Use of Quetiapine in Children and Adolescents

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The atypical antipsychotic quetiapine has been examined in children and adolescents in a randomized clinical trial, a number of open-label studies, and several chart review studies. Although only a small amount of information exists, most studies indicate that quetiapine is effective and well tolerated in various pediatric populations. Because quetiapine appears to be well tolerated in the young and associated with manifest salutary effects, it seems to be a promising agent that has potential for use in children and adolescents. This article reviews studies of quetiapine in the treatment of children and adolescents with a variety of psychiatric disorders. Despite these encouraging findings, the number of studies is small, and some have methodological limitations. Methodologically rigorous studies with substantive numbers of subjects are needed to confirm or refute these preliminary impressions.

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The treatment of children and adolescents with antipsychotics presents challenges because of the increased vulnerability of this population to side effects.[1] The tendency of typical antipsychotics to produce extrapyramidal symptoms (EPS) and hyperprolactinemia can have a significant negative impact on patient adherence to treatment regimens. At the same time, the atypical antipsychotics have their own adverse effect profiles, which may include sedation and weight gain; however, the propensity to produce these adverse effects varies among the atypical antipsychotics.[2]

In the 5 years since its introduction in the United States, most trials of the atypical antipsychotic quetiapine in children and adolescents have been open label in design or retrospective chart-review reports (Table 1). Although some studies of quetiapine in children and adolescents have included patients with a wide variety of diagnoses, a few have examined its use in a specific patient population. This article reviews the results of the studies using quetiapine in the treatment of children and adolescents.

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DRUG METABOLISM

One of the first studies was an investigation of the pharmacokinetics of quetiapine in a cohort of 10 adolescents (aged 12.3–15.9 years) with schizoaffective disorder or bipolar disorder with psychotic features.[6] In this open-label pharmacokinetic clinical trial, the dosage started at 25 mg twice daily and reached 400 mg twice daily by day 20. At various times during the trial and at the end of the trial on day 23, assessments were performed of plasma quetiapine concentrations and of the effectiveness and safety of the drug. Quetiapine pharmacokinetics were found to be dose proportional in these adolescents and were similar to those previously reported for adults.[12] Positive and negative symptoms, as well as EPS, improved in these patients. No serious adverse events or important laboratory abnormalities were reported. Data from this study suggest that quetiapine may be effective and well tolerated in adolescents and that similar drug administration strategies may be used safely in adolescents with both mood and psychotic symptoms.

MOOD DISORDERS

Patients with bipolar disorder experience wide fluctuations in mood, often characterized by hyperactivity, irritability, and exaggerated self-confidence, that alternate with depressive episodes characterized by sadness and helplessness.[13] The use of quetiapine as adjunctive treatment to divalproex for acute mania in adolescents (aged 12–18 years) was studied in a 6-week, double-blind, placebo-controlled trial.[3] Thirty hospitalized adolescents with bi-

Table 1. Summary of Reports of Quetiapine in the Treatment of Children and Adolescents[a]

Clinical Trial	N	Duration	Type of Study	Overall Efficacy	Safety and Tolerability
Bipolar disorder					
DelBello et al, 2001[3]	30	42 d	Double-blind, placebo-controlled adjunct to divalproex	Quetiapine + divalproex more effective in reducing symptoms than divalproex alone	No significant group differences in EPS, weight, prolactin levels
Reimherr, 2001[4b]	10	NA	Open-label	Improvement in psychotic symptoms and behavior	No EPS
Multiple diagnoses[c]					
Hamner and McConville, 2001[5]	10	23 d	Open-label; prolactin levels	NA	No statistically significant difference in prolactin levels from baseline
McConville et al, 2000[6]	10	23 d	Open-label; pharmacokinetics; rising dose	Significant improvement in positive and negative symptoms	Dose-proportional pharmacokinetics Common adverse events: postural tachycardia and insomnia; EPS improved
Grcevich et al, 2001[7]	14	Mean = 327 d	Retrospective chart review; treatment-resistant patients	Improvement in psychotic symptoms	Most common adverse events were weight gain (7/14, 9.4 kg), increased appetite (4/14)
Grcevich et al, 2001[8]	97	NA	Chart review (safety); quetiapine vs risperidone vs olanzapine	NA	Weight gain most common adverse event, was least for quetiapine Frequency of EPS was least for quetiapine
McConville et al, 2001[9]	10	Mean = 445 d	Open-label, long-term	Improvement in positive and negative symptoms	Most common adverse events were somnolence (6/10) and headache (5/10) No EPS
Shaw et al, 2001[10]	15	8 wk	Open-label	Significant improvement in psychotic symptoms	Most common adverse events were somnolence, agitation, headache Prolactin levels unchanged Average weight gain = 4.1 kg
Autistic disorder					
Martin et al, 1999[11]	6	16 wk	Open-label	2/6 were responders and showed improvement	4 withdrew due to lack of efficacy or side effects (sedation)

[a]Abbreviations: EPS = extrapyramidal symptoms, NA = not applicable or not available.
[b]Patients with bipolar disorder and attention-deficit/hyperactivity disorder.
[c]Patients with a variety of psychotic disorders.

polar I disorder, manic or mixed episode, were randomly assigned to receive divalproex (20 mg/kg) plus adjunctive treatment with quetiapine (N = 15) or divalproex (20 mg/kg) plus placebo (N = 15) for 6 weeks. The mean dosage of quetiapine was 432 mg/day, and 22 patients completed the study. Both treatment groups, divalproex plus placebo and divalproex plus quetiapine, demonstrated a significant reduction in manic, depressive, and psychotic symptoms; however, there was a significantly greater reduction in the divalproex plus quetiapine group. The most common adverse events were sedation (33% for divalproex plus placebo vs. 80% for divalproex plus quetiapine), nausea (40% vs. 27%), and headache (47% vs. 47%); all were rated as mild to moderate by patients and caregivers. Consequently, this randomized, double-blind clinical study provides evidence that, in severely ill and hospitalized teenagers who present in a manic or mixed state, quetiapine as an adjunct to divalproex has good tolerability and is more effective in acutely relieving manic, depressive, and psychotic symptoms than is divalproex alone.

The effectiveness of quetiapine in treating 10 adolescents diagnosed with both bipolar disorder and attention-deficit/hyperactivity disorder (ADHD) was examined in an open-label study.[4] Quetiapine was given in doses of 75 mg/day to 600 mg/day, was well tolerated, and produced no EPS. The patients experienced substantial relief of their psychotic symptoms, hallucinations and delusions disappeared, mood disorders stabilized, and aggressive behavior improved markedly. Thus, quetiapine was effective in reducing symptoms in this group of adolescents with bipolar disorder and comorbid ADHD, without producing EPS.

PSYCHOTIC DISORDERS

Childhood-onset schizophrenia is a rare, clinically severe form of schizophrenia that is associated with disrupted cognitive, linguistic, and social development, which occurs before the appearance of psychotic symptoms.[14] It has been estimated that 0.1% to 1% of patients with schizophrenia and its related disorders present before the age of 10 years, with 4% presenting before the age of 15 years.[15] The rate of onset increases during adolescence, with peak ages at onset ranging from 15 to 30 years. Be-

cause of the possible relationship between the early diagnosis and treatment of schizophrenia during adolescence and improved long-term outcome,[16,17] studies of the efficacy and safety of atypical antipsychotics in this patient population are especially critical.

Effectiveness

Most published reports of the use of atypical antipsychotics in children and adolescents with various psychotic disorders focus on short-term treatment. For example, in an 8-week, open-label study in 15 adolescents (mean age = 15.1 years; range, 13–17 years), quetiapine (final mean dose = 467 mg/day) produced a significant improvement in psychotic symptoms as measured by the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions scale (CGI), Positive and Negative Syndrome Scale, and Young Mania Rating Scale.[10]

Information about the long-term effects of atypical antipsychotics in children and adolescents is critically needed. In a long-term, open-label study (an open-label extension study of the aforementioned pharmacokinetic trial) of the safety, tolerability, and clinical effectiveness of quetiapine in 10 adolescents with various psychotic disorders, the patients were treated for a mean ± SD total duration of 445 ± 155 days with a mean daily dose of 600 ± 122 mg/day.[9] Treatment with quetiapine produced improvements in positive and negative symptoms (assessed using the BPRS, CGI, and modified Scale for the Assessment of Negative Symptoms) that were maintained during the open-label extension. Hence, in this study, quetiapine showed long-term effectiveness in reducing psychotic symptoms in a small cohort of adolescent patients.

In a retrospective analysis of quetiapine in the treatment of psychotic illnesses in children and adolescents (mean age = 11.6 years; range, 7.0–16.9 years), the results for 14 patients were examined.[7] Most (9/14) of the patients were diagnosed with early-onset schizophrenia. Eleven of the patients had been previously treated with 1 or more antipsychotics (9, risperidone; 3, olanzapine; 3, haloperidol; 2, thioridazine). Seven of these patients had been switched to quetiapine because of ineffectiveness of the previous antipsychotic regimen, and 4 were switched because of an inability to tolerate antipsychotic-related side effects. The mean final treatment dosage of quetiapine was 309 mg/day, and the mean treatment duration was 327 days (range, 7–969 days). Treatment with quetiapine reduced psychotic symptoms at endpoint and reduced the severity of illness as measured by BPRS and CGI scores. Consequently, in this study, quetiapine was shown to be effective in adolescent patients who had not responded to treatment with other antipsychotic medications. This result suggests that there are distinctions in clinical response among the atypical antipsychotics, which has also been reported by Szigethy et al.[18]

Safety and Tolerability

Extrapyramidal symptoms. No EPS and improved EPS have been reported in the clinical studies of children and adolescents with various psychotic disorders.[6,9] The comparative side effects associated with the use of the atypical antipsychotics risperidone, quetiapine, and olanzapine were examined in a chart review of 97 children and adolescents treated in an outpatient mental health clinic.[8] EPS occurred in 14 of 75 risperidone patients, 1 of 16 olanzapine patients, and 1 of 25 quetiapine patients. Thus, in this retrospective study, the frequency of EPS was lowest in patients treated with quetiapine (4%) compared with patients treated with olanzapine (7%) and risperidone (19%).

Prolactin. In adults, treatment with quetiapine has been associated with plasma prolactin levels that are no different from placebo.[19] Prolactin levels were unchanged in an 8-week, open-label study in children and adolescents with psychotic symptoms.[10] Data on prolactin levels were examined from the previously described, open-label, pharmacokinetic study in which 10 adolescents received quetiapine doses ranging from 50 mg/day to 800 mg/day over 21 to 27 days.[5] Plasma prolactin levels decreased from baseline for girls and remained unchanged for boys. Hence, quetiapine did not produce sustained elevations of prolactin levels in these adolescents. These results suggest that treatment with quetiapine generally does not lead to prolactin elevation.

Weight gain. An important side effect associated with treatment with atypical antipsychotics is weight gain; however, the propensity for producing this adverse effect differs among the various antipsychotics.[20,21] In a retrospective chart review of the treatment of 97 patients with various atypical antipsychotics (quetiapine, risperidone, and olanzapine), weight gain was the most common side effect observed with all 3 antipsychotics.[8] The mean weight gain after 3 months was 3.9 kg (8.7 lb) with risperidone, 3.3 kg (7.3 lb) with quetiapine, and 6.4 kg (14.2 lb) with olanzapine. Quetiapine patients were less likely to gain more than 4.5 kg (10.0 lb) during the first 3 months of treatment compared with olanzapine patients ($p < .05$). Thus, although weight gain may be an issue in the treatment of youths with quetiapine, preliminary evidence suggests that this side effect does not appear to interfere with therapeutic effectiveness.

Sedation and somnolence. In some open-label studies of quetiapine, sedation has been a common side effect. For example, somnolence was the most common adverse effect among the 15 patients in an 8-week, open-label study[10] and among the 10 adolescents in the long-term, open-label extension of the pharmacokinetic study (60%; 6/10 patients).[9] Although sedation appears to be a common side effect in the acute and maintenance treatment of young patients prescribed quetiapine, the degree of sedation that occurs does not appear to interfere with drug

therapy, because the sedation is frequently transient and does not lead to drug withdrawal.

AUTISTIC DISORDER

In one small study of 6 male children with autistic disorder, quetiapine was reported as being effective in 2 of the subjects.[11] Three subjects were discontinued from the study due to dose-limiting sedation, a side effect frequently seen early in the course of therapy.

SUMMARY

The use of quetiapine in children and adolescents has been examined in a randomized clinical trial, a number of open-label studies, and several chart-review studies. One of the first studies was an investigation of the pharmacokinetics and effectiveness of the drug in adolescents with schizoaffective disorder or bipolar disorder with psychotic features.[6] Quetiapine exhibited pharmacokinetics that were dose proportional and similar to those previously reported for adults. This study provides evidence to suggest that treatment with quetiapine is both well tolerated and effective in children and adolescents.

Various studies have provided further data to support the notion that quetiapine may be effective in reducing psychotic symptoms in children and adolescents with a variety of clinical diagnoses. In a randomized, double-blind, placebo-controlled trial,[3] there was a significantly greater reduction of psychotic symptoms in patients with bipolar disorder who received divalproex plus quetiapine rather than divalproex plus placebo. Quetiapine was also well tolerated and effective in treating adolescents with comorbid bipolar disorder and ADHD. Furthermore, it is possible that quetiapine may be effective in some adolescents who have not responded to or could not tolerate treatment with other antipsychotics. Finally, a small long-term study[9] of quetiapine in the treatment of adolescents with various psychotic disorders has shown that effectiveness is retained for over 1 year, with no development of EPS.

A number of studies have specifically investigated the safety and tolerability of quetiapine in children and adolescents. In one study,[8] the frequency of EPS was least in patients treated with quetiapine when compared with olanzapine and risperidone. Also, in several studies[3,5,10] in pediatric patients, quetiapine did not produce sustained elevations of plasma prolactin levels. Weight gain is a significant side effect experienced by some patients who take atypical antipsychotics. In a retrospective chart review,[8] patients treated with quetiapine generally experienced a tolerable degree of weight gain. Another common side effect experienced by patients who receive quetiapine is sedation; however, for most patients this does not appear to interfere with long-term treatment and is relatively transient.

Available data from case reports of quetiapine in adolescents with various diagnoses also show promising results. For example, quetiapine has been reported to improve symptoms in patients with tic disorders and Tourette's syndrome.[22,23] In another case study, quetiapine was still effective with no apparent adverse effects after 28 months of treatment in an adolescent girl diagnosed with schizophrenia.[24]

Thus, in a number of studies of varying methodological rigor, treatment with quetiapine has been reported to be effective and safe in different pediatric populations and has shown a low propensity to induce such side effects as weight gain and EPS. The atypical antipsychotics are not interchangeable, and, if a youth does not respond to 1 atypical antipsychotic, a switch to quetiapine might be effective.[7,18] However, large-scale, prospective, randomized trials are lacking; consequently, these results should be considered preliminary and should be confirmed in larger, randomized clinical trials.

Drug names: divalproex (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

REFERENCES

1. Lewis R. Typical and atypical antipsychotics in adolescent schizophrenia: efficacy, tolerability, and differential sensitivity to extrapyramidal symptoms. Can J Psychiatry 1998;43:596–604
2. Findling RL, McNamara NK, Gracious BL. Paediatric uses of atypical antipsychotics. Exp Opin Pharmacother 2000;1:935–945
3. DelBello M, Schwiers M, Rosenberg HL, et al. Quetiapine as adjunctive treatment for adolescent mania. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
4. Reinherr FW. Quetiapine effectively treats bipolar disorder and attention-deficit hyperactivity disorder in adolescent patients. Presented at the annual meeting of the Institute on Psychiatric Services; Oct 10–14, 2001; Orlando, Fla
5. Hamner MB, McConville B. Quetiapine does not produce sustained elevations of prolactin levels. Presented at the 18th annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 23–28, 2001; Honolulu, Hawaii
6. McConville BJ, Arvanitis LA, Thyrum PT, et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry 2000;61:252–260
7. Grcevich S, Delong VY, Dass SK. A retrospective analysis of quetiapine in the treatment of psychosis in children and adolescents. Presented at the 18th annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 23–28, 2001; Honolulu, Hawaii
8. Grcevich S, Melamed L, Richards R, et al. Comparative side effects of atypical antipsychotics in children and adolescents. Presented at the 8th biennial meeting of the International Congress on Schizophrenia Research; April 28–May 2, 2001; Whistler, Canada
9. McConville B, Carrero L, Sweitzer D, et al. Safety, tolerability, and clinical effectiveness of quetiapine in adolescents with selected psychotic disorders: a long-term, open-label study. Presented at the 8th biennial meeting of the International Congress on Schizophrenia Research; April 28–May 2, 2001; Whistler, Canada
10. Shaw JA, Lewis JE, Pascal S, et al. A study of quetiapine: efficacy and tolerability in psychotic adolescents. J Child Adolesc Psychopharmacol 2001; 11:415–424
11. Martin A, Koenig K, Scahill L, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9:99–107
12. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine:

an atypical antipsychotic. Clin Pharmacokinet 2001;40:509–522
13. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 2001;3:202–210
14. Jacobsen LK, Rapoport JL. Research update: childhood-onset schizophrenia: implications of clinical and neurobiological research. J Child Psychol Psychiatry 1998;39:101–113
15. McClellan JM. Early-onset schizophrenia. In: Sadock BJ, Sadock VA, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2000:2782–2789
16. DeQuardo JR. Pharmacologic treatment of first-episode schizophrenia: early intervention is key to outcome. J Clin Psychiatry 1998;59(suppl 19): 9–17
17. Wyatt RJ, Henter I. Rationale for the study of early intervention. Schizophr Res 2001;51:69–76
18. Szigethy E, Brent S, Findling RL. Quetiapine for refractory schizophrenia. J Am Acad Child Adolesc Psychiatry 1998;37:1127–1128
19. Arvanitis LA, Miller BG, for the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
20. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(suppl 7):22–31
21. Sussman N. Review of atypical antipsychotics and weight gain. J Clin Psychiatry 2001;62(suppl 23):5–12
22. Chan-Ob T, Kuntawongse N, Boonyanaruthee V. Quetiapine for tic disorder: a case report. J Med Assoc Thai 2001;84:1624–1628
23. Parraga HC, Parraga MI, Woodward RL, et al. Quetiapine treatment of children with Tourette's syndrome: report of two cases. J Child Adolesc Psychopharmacol 2001;11:187–191
24. Hayden F. Long-term remission of schizophrenia in an adolescent treated with quetiapine. J Child Adolesc Psychopharmacol 2001;11:289–293