo group (Fisher exact test, p = .06). The most frequently reported side effects were tiredness (risperidone, N = 11; placebo, N = 1), sleeping problems (risperidone, N = 2; placebo, N = 5), headache (risperidone, N = 4; placebo, N = 2), sialorrhea (risperidone N = 4; placebo, N = 0), and nausea (risperidone, N = 3; placebo, N = 0). Tiredness was transient in all cases. Infrequently reported side effects included dizziness (risperidone, N = 2; placebo, N = 1), fatigue (risperidone, N = 2; placebo, N = 0), and somnolence (risperidone, N = 2; placebo, N = 0). The frequency of adverse effects was independent of the use of prior medication.

Overall, the ratings of extrapyramidal side effects were low in all subjects (Figure 2 and Table 3). Slight extrapyramidal symptoms were found at baseline, probably due to the use of neuroleptics by some subjects in the period before the trial. Treatment with risperidone was associ-

Figure 2. Evolution of the Mean Scores for the Various Extrapyramidal Symptom Rating Scale Clusters[a]



[a]Abbreviation: CGI-Severity = Clinical Global Impressions-Severity of Illness scale.
*p < .05, treatment effects.
†p < .05, within-group changes between washout and baseline.

Table 3. Subjects With Extrapyramidal Symptoms at Endpoint

	Risperidone (N = 19)				Placebo (N = 17)				
	Mild		Moderate		Mild		Moderate		
Symptom	N	%	N	%	N	%	N	%	p Value[a]
Slowness	5	26	0	0	0	0	1	6	NS
Problems with walking or balance	2	11	0	0	1	6	1	6	NS
Difficulty swallowing or talking	4	21	0	0	0	0	0	0	< .05
Stiffness	3	16	0	0	2	12	0	0	NS
Dystonia	0	0	0	0	0	0	0	0	NS
Akathisia	3	16	0	0	3	18	2	12	NS
Tremors	4	21	0	0	2	12	0	0	NS
Oculogyric crisis	0	0	0	0	0	0	0	0	NS
Orofacial dyskinesia	0	0	0	0	0	0	1	6	NS
Dyskinesia of limbs or trunk	0	0	0	0	0	0	0	0	NS

[a]Chi-square test.

ated with a small but significant increase in parkinsonism (cluster II of the ESRS) at endpoint, when compared with changes for treatment with placebo (mean ± SD score for risperidone = 1.3 ± 2.5 at baseline and 1.9 ± 1.7 at endpoint; for placebo, 1.5 ± 1.9 and 1.0 ± 1.9, respectively; treatment effect, p < .05). For the other ESRS clusters, no significant changes were found during the double-blind period. At washout, ESRS scores of cluster I and II decreased significantly for the risperidone group (p < .05). None of the subjects received additional anticholinergic medications. Mean body weight had increased by 2.3 kg (3.5%; range, –1 to +6 kg) in the risperidone group and by 0.6 kg (1.1%; range, –4 to +6 kg) in the placebo group during the double-blind treatment (p < .05). The number of subjects with a weight gain of at least 2 kg was 9 in the risperidone group and 6 in the placebo group.

No abnormalities of clinical importance were observed during treatment in any of the hematologic or biochemical parameters, including liver function tests, electrolytes, and thyroid function, nor was there any significant change in blood pressure and heart rate measurements. The mean ± SD plasma concentration of prolactin increased significantly in the risperidone group when compared with placebo (risperidone: baseline = 16.6 ± 22.1 ng/mL, endpoint = 33.4 ± 22.4; placebo: 12.3 ± 9.4 ng/mL and 6.9 ± 5.4 ng/mL, respectively; treatment effect, p < .01). No prolactin-related adverse experiences were reported. No clinically relevant ECG abnormalities were found during this trial. There was no systematic effect of risperidone on the rate-corrected QT interval (QTc) of the ECG (risperidone: baseline = 0.401 ± 0.24 seconds, endpoint = 0.404 ± 0.18 seconds; placebo: baseline = 0.388 ± 0.25 seconds, endpoint = 0.386 ± 0.23 seconds).

DISCUSSION

Compared with placebo, risperidone significantly reduced pathologic aggression as reflected by changes on the CGI-S, our primary efficacy measure. Treatment ef-

fects on the CGI-S were already found after 2 weeks and continued to be present after 4 and 6 weeks. Consistent with this finding are similar tendencies in favor of a reduction of aggression and related behavior problems following treatment with risperidone as reported by the ward personnel on the OAS-M and ABC and by the teachers on the ABC. Risperidone appeared to affect particularly physical aggression and aggression to property at the ward and hyperactivity at school. The effect sizes were in the range between 0.6 and 0.9 standard deviation and were clinically meaningful.

One of the reasons that treatment effects were more clear-cut in the eyes of the investigators than at the ward or at school may be measurement error. Despite our efforts to have a limited number of nurses and teachers who were to evaluate the behavior of the subjects, due to holidays and schedule changes 63 nurses and 22 teachers appeared to have contributed to the behavior ratings at the end of the trial. That behavioral changes related to risperidone could be observed at the ward and at school more easily in a situation of acute withdrawal than in that of a gradual titration fits with the possibility of measurement error. Contextual factors may explain why risperidone failed to affect aggression at school as measured by the OAS-M. The school situation is much more structured than the situation at the ward. Correspondingly, the intensity of aggression at school was generally lower than that at the ward, as was reflected in the OAS-M scores.

The daily dosages of risperidone at endpoint ranged between 1.5 and 4 mg (mean = 2.9 mg). These dosages were far below the preset maximum daily dose of 10 mg and were in accordance with the dosages used in our open-label study.[39] The dosages were somewhat higher than those used (mean = about 1.5 mg/day) in a number of open-label studies in children and adolescents with pervasive developmental disorders,[30,33–35,48] comparable to that given (mean = 2.7 mg/day) in another study in adolescents with pervasive developmental disorders,[36] and lower than those reported (mean = about 6 mg/day) in open-label studies of adolescents with schizophrenia.[37,49] Our relatively high starting dose of 0.5 mg twice daily reflects insights at the time the study was performed (1994–1996). Although this starting dose was well tolerated by all subjects, for current clinical practice a starting dose of 0.25 mg/day for subjects weighing less than 25 kg and 0.5 mg/day for subjects weighing 25 kg or more is recommended. Since the highest dosage of risperidone prescribed was 4 mg, on the basis of this study no conclusions can be drawn about the use of higher dosages.

It is unlikely that the continuation of prior medications in 12 subjects until the start of the double blind seriously confounded the study by way of problematic drug interactions. Given the half-lives of the neuroleptics involved (20–40 hours and up to 50 hours for pimozide) and the rather short half-lives of methylphenidate and oxazepam, only in the first days of the double-blind period would relevant levels of prior medications have been present.

The treatment with risperidone was well tolerated. Extrapyramidal side effects were virtually absent. In 1 subject in the risperidone group, extrapyramidal symptoms present at baseline had disappeared at endpoint. These findings are in accordance both with the reports on the favorable side effect profile of risperidone in the adult literature[50] and with preliminary publications on risperidone in the pediatric population.[31,34,35,37,40] In 1 study with risperidone in the younger population that reported a higher rate of extrapyramidal symptoms,[51] risperidone was titrated rapidly by 0.5 mg b.i.d. on each successive day to high dosages. Our procedures to determine side effects, however, were somewhat limited because ESRS data were collected only at the start and the end of the double-blind period rather than weekly or biweekly. Further, since no standard scale for nonmotor side effects was used, these side effects may have been underreported.

Weight gain was less than that found in open-label treatment with risperidone in children and adolescents with chronic tic disorders[40] and developmental disorders.[31,33,36,48] Our data support the importance of a placebo-controlled design in studying side effects of medication, since weight gain up to 6 kg (10%) in the placebo-treated subjects was also observed. The most frequent subjective complaint was transient tiredness. The plasma concentration of prolactin increased, but prolactin-related effects such as galactorrhea, erectile dysfunction, and gynecomastia have not been noted as side effects. This is in agreement with the findings of a retrospective analysis of 4 large double-blind trials with risperidone in adults with chronic schizophrenia.[52]

Clinical Implications

The present controlled study suggests that risperidone medication is an effective and relatively safe component of a comprehensive treatment approach for adolescents with subaverage intellectual abilities and severe aggression. There are also a number of qualifications to the effect of risperidone on aggression in the present study. Our sample was diagnostically heterogeneous, and different findings might be found within single diagnostic categories. We took only indices of overt aggression and did not measure changes of covert aggressive acts such as stealing and cheating. The results pertain to a short-term treatment, and additional data are necessary to evaluate the long-term efficacy and safety of risperidone in the treatment of aggression in adolescents. Not only direct effects of medication on aggressive behaviors matter; indirect effects are important as well, in that subjects taking risperidone were judged to be more responsive to the psychosocial treatment modalities offered to them and could be managed more easily by the professional staff and by their caregivers.

More research is needed on the efficacy and safety of risperidone in treating aggression in adolescents, given both the results and the limitations of this small-scale controlled study. Future studies including larger samples might also focus on gains in scholastic achievement and general level of functioning related to risperidone and incorporate more fine-grained measures of motor and nonmotor side effects.

Drug names: biperiden (Akineton), carbamazepine (Tegretol and others), clonidine (Catapres and others), fluoxetine (Prozac), methylphenidate (Ritalin), oxazepam (Serax and others), pimozide (Orap), risperidone (Risperdal).

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