Randomized Controlled Pilot Study of Quetiapine in the Treatment of Adolescent Conduct Disorder

Daniel F. Connor, M.D.,¹ Thomas J. McLaughlin, Sc.D.,² and Mary Jeffers-Terry, R.N., C.S.²

ABSTRACT

Objective: The aim of this study was to examine whether quetiapine is superior to placebo in the treatment of adolescents with conduct disorder.

Methods: This was a 7-week, randomized, double-blind, placebo-controlled pilot study with two parallel arms. Nine youths were randomly assigned to receive quetiapine, and 10 youths were randomly assigned to receive placebo. Patients were assessed weekly throughout the trial. Quetiapine was dosed twice daily, and medications could be titrated flexibly through the end of study week 5. The dose was fixed for the final 2 weeks of the study. The primary outcome measures were the clinician-assessed Clinical Global Impressions–Severity (CGI-S) and–Improvement (CGI-I) scales. Secondary outcome measures included parent-assessed quality of life, the overt aggression scale (OAS), and the conduct problems subscale of the Conners’ Parent Rating Scale (CPRS-CP).

Results: The final mean dose of quetiapine was 294 ± 78 mg/day (range 200–600 mg/day). Quetiapine was superior to placebo on all clinician-assessed measures and on the parent-assessed quality of life rating scale. No differences were found on the parent-completed OAS and CPRS-CP. Quetiapine was well tolerated. One patient randomized to quetiapine developed akathisia, requiring medication discontinuation. No other extrapyramidal side effects occurred in patients receiving active drug.

Conclusions: This methodologically controlled pilot study provides data that quetiapine may have efficacy in the treatment of adolescents with conduct disorder. Because of the preliminary nature of the study, further research with larger samples is needed to confirm these findings.

INTRODUCTION

Conduct disorder is a highly heterogeneous condition and is a common psychiatric disorder occurring in 2–16% of nonreferred youths assessed in the community (American Psychiatric Association 1994; American Academy of Child and Adolescent Psychiatry 1997). In clinically referred children and adolescents, conduct problems may occur in up to 30–50% of

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referrals and are one of the major reasons children and adolescents come to psychiatric care, regardless of treatment setting (Kazdin 1995; Steiner 1997; Connor et al. 1998; Connor 2002). For adult psychiatric disorders, 25–60% of all patients, regardless of diagnosis, have a prior history of juvenile-onset conduct or oppositional defiant disorder (Kim-Cohen et al. 2003). In the National Comorbidity Survey Replication, the average age of onset of impulse control disorders, including conduct disorder, was 14 years old (Kessler et al. 2006).

Conduct disorder is a very heterogeneous condition with high rates of co-morbid attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, substance use disorders, developmental trauma disorders, psychosis, and neuropsychiatric vulnerabilities found in these youngsters (Connor 2002). Such youths have a poor prognosis. The presence of conduct problems, oppositional and defiant behaviors, and antisocial behaviors is associated with serious long-term sequelae for these youths. Conduct-disordered adolescents with early-onset, stable aggression are at risk for continued aggression as adults and the development of adult antisocial personality disorder (Frick 1998), increased rates of substance use disorders (Connor 2002), long periods of unemployment (Scott 1998), high rates of legal difficulties (Steiner and Cauffman 1998), and increased rates of relationship and marital difficulties compared to the longitudinal histories of adolescents without early-onset aggression (Scott 1998).

A variety of treatments has been considered for these youths, including behavior modification, family therapy, community wraparound services, and cognitive-behavioral social skills training (Borduin et al. 1995; Kazdin 1997; Henggeler et al. 2002). Because of the continuing need to identify effective clinical treatments for these youths, pharmacological approaches to conduct problem behaviors have also been considered. Medication interventions may include typical and atypical antipsychotics, mood stabilizers, antidepressants, stimulants, and adrenergic agents (Connor 2002; Pappadopulos et al. 2003; Schur et al. 2003; Steiner et al. 2003; Pappadopulos et al. 2006).

Although typical antipsychotics have been used extensively in psychiatry for the treatment of severe aggression and conduct problems (Pappadopulos et al. 2003), few studies have examined the efficacy and safety of the newer atypical antipsychotics in adolescents with conduct disorder, severe conduct problems, and excessive maladaptive aggression. The atypical antipsychotics have a more benign adverse-event profile with respect to neurologic side effects than typical antipsychotic medications such as haloperidol or chlorpromazine, and possess less risk for extrapyramidal effects, tardive dyskinesia, and Parkinsonian symptoms. However, atypical antipsychotics are not without risk, and there is emerging concern that these medications may be associated with increased risk for metabolic-adverse events, such as weight gain and insulin resistance (Fleischhaker et al. 2006).

Extant evidence indicates that atypical antipsychotics are effective for the treatment of children and adolescents with conduct problems and disruptive behavioral disorders. A recent meta-analysis of the effects of pharmacotherapy on aggression in children and adolescents found an effect size of 0.9 for the effects of risperidone on persistent behavioral disturbances in youths with conduct disorder and subaverage intelligence quotient (IQ) (Pappadopulos et al. 2006). Another meta-analysis of nonstimulant medication effects for overt aggression in clinically referred children less than 20 years of age found a moderate effect size of 0.68. Antipsychotics were statistically superior to other medication classes (mood stabilizers, antidepressants, adrenergic agents) in the treatment of overt aggression in this meta-analysis (Connor et al. 2003).

To date, five methodologically controlled trials of risperidone for conduct disorder, aggression, and conduct problems, involving a total of 400 pediatric subjects, have been published (Findling et al. 2000; Van Bellingen and De Troch 2001; Aman et al. 2002; McCracken et al. 2002; Snyder et al. 2002). What is striking is that all five controlled studies find statistical support for the reduction of conduct and disruptive behavioral problems with risperidone compared to placebo. Four of five studies involve youth with cognitive delay or subaver-
age IQ (a special population). Several studies have reported risperidone’s long-term safety profile in aggressive patients with and without developmental delay (Turgay et al. 2002; McConville et al. 2003; Findling et al. 2004a; Cronenberghs et al. 2005).

Currently there are limited data about other atypical antipsychotics in conduct disorder. Broadening the range of available treatments is important because risperidone has been associated with extrapyramidal symptoms (EPS) in higher doses, weight gain, and hyperprolactinemia (Findling et al. 2000b; Findling et al. 2003). Quetiapine is an atypical antipsychotic that exhibits high affinity for central nervous system (CNS) serotonin 5HT2A and 5 HT2C receptors and dopamine D2 receptors. Partial agonism at 5HT1A receptors may occur. A higher selectivity for 5HT2 receptors relative to D2 receptors is believed to contribute to the atypical antipsychotic properties of quetiapine and its low extrapyramidal side effects liability.

This compound demonstrates efficacy in adults for schizophrenia (Cole and Rabasseda 2004; Tandon 2004; Pierre et al. 2005), bipolar disorder (Pae et al. 2005; Valerius et al. 2005; Vjeta et al. 2005), and in the treatment of bipolar I and II depression (Calabrese et al. 2005). Published reports in the child and adolescent population of quetiapine include treatment for psychotic disorders (Shaw et al. 2001), bipolar disorder (DelBello et al. 2006), tic disorders (Barzman et al. 2004), and as add-on medication for treatment-resistant adolescent depression (Pathak et al. 2005). A previous open-label study finds quetiapine helpful for aggression in youths with conduct disorder (Findling et al. 2006) with beneficial maintenance effects extending out to 26 weeks (Findling et al. 2007). A prospective open-label study finds quetiapine addition to methylphenidate effective in reducing symptoms of ADHD and aggression in adolescents with ADHD who did not respond to monotherapy alone (Kronenberger et al. 2007). Overall, quetiapine appears well tolerated, with a lower incidence of EPS than typical antipsychotics, less hyperprolactinemia than risperidone, and perhaps less weight gain risk that risperidone (Findling 2002; Haddad and Wieck 2004).

We completed a randomized, double-blind, placebo-controlled pilot trial of quetiapine to assess efficacy and safety for conduct problem behaviors and excessive maladaptive aggression in 12- to 17-year-old adolescents with conduct disorder. We chose to study adolescents with conduct disorder because moderate to severe conduct problems and overt aggression in adolescence are associated with a poor prognosis, diminished quality of life, increased family conflict and distress, increased injury rates, and increased health care costs compared to teenagers who do not have conduct disorder (Scott et al. 2001; Connor 2002; Haddad and Wieck 2004; Connor and McLaughlin 2006). It was hypothesized that quetiapine would be effective in reducing conduct problem behaviors including aggression and be well tolerated.

**METHODOLOGY**

This was a single-site, randomized, double blind, placebo-controlled 7-week outpatient pilot study. Patients were recruited by advertisement, referrals, and word-of-mouth, and from newly evaluated patients to a pediatric psychopharmacology service at the University of Massachusetts Medical Center in Worcester, Massachusetts. The study was completed between November, 2003, and May, 2005. Enrolled patients were paid a stipend of $20 per completed visit as compensation for their time and effort in the study. Eligible patients 12–17 years old were screened at week 1 and given single-blind placebo for 1 week. For patients receiving preexisting medications, a 1-week washout was required for stimulants and a 4-week washout was required for other psychoactive medications before study entry. Subjects on single-blind placebo no longer meeting study inclusion criteria at week 2 (randomization) were excluded from further participation. Subjects were randomized to quetiapine or placebo on a 1-to-1 basis at week 2 and seen weekly for 6 study weeks on drug or placebo. Outcome and safety measures were completed weekly. Nine subjects were randomized to quetiapine and 10 subjects to placebo.

The institutional review board for research in human subjects approved this study. Prior to the initiation of any study procedures parent/guardian written consent and patient writ-
ten assent for study participation were obtained.

Subjects

To be eligible for study participation, subjects had to be between the ages of 12 and 17 years inclusive and to meet criteria for a primary psychiatric diagnosis of conduct disorder. In addition, patients had to have a moderate-to-severe degree of aggressive behavior as documented by an overt aggression scale score ≥25 and at least moderate severity of symptoms as documented by a Clinical Global Impressions–Severity (CGI-S) score ≥4 at screen. This level of aggression means an adolescent has daily to weekly threats of violence toward others, explosive, impulsive episodes of property destruction, and/or physical fighting that impairs functioning at home, at school, and in the community. Current psychosocial therapies were allowed in the protocol as long as therapy was not changed (initiated or stopped) during the study. Exclusion criteria included: (1) a co-morbid psychiatric diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified (NOS), bipolar disorder, psychotic depression, or bipolar disorder NOS; (2) alcohol or substance abuse or dependence within 3 months of study entry; (3) significantly subaverage IQ as assessed by the clinician based on the subject’s school history; (4) current or past history of lenticular abnormality or juvenile cataracts; (5) seizure disorder; (6) concurrent administration of any psychoactive medication, including stimulants; (7) pregnant or lactating females; (8) women of childbearing potential not using a medically accepted means of birth control; and (9) any unstable medical disease that in the opinion of the clinician contraindicated study participation.

Screening procedures

Patients were screened by a board-certified child and adolescent psychiatrist using the Schedule for Affective Disorders and Schizophrenia–Epidemiologic Version-V (KSADS-E) (Orvaschel 1995). Interrater reliability at this site using the KSADS-E interview has been reported previously (Bambauer and Connor 2005). Parents completed the Overt Aggression Scale (OAS) (Yudofsky et al. 1986), and the Conners’ Parent Rating Scale (CPRS, 48-item version) (Conners 1990). Child quality of life at study end point compared to baseline was measured using the parent-completed Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al. 1993). The screening child psychiatrist completed the CGI-S (Guy, 1976). Adolescents underwent a screening physical examination including vital signs and direct ophthalmoscopy, electrocardiogram (ECG), and had blood drawn for laboratory investigations.

Study procedures

Patients were screened at visit 1 (week 1). Subjects meeting study inclusion/exclusion criteria and giving consent and assent were given single-blind placebo for 1 week. Significant improvement in conduct problems and aggression or failure to adhere to study protocol during placebo lead-in excluded further study participation. Randomization to quetiapine or placebo occurred at week 2. Study dose could be increased every 3 days depending on effectiveness and patient tolerability through study week 5. The dose then became fixed for the final 2 weeks of the study. Patients were seen weekly during the 7 weeks of the study.

Study medication

Quetiapine and placebo were administered on a twice-daily schedule, morning and evening. Following previous studies of quetiapine in 12- to 17-year-old youths (McConville et al. 2000), dosing began at 25 mg twice daily (b.i.d.) and could be increased by a maximum of 25 mg bid every 3 days through day 14 of the protocol. Titration was flexible and could be slowed or reduced if adverse events became problematic in the first two study weeks. By day 14, all subjects achieved a daily dose of at least 200 mg quetiapine (100 mg b.i.d.). At day 14, dosing continued to be flexible based on clinician assessed benefits and patient tolerability. After day 14, dosing could be increased by 50 mg b.i.d. to a daily total of 800 mg (400 mg b.i.d.) at the discretion of the study physician. Dose was titrated until parent report of
meaningful clinical benefit or problematic side effects occurred. Total dose was reached at the end of week 5. The dose became fixed for the final 2 weeks of the study.

Study medication was blinded and encapsulated by placing whole tablets into identical-looking capsules by the institutional research pharmacist. Patients were dispensed weekly medications in bottles and asked to return all unused study drug at the next study visit. Pill counts were measured weekly to document compliance. Compliance less than 80% or greater than 120% with prescribed study medication were reasons for subject exclusion. No subjects were excluded from the study for lack of medication compliance. On the basis of pill count, the average medication compliance rate was 93% in the study.

**Concomitant medications**

No concomitant psychotropic medications were allowed during this study. No rescue medications for aggression were permitted. Oral benztropine was permitted as needed for EPS.

**Outcome measures**

The clinician ascertained CGI-S scale and CGI-I scales (Guy 1976) were the primary assessment instruments. The CGI is a clinician-completed scale used extensively in pediatric clinical trials research. The CGI-S scale assesses the overall severity of a patient’s psychiatric condition on a 7-point scale with scores ranging from 1 (“not ill”) to 7 (“extremely severe”). Blinded study child psychiatrists assessed the CGI-S scale weekly. The CGI-I scale assesses patient overall improvement of symptoms compared with symptoms at study baseline. It is rated on a 7-point scale with scores ranging between 1 (“very much improved”), 2 (“improved”), 4 (“no change from baseline”), to 7 (“very much worse”). The CGI-I scale was assessed at study end point. Patients rated as having CGI-I scores of 1 or 2 were rated as overall improved at study end point.

Other measures included the OAS (Yudofsky et al. 1986) rated weekly by parents. The OAS assesses the severity and frequency of overt aggression, including verbal threats of violence, property destruction, self-injurious behavior, and physical assault with a scoring range between 0 and 240, with higher scores denoting more severe symptoms. The total OAS score for all aggressive incidents for that week as assessed by parent report was used in this study.

The CPRS is a 48-item parent-completed rating scale that assesses for a variety of child behavioral and emotional difficulties (Conners 1990). Answers are rated on a scale from 0 (“not at all”) to 3 (“very much”). The conduct problems subscale (scoring range between 0 and 24, with higher scores denoting more severe symptoms), which assesses behaviors associated with conduct problems and aggression, was completed by parents weekly and used as an outcome measure.

Parents completed the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al. 1993) at baseline and at the final study visit. The Q-LES-Q measures parent-reported child life enjoyment and satisfaction across 13 domains of daily life with scores ranging between 15 (poor quality of life) and 75 (excellent quality of life). For this study, the total score was used as an outcome measure.

**Safety measures**

Medication-induced adverse events were ascertained by the general question method for the child and by parent-completed antipsychotic side effects rating scale (Greenhill et al. 2004). The side effects rating scale lists 17 antipsychotic medication side effects on a 0–9 Likert-type scale. Adverse event rating scales were scored for the total number of side effects reported and average severity of all side effects per week.

Neurological side effects were assessed weekly by the Neurological Rating Scale (Simpson and Angus 1970), the Barnes Akathisia Scale (Barnes 1989), and at baseline and final visit with the Abnormal Involuntary Movement Scale (AIMS) (Munetz and Benjamin 1988).

At baseline and final study visit, blood was drawn for a complete blood count, differential, and platelet count, liver function tests, and prolactin level. Urinalysis was obtained at baseline and at the final visit. For females, a urine preg-
nancy test was obtained at screening. Vital signs including sitting blood pressure, sitting pulse, and weight were obtained at each visit throughout the study. Height was obtained at the first and last visit. Body mass index (BMI) was calculated at baseline and at the final study visit. Electrocardiograms (ECGs) were completed at baseline and at the final study visit.

Statistical analyses

Statistical analyses consisted of descriptive and intent-to-treat (ITT) modeling procedures. Descriptive statistics for baseline characteristics included t-tests and chi-square statistics to validate randomization. Tests and estimates of intent to treat differences for study outcomes (CGI-S, OAS, CPRS-CP) were based on mixed-effects models in which patient-level baseline and slope (response over time) were considered random effects and treatment status, time, and the interaction of these variables were fixed effects. Time at the end of follow up (time point 7) was coded as 0 to contrast the difference between levels of study outcomes between experimental and control groups. An

![Study patient flow diagram. Of 68 eligible patients offered the study, 19 were randomized.](image)
unstructured covariance structure was used. Goodness of fit was assessed with Akaike’s information criterion (AIC). Given that there was a statistically significant difference in baseline OAS scores, this variable was controlled for in all ITT analyses. The mixed-effects longitudinal analyses allowed us to use all data from all patients regardless of dropout and allowed us to test ITT treatment differences at each time point of observation separately and together, with increased power and accounting for any group differences such as differences in baseline measures of OAS.

Effect sizes were estimated according to the method of Cohen (Cohen 1988). For the Q-LES-Q outcome measure we compared group means in the two study groups using t-tests of significance. Other outcome measures including safety measures, number of study completers, and CGI-I scores were assessed using t-tests and chi-square statistics. All analyses were conducted in SAS, version 9.1.3, using Proc Mixed and NLMIXED for the growth curve analyses and Proc TTEST for comparison of group means. Significance was set at \( p = 0.05 \) (two-tailed).

**RESULTS**

**Patient flow**

Of 68 eligible adolescent patients and parents offered study participation, 48 declined (see Fig. 1). Most parents declined participation because they did not wish to discontinue their adolescent’s current medications, often stimulants for co-existing ADHD (\( n = 27 \)). Other reasons included parental fears that the aggressive teenager would be randomized to placebo and continue to be aggressive during the study (\( n = 15 \)). When offered study participation, 4 parents and 2 adolescents refused outright with no reason given, leaving 20 subjects who were screened at visit 1. During single-blind placebo lead-in, 1 patient violated study protocol and was dropped leaving 19 subjects eligible for randomization at visit 2. Of the 19 eligible patients, only 1 was receiving current medication, a stimulant, and he underwent a 1-week medication washout per protocol. Nine subjects were randomized to quetiapine and 10 subjects were randomized to placebo.

**Patient characteristics**

Demographic characteristics of the 19 subjects are presented in Table 1. The average age of patients was 14.1 ± 1.6 years with a range of 12–17 years. Ethnicity was Caucasian in 76%, Hispanic in 16%, and African American in 10%. The majority of patients were male (74%). The average age of the placebo group (15.0 ± 1.4 years) was significantly older than the average age of patients randomized to quetiapine (13.1 ± 1.2 years) \( (p = 0.006) \). The distribution of females was similar across both groups \( (n = 2 \) in the quetiapine group and \( n = 3 \) in the placebo group. The majority of randomized patients had previous psychiatric treatment, including outpatient treatment (84%) and/or inpatient treatment (26%). Slightly less than half of patients had a previous substance abuse his-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quetiapine (( n = 9 ))</th>
<th>Placebo (( n = 10 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td>Quetiapine (( n = 9 ))</td>
<td>Placebo (( n = 10 ))</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>13.1 ± 1.2</td>
<td>15.0 ± 1.4</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>7 (78)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>7 (78)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>2 (22)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Previous outpatient treatment</td>
<td>8 (88)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Previous inpatient treatment</td>
<td>2 (22)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>4 (44)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>History of legal involvement**</td>
<td>3 (33)</td>
<td>10 (100)</td>
</tr>
</tbody>
</table>

Abbreviations: SD = Standard deviation.

\( *t_{[17]} = 3.15, p < 0.05. \)

\( **X^2_{[1]} = 9.7, p < 0.01. \)
tory (42%) and 68% had a legal history involving either a delinquent child petition to the courts, arrest, and/or probation.

Table 2 presents psychiatric diagnoses at the screening visit. Consistent with study inclusion criteria, 100% of patients had a current diagnosis of conduct disorder. Oppositional defiant disorder (ODD) was present in 95% and ADHD in 79% of the 19 patients. Co-morbid anxiety disorders were present in between 5% (posttraumatic stress disorder, PTSD) and 37% (generalized anxiety disorder, GAD) of subjects, and 47% of patients met criteria for either dysthymia or major depression at study entry. The average number of psychiatric diagnoses was 4.6 ± 1.2 with a range between two and six diagnoses per subject. Per exclusion criteria, no subject had a psychotic or bipolar disorder.

Psychiatric medication history is presented in Table 3. The majority of patients had a history of antidepressant and/or stimulant use prior to study entry. Mood stabilizers, lithium, and/or an atypical antipsychotic were previously prescribed to 37% of patients. A history of combined pharmacotherapy was found for 37% of subjects. The average number of medications used before study participation was 2.3 ± 1.4 medications with a range between one and five medications. Only 16% of the sample had no previous medication use.

### QUETIAPINE DOSING

At study end point, the mean total daily quetiapine dose was 294 ± 78 mg/day, with a
range of 200–600 mg/day. Two patients received quetiapine 200 mg (22%), 1 received 250 mg (11%), 3 received 300 mg (33%), 2 received 400 mg (22%), and 1 received 600 mg (11%). The average weight-adjusted dose was 4.5 ± 2.5 mg/kg per day of quetiapine at the final study visit. The average placebo dose was 530 ± 245 mg/day. The average placebo dose was less than the maximum of 800 mg/day because many patients randomized to placebo did not complete the full 7 weeks of the study.

Effectiveness

Table 4 reports observed differences (mean ± SD) in the CGI-S, OAS, and CPRS-CP outcomes measures. Table 5 reports results of the mixed-effects modeling of treatment effects of quetiapine for the CGI-S, OAS and CPRS-CP instruments. The mixed-effects modeling analyses revealed that the mean differences between the experimental and control groups were 0.41 (p = 0.92), 0.33 (p = 0.34), 0.70 (p = 0.07), 1.06 (p = 0.02), 1.43 (p = 0.009), and 1.80

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**Table 4. Rating Scale Scores (Mean and Standard Deviation) by Study Week for Outcomes Measures**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 2 (randomization)</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5.9 (0.6)</td>
<td>4.4 (0.9)</td>
<td>4.0 (1.0)</td>
<td>3.9 (1.5)*</td>
<td>3.6 (1.5)*</td>
<td>3.4 (1.1)*</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5 (1.2)</td>
<td>4.9 (1.4)</td>
<td>5.0 (0.9)</td>
<td>5.1 (0.6)*</td>
<td>5.0 (0.9)</td>
<td>5.0 (0.6)</td>
</tr>
<tr>
<td>OAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>73.2 (34.3)</td>
<td>46.8 (47.6)</td>
<td>44.2 (52.4)</td>
<td>39.9 (45.2)</td>
<td>41.0 (53.2)</td>
<td>43.3 (55.6)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40.4 (23.8)</td>
<td>44.6 (30.9)</td>
<td>43.3 (24.1)</td>
<td>43.9 (30.4)</td>
<td>49.6 (29.3)</td>
<td>49.4 (27.8)</td>
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<tr>
<td>CPRS-CP</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Quetiapine</td>
<td>17.1 (5.1)</td>
<td>12.8 (7.9)</td>
<td>12.9 (7.3)</td>
<td>12.4 (7.5)</td>
<td>11.3 (3.6)</td>
<td>11.3 (7.7)</td>
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<tr>
<td>Placebo</td>
<td>11.4 (3.6)</td>
<td>11.8 (4.2)</td>
<td>11.8 (5.4)</td>
<td>10.8 (5.2)</td>
<td>11.6 (7.3)</td>
<td>12.2 (4.4)</td>
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<tr>
<td>Q-LES-Q</td>
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</tr>
<tr>
<td>Quetiapine</td>
<td>36.9 (8.6)</td>
<td></td>
<td></td>
<td></td>
<td>48.2 (10.2)*</td>
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</tr>
<tr>
<td>Placebo</td>
<td>39.3 (9.5)</td>
<td></td>
<td></td>
<td></td>
<td>35.2 (8.0)*</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CGI-S = Clinical Global Impressions–Severity; OAS = Overt Aggression Scale; CPRS-CP = Conners' Parent Rating Scale–Conduct Problems Subscale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

*aDifference in study outcome is estimated at the last time of observation (week 7).

**Table 5. Experimental Effects on Outcomes Measures**

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Standard error</th>
<th>t test</th>
<th>p value</th>
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<tr>
<td>Experimental effects on CGI-severity</td>
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<tr>
<td>Intercept</td>
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<td>0.45</td>
<td>11.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time</td>
<td>−0.06</td>
<td>0.10</td>
<td>−0.60</td>
<td>0.56</td>
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<tr>
<td>Experimental statusa</td>
<td>−1.80</td>
<td>0.65</td>
<td>−2.79</td>
<td>0.007</td>
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<tr>
<td>Experimental status × time</td>
<td>−0.37</td>
<td>0.15</td>
<td>−2.53</td>
<td>0.013</td>
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<tr>
<td>Experimental effects on CPRS-CP</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>11.6</td>
<td>2.1</td>
<td>5.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time</td>
<td>0.7</td>
<td>0.25</td>
<td>0.29</td>
<td>0.78</td>
</tr>
<tr>
<td>Experimental statusa</td>
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<td>2.99</td>
<td>−0.30</td>
<td>0.76</td>
</tr>
<tr>
<td>Experimental status × time</td>
<td>−1.01</td>
<td>0.37</td>
<td>−2.79</td>
<td>0.01</td>
</tr>
<tr>
<td>Experimental effects on OAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>49.5</td>
<td>14.5</td>
<td>3.41</td>
<td>0.003</td>
</tr>
<tr>
<td>Time</td>
<td>1.73</td>
<td>1.91</td>
<td>0.90</td>
<td>0.38</td>
</tr>
<tr>
<td>Experimental statusa</td>
<td>−13.68</td>
<td>21.09</td>
<td>−0.65</td>
<td>0.52</td>
</tr>
<tr>
<td>Experimental status × time</td>
<td>−6.62</td>
<td>2.79</td>
<td>−2.38</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Abbreviations:** CPRS-CP = Conners Parent Rating Scale–Conduct Problems Subscale; OAS = Overt Aggression Scale.

*aDifference in study outcome is estimated at the last time of observation (week 7).
(p = 0.007) for visits 2 (randomization) through visit 7 (study end point) (see Fig. 2). The time point 0 in Fig. 2 is visit 2 randomization to time point 5 which is study visit 7. Regression results from the mixed-effects models showed a significant decline in CGI-S scores from baseline to the end of observation (Table 5). Scores in the intervention group were estimated to be 1.80 units lower than in control patients (95% CI = −0.53, −3.10), associated with an effect size of 1.6 (95% CI = 0.9, 3.0) (difference in mean scores divided by the pooled standard deviation, SD).

We were unable to detect differences between the experimental and control group for CPRS-CP or OAS. (See Table 4 for observed rating scale scores by week for these measures.) With a total of 10 and 9 patients in the two arms of this pilot trial and with a baseline observed SD of 33 for the OAS measure, the probability that this study could detect a treatment difference (two-sided, α = 0.05) is 14% for a difference in OAS outcomes of 14 units. For the CPRS-CP outcome the comparable power estimate is less than 10%, assuming a SD of 5 and a difference of 1. Thus, we had very low power to detect differences in these two measures. Post hoc power analysis for the OAS outcome to inform future studies aimed at detecting moderate effect sizes of 0.4–0.6 indicate that to detect a treatment difference of 14 units between the two groups, a total of 180 patients in the experimental and control arms would be required, i.e., 90 in each group. To detect a difference of 2.5 units for the CPRS-CP variable with a standard deviation of 5, a total of 128 patients or 64 patients per arm would need to be recruited.

At study end point, 8 of 9 subjects randomized to quetiapine were judged improved (CGI-I ≤ 2), compared to only 1 of 10 subjects randomized to placebo (χ²[1] = 11.8, p = 0.0006). Q-LES-Q measures were observed and reported by parents at the beginning and conclusion of the study. Parents reported a significant improvement in the Q-LES-Q quality of life and enjoyment measure in subjects receiving quetiapine compared to those randomized to placebo. The mean improvement on the Q-LES-Q was 11.3 units in subjects receiving quetiapine compared to a decline of 4 units in the placebo group (t[17] = 3.21, p = 0.005) (see Table 4 for observed data).

**Study completion and outcomes**

The number of subjects completing all 7 weeks of the study significantly differed across groups with 8 of 9 patients randomized to quetiapine but only 3 of 10 subjects randomized to placebo completing the protocol (χ²[1] = 6.74, p = 0.009). Seven of 9 patients randomized to quetiapine chose to continue quetiapine at study completion compared to only 1 of 10 subjects randomized to placebo (χ²[1] = 8.93, p = 0.003).

**Tolerability and side effects**

**Adverse events.** At each study visit, parents completed a rating scale listing 17 potential ad-

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**FIG. 2.** Clinician Global Impressions–Severity Scores over time across the two study groups. In the figure, time point 0 represents randomization at study visit 2 and time point 5 represents study end point at visit 7. *p < 0.05.
verse events of antipsychotic treatment scored on a Likert-type scale ranging from 0 (not frequent or serious) to 9 (very frequent or serious). The total number of side effects and the mean severity of side effects were compared across groups. In the quetiapine group the average number of side effects endorsed by parents (6.1) did not differ statistically from the average number of side effects endorsed in the placebo group (8.9) \( t_{[17]} = 1.66, p = 0.12 \). Mean severity of side effects did not differ across the two groups (4.6 quetiapine versus 3.4 placebo) \( t_{[17]} = 1.46, p = 0.16 \). The number of subjects endorsing specific side effects is reported in Table 6. Where there existed significant differences across groups in parent-reported side effects, they occurred more often in the placebo group. The study physician asked adolescents at each visit about side effects using the general question method (Greenhill et al. 2004). Across the two groups there were no significant differences in self-report side effects of sedation \( p = 0.94 \), social withdrawal \( p = 0.71 \), decreased energy \( p = 0.41 \), weight gain \( p = 0.57 \), irritability \( p = 0.10 \), or drooling \( p = 0.46 \).

**Cardiovascular side effects.** Sitting pulse and blood pressure were obtained at each study visit. There were no significant differences in systolic or diastolic blood pressure across groups. At the end of the study, the quetiapine group had a significantly higher average sitting pulse (8.6 bpm) compared to the placebo group \( t_{[76]} = 2.59, p = 0.01 \).

Initial and final ECGs were available on 9 patients randomized to quetiapine and 5 patients randomized to placebo. There were no significant differences across groups at end point in average ECG QTc interval \((432 \pm 17.6 \text{ msec versus } 428 \pm 71.1 \text{ msec}; t = -0.38, p = 0.7)\) or QRS duration \((88 \pm 14 \text{ msec versus } 91 \pm 5.2 \text{ msec}; t = -1.0, p = 0.3)\).

**Weight gain and body mass index.** The average weight gain in the quetiapine group was 2.3 kg compared to an average weight gain in the placebo group of 1.1 kg, comparing weights at the initial and final visits. This was a non-significant difference \( t_{[17]} = 0.77, p = 0.46 \). As assessed at study completion there was no difference in BMI across the two groups \( t_{[17]} = 1.44, p = 0.17 \).

**Prolactin.** Mean change values in prolactin levels were available on 9 patients randomized to quetiapine \((7.1 \pm 2.7 \text{ ng/ml})\) and for 5 subjects randomized to placebo \((7.6 \pm 4.7 \text{ ng/ml})\). No significant differences across groups were found \( t_{[12]} = 0.86, p = 0.71 \).

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**Table 6. Number of Subjects Reporting Adverse Event**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Quetiapine ( n = 9 )</th>
<th>Placebo ( n = 10 )</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>6 (66)</td>
<td>9 (90)</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (66)</td>
<td>7 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased energy</td>
<td>3 (33)</td>
<td>5 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased mental alertness</td>
<td>3 (33)</td>
<td>9 (90)</td>
<td>0.01(^a)</td>
</tr>
<tr>
<td>Diminished emotional expression</td>
<td>1 (11)</td>
<td>7 (70)</td>
<td>0.009(^a)</td>
</tr>
<tr>
<td>Diminished facial expression</td>
<td>1 (11)</td>
<td>6 (60)</td>
<td>0.03(^a)</td>
</tr>
<tr>
<td>Drooling</td>
<td>2 (22)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Irritability</td>
<td>7 (78)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>Muscle stiffness</td>
<td>1 (11)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Overeating</td>
<td>1 (11)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Pacing</td>
<td>4 (44)</td>
<td>5 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Restlessness</td>
<td>7 (78)</td>
<td>7 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>School refusal</td>
<td>2 (22)</td>
<td>4 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation</td>
<td>6 (67)</td>
<td>9 (90)</td>
<td>NS</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>4 (44)</td>
<td>5 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0)</td>
<td>3 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight gain</td>
<td>3 (33)</td>
<td>1 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS = Not significant.

\(^a\)Reported significantly more often in placebo group.
Laboratory measures. No abnormalities were detected in any patient on complete blood count, differential, platelet count, serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), or urinalysis.

Neurological side effects. No neurological abnormalities were observed during the course of the study as measured by the Neurological Rating Scale or the Abnormal Involuntary Movement Scale. One patient developed clinically noticeable akathisia on quetiapine 600 mg/day beginning at study week 6. This patient had a prior history of traumatic brain injury after being struck by a motor vehicle while riding his bicycle at age 11. He was unconscious for 1 week and has retrograde and anterograde amnesia for the event. His history of CNS insult may have increased his risk for side effects from atypical antipsychotics (Connor et al. 2001). His akathisia cleared within 48 hours of quetiapine discontinuation. No patient required benztropine for acute EPS during the study.

DISCUSSION

Results showed statistically significant improvements in those subjects randomized to quetiapine compared to placebo on clinician-assessed measures of global severity, clinician-assessed measures of global improvement at study end point, and parent-assessed quality of life measures. Clinician-ascertained improvements were statistically significant after 3 weeks on drug. However, scores on parent-completed aggression severity rating scales did not show significant differences on drug compared with placebo. There may be several reasons why parent-reported measures of aggression differed from clinician-assessed measures of severity and improvement. Quetiapine is an atypical antipsychotic agent that interacts with a wide range of neurotransmitter receptors, including serotonin and dopamine, known to be important in the regulation of behavior, mood, and affect (Calabrese et al. 2005). Quetiapine has effects on multiple psychiatric disorders including psychosis, tic disorders, antisocial behaviors, and mood, and is currently Food and Drug Administration (FDA)-approved in adults for schizophrenia, bipolar mania and depression (Shaw et al. 2001; Barzman et al. 2004; Pathak et al. 2005; DelBello et al. 2006; Findling et al. 2006). Quetiapine-induced improvements in affect lability, negative internal mood states, frustration tolerance, and impulse dyscontrol might account for some of the global improvements detected by clinicians and parents in our conduct-disordered sample. Thus, a drug acting on multiple CNS systems, known to demonstrate effectiveness in multiple psychiatric disorders, and given to a very heterogeneous group of adolescents with conduct disorder (mean number of co-morbid diagnoses = 4.6), could have multiple effects in our study sample and account for results in which more global clinician and parent measures demonstrated significant differences but more specific measures of aggression did not.

There may be additional reasons why quetiapine failed to separate from placebo on measures of aggression. Small sample size and a lack of statistical power to detect differences in this preliminary study may have contributed to lack of effect for parent rated aggression measures. The quetiapine dose range may have been too low, leading to a lack of parent-reported effect on the OAS and CPRS-CP. Future studies should explore higher dose ranges of quetiapine. Although the OAS and CPRS conduct problems subscale did not separate from placebo in our study, these instruments are treatment sensitive (Connor et al. 1997) and our negative results might be due to low statistical power and type II error. However, other measures of aggression such as the Rating of Aggression Against People and/or Property Scale (RAAPPS) (Kemph et al. 1993), Nisonger Child Behavior Rating Form (NCBRF) (Aman et al. 1996), or the physical aggression subscale of the OAS (Yudofsky et al. 1986) have demonstrated effectiveness in previous medication studies (Findling et al. 2000a; Connor et al. 1997) for early-onset aggressive behavior and might be considered in future studies. It is possible that a 7-week study (6 weeks on active drug) is too short to reveal robust parent-reported effects on rating scales assessing aggressive behaviors in adolescents with conduct disorder. For ex-
ample, although open-label studies of quetiapine for aggression report a 4-week time to improvement on drug (Findling et al. 2006), a previous randomized, controlled study of risperidone reported effects relative to placebo beginning at week 7 of a 10-week study (Findling et al. 2000a). Given the episodic nature of aggressive behaviors and the natural waxing and waning of conduct problems, future aggression studies should consider a longer duration on quetiapine. Parents may have underestimated their offspring’s conduct problem severity, possibly because of a social desirability bias (Sjostrom and Holst 2002), leading to symptom under-reporting on parent-completed aggression rating scale measures and a floor effect in total scores resulting in statistical nonsignificance across the two study groups. For example, a previous study of aggression and psychiatric diagnosis in youths with conduct disorder psychiatrically referred to an outpatient clinic in our hospital reported an average OAS score of 60.3 ± 23.5 at evaluation (Connor and McLaughlin, 2006). Although this score favorably compares with the average OAS score of the group randomized to quetiapine (73.2 ± 34.3), it is much more than the average OAS score of the group randomized to placebo (40.4 ± 23.8), suggesting the possibility of parent under-reporting of aggression at least in some of our sample. Additionally, because children and adolescents with conduct disorder often grow up in families characterized by high rates of parental and familial psychopathology, substance use, and/or parental antisocial behaviors (Connor 2002), parents of teenagers with conduct disorder may fail to recognize the severity of the teenager’s symptoms, leading to under-reporting on parent-completed rating scales.

Subjects assigned to the quetiapine group were significantly more likely to complete all seven study visits and to continue active drug treatment after study completion. This result suggests the possibility of improved adherence to treatment in adolescents assigned to the active drug group. The reasons for this are unclear, but may possibly be related to general symptom improvement and diminished symptom severity in those receiving active drug, leading to an improved quality of life and enhanced willingness to continue with active treatment after study completion. Given large treatment noncompliance rates associated with adolescent conduct disorder, the possibility of enhanced adherence to treatment with active medication is an area deserving of further research.

Quetiapine was generally well tolerated during the study. No statistically significant differences were found in overall side effect severity, number, or specific adverse events including sedation. No differences across groups were found on laboratory measures, including prolactin levels, or on the ECG QRS or QTc intervals. However, it should be noted that small sample size and resulting low statistical power might have contributed to the absence of statistical differences for adverse effect ratings. The quetiapine group and the placebo group had no significant differences in systolic or diastolic blood pressure. However, the quetiapine group did have a statistically higher average pulse on drug compared to the placebo group. Increases in pulse have been reported previously in adolescents receiving quetiapine (McConville et al. 2000), and may be due to the \( \alpha-1 \)-blocking effects of quetiapine (AstraZeneca Pharmaceuticals 2002). Overall, the tolerability of quetiapine in our study was similar to previous studies of quetiapine in children and adolescents (McConville et al. 2000; Findling 2002; Findling et al. 2004a).

The quetiapine group gained an average of about 1 kg more in weight that the placebo group over 7 study weeks. However, this was not statistically significant. BMI did not differ across the groups. It is possible that weight gain with quetiapine might have become significant if our study had more statistical power or a longer duration. Additionally, weight gain on quetiapine may be quite significant for some individuals, especially with longer treatment durations. Given the emerging importance of atypical antipsychotic-induced metabolic effects, future studies should assess weight gain and BMI, because the potential for weight gain is a contributory factor to potential metabolic adverse effects from this class of medication.

A low incidence of extrapyramidal side effects has been reported in children and adolescents treated with quetiapine. In a chart review of 25
children and adolescents treated with quetiapine in an ambulatory clinic, 1 of 25 youngsters (4%) experienced EPS (Findling 2002). We report 1 subject in our study with a previous history of traumatic brain injury that developed acute akathisia on quetiapine 600 mg/day requiring medication discontinuation. EPS cleared within 48 hours of quetiapine discontinuation. No abnormal involuntary movement disorders or dyskinesias occurred during the study. No benzotropine was needed by any patient in the study.

Our study has several additional limitations that must be considered. A majority of adolescents offered participation in our study declined to participate. This may have lead to a selection bias in our sample such that those consenting to participate may have unique characteristics that may limit the generalizability of our findings. Such characteristics might include increased hope that symptom improvement will occur if the teenager enters a research study or less severe conduct symptoms leading to increased compliance with asenting to a study. As noted above, our sample size was small leading to a diminished statistical power to detect differences in outcome and adverse event variables across the two study groups. Our small sample size may have led to a failure of randomization to equate the two study groups on age at screening. Patients randomized to the placebo group were significantly older than patients randomized to the quetiapine group. However, because overt aggression generally declines with age (Connor 2002), this would serve to lessen group differences with those receiving quetiapine, possibly leading to less significant results. Despite this limitation, we were able to show significant differences across groups on several clinician- and parent-reported outcome measures. The sample was largely male and the number of females in the study was too small to justify a subanalysis of results stratified by gender. Thus, the effects of quetiapine in females with conduct disorder must await further study.

CONCLUSIONS

Data from this methodologically controlled pilot study suggest that quetiapine may be broadly beneficial in adolescents meeting diagnostic criteria for conduct disorder. Significant results were found for global assessment and quality of life measures. Although these measures are not specific for aggression or conduct disorder, they do suggest that quetiapine has possible benefits in this highly co-morbid group of impaired adolescents. Because our preliminary results do not support specific treatment effects for aggression, clinicians should routinely monitor outcomes in adolescents with conduct disorder to gauge treatment responsiveness for individual patients. Quetiapine appears well tolerated. Results suggest that larger controlled trials of quetiapine in conduct disorder are indicated to further consider this agent’s efficacy, safety, and tolerability.

DISCLOSURES

Dr. Connor is a consultant for Shire Pharmaceuticals. He has received grant support from Shire Pharmaceuticals and Astra Zeneca Pharmaceuticals. This study was supported by an Investigator Initiated Grant to Dr. Connor from Astra Zeneca Pharmaceuticals. Drs. Connor and McLaughlin analyzed all of the data and completed all of the writing of this submission. Dr. McLaughlin and Ms. Jeffers-Terry have no financial ties or conflicts of interest to disclose.

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American Academy of Child and Adolescent Psychiatry: Practice parameters for the assessment and treatment


QUETIAPINE TREATMENT OF ADOLESCENT CD


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