A Retrospective Analysis of Quetiapine in the Treatment of Pervasive Developmental Disorders

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Background: The purpose of this study was to examine the effectiveness and tolerability of quetiapine for aggression, hyperactivity, and self-injury in pervasive developmental disorders (PDDs).

Method: The medical records of all patients with PDDs diagnosed according to DSM-IV criteria and treated with quetiapine were retrospectively reviewed. Patients who received quetiapine for at least 4 weeks and who were not concurrently treated with another antipsychotic or mood stabilizer were included. Improvement was measured with the Clinical Global Impressions-Improvement scale (CGI-I), with response determined by ratings of "much improved" or "very much improved." Data were collected from May 15, 2003 through November 30, 2003.

Results: Of 857 records reviewed, 20 patients (16 male, 4 female) (mean ± SD age = 12.1 ± 6.7 years; range, 5–28 years) received a quetiapine trial (mean ± SD dosage = 248.7 ± 198.4 mg/day; range, 25–600 mg/day) over a mean duration of 59.8 ± 55.1 weeks (range, 4–180 weeks). Eight (40%) of 20 patients were judged "responders" to quetiapine; the mean CGI-I score for the entire group was 3.0 ± 1.1 (minimally improved). A statistically significant improvement ($p = .002$) was found between a mean pretrial CGI-Severity of Illness scale (CGI-S) score of 5.1 ± 0.6 (markedly ill) and a posttrial CGI-S score of 4.2 ± 1.1 (moderately ill). Adverse effects occurred in 50% (N = 10) of patients and led to drug discontinuation in 15% (N = 3) of patients.

Conclusion: Quetiapine was modestly effective for maladaptive behavior in patients with a PDD. Controlled studies are needed to further assess these preliminary findings.

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Pervasive developmental disorders (PDDs) are profound neuropsychiatric conditions characterized by a severe and lifelong impairment in social interaction and communication, along with restricted interests and activities.[1] In addition to these core disturbances, PDDs are commonly associated with severe, maladaptive behavior, including aggression, hyperactivity, and self-injury.[2] Although nonpharmacologic treatments such as applied behavioral analysis and educational interventions are essential, medication is often required in the management of interfering symptoms.

The typical antipsychotics, potent dopamine-2 (D_2) receptor antagonists, were among the first medications used to target maladaptive behavior in PDDs. Despite their efficacy, these drugs were associated with the emergence of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).[3] These concerning adverse effects contributed to the development of the atypical antipsychotics.[4] Their profile of antagonism at serotonin (5-HT) and dopamine receptors has been postulated to result in an improved tolerability profile.[5] Although the atypical antipsychotics risperidone[6,7] and olanzapine[8,9] have been shown to be effective for the treatment of maladaptive symptoms in PDDs in

controlled and open-label studies, respectively, these drugs are often associated with significant weight gain.[10]

Quetiapine, a more recently marketed atypical antipsychotic, binds to several neurotransmitter sites, including D_1, D_2, 5-HT_{2A}, 5-HT_{1A}, and histamine H_1 receptors.[11] This profile of action is hypothesized to contribute to the drug's antipsychotic properties, low EPS liability, and possibly a decreased propensity for weight gain.[12–14]

There are 3 known reports of quetiapine in the treatment of individuals with PDDs. Martin and colleagues[15] conducted a 16-week, open-label study of quetiapine (dosage range, 100–350 mg/day) in 6 children and adolescents (age range, 6–15 years) with autistic disorder. Two of 6 subjects were judged responders, as determined by a Clinical Global Impressions-Improvement scale (CGI-I) score of "much improved" or "very much improved." The remaining 4 subjects discontinued treatment prematurely. Three subjects withdrew because of sedation or lack of response, and 1 subject dropped out after a possible seizure. Increased appetite and weight gain (range, 0.9–8.2 kg) were also reported. The investigators concluded that quetiapine was poorly tolerated and generally ineffective in this diagnostic group.

Jou et al.[16] reported on an open-label study of quetiapine (mean dosage = 477 mg/day; range, 265–689 mg/day) in 14 youth (mean age = 12 years; range, 7–17 years) with diagnoses of both a PDD and mental retardation (N = 10) or mental retardation only (N = 4) over a mean duration of 22 weeks (range, 10–48 weeks). Subjects receiving concomitant medications were included in the study if their dosages were held constant during the trial. In the PDD group, a significant improvement was found in symptoms of hyperactivity and inattention as measured by the Conners Parent Scale. Six (60%) of 10 subjects were judged responders as determined by a rating of much improved or very much improved on the CGI-I. Adverse effects were mild and included sedation (N = 2) and sialorrhea (N = 1). Mean weight gain for these 10 subjects was 1.0 kg (range, –9.6 to +7.3 kg). Among the 4 subjects in the mental retardation group, 3 were judged responders based on the above criteria. This subgroup of 4 subjects lost weight during treatment with quetiapine (mean weight loss = –2.1 kg; range, –9.1 to +1.8 kg).

More recently, a 12-week, open-label study of quetiapine (mean dosage = 291.7 mg; range, 100–450 mg/day) in 9 adolescent males (mean age = 14.6 years; range, 10–17 years) with autistic disorder was conducted by Findling and colleagues.[17] Six (67%) of 9 subjects completed the trial. Two (22%) of 9 subjects were judged responders based upon ratings of much improved or very much improved on the CGI-I. Two subjects discontinued quetiapine due to sedation (N = 1) and agitation/aggression (N = 1). Overall, adverse effects reported for the group included sedation (N = 7), weight gain (N = 5), agitation (N = 4), and aggression (N = 2).

The limited number of reports on the use of quetiapine in patients with a PDD indicates an ongoing need for additional research on the use of the drug in this diagnostic group. This retrospective analysis was conducted to further investigate the effectiveness and tolerability of quetiapine in patients with a PDD.

METHOD

Subjects

The study sample consisted of outpatients treated at the James Whitcomb Riley Hospital for Children Christian Sarkine Autism Treatment Center (Indianapolis, Ind.). All patients were diagnosed by one of 2 board-certified child and adolescent psychiatrists (D.J.P. or C.J.M.) using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[1] Individuals included in the study met DSM-IV criteria for a PDD (autistic disorder, Asperger's disorder, or PDD not otherwise specified [NOS]) and had received treatment with quetiapine for at least 4 weeks. Concomitant medications, except antipsychotics or mood stabilizers, were permitted if the dosage was held constant for the duration of the trial. The study was approved by the Indiana University Institutional Review Board, and a waiver of written informed consent was granted.

Procedure

Data recorded from review of medical records included DSM-IV diagnoses (Axes I–III), race, age, sex, prior atypical antipsychotic drug trials and reasons for discontinuation, target symptoms, quetiapine dosage and trial duration, concomitant medications, and adverse effects. Baseline and endpoint measures of illness severity were determined during treatment visits by ratings on the CGI-Severity of Illness scale (CGI-S).[18] The CGI-S is rated from 1 to 7 (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill). Global improvement, focused on target symptoms of aggression, self-injury, irritability, and hyperactivity, was measured by the CGI-I during treatment visits.[18] The CGI-I is rated from 1 to 7 (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Patients were considered treatment responders if assigned a posttrial CGI-I rating of 1 or 2. CGI-S and CGI-I scores were determined by the treating psychiatrists (D.J.P. or C.J.M.), each of whom had previously achieved reliability on the administration of these measures.[19] Data were collected from May 15, 2003 through November 30, 2003.

Data Analysis

Data were coded and entered into the Statistical Package for Social Sciences (SPSS) version 11.5.0.[20] Descrip-

tive statistics were calculated and presented as mean ± SD and range, unless otherwise noted. The Wilcoxon signed rank test (2-tailed) was used to examine differences between baseline and endpoint CGI-S scores. The Fisher exact test and Student t test were used to assess categorical and continuous data, respectively. Statistical significance was set at $p \leq .05$ (2-tailed).

RESULTS

Review of all medical records (N = 857) found that 20 patients (16 male, 4 female) (mean ± SD age = 12.1 ± 6.7 years; range, 5–28 years) met inclusion criteria for the study. Of the 20 patients, 12 (60%) had a diagnosis of autistic disorder and 8 (40%) were diagnosed with PDD NOS; 13 (65%) had a comorbid diagnosis of mental retardation (mild [N = 3], moderate [N = 8], severe [N = 2]).

The mean quetiapine dosage prescribed during the trial was 248.7 ± 198.4 mg/day (range, 25–600 mg/day) and mean trial duration was 59.8 ± 55.1 weeks (range, 4–180 weeks). Five (25%) of 20 patients were receiving a concomitant medication (clonidine [N = 2], fluoxetine [N = 1], guanfacine [N = 1], sertraline [N = 1]) during the quetiapine trial. Sixteen (80%) of the 20 individuals were treated with quetiapine after a trial of at least 1 other atypical antipsychotic. In this group, the primary reasons for discontinuation of the previous drug included significant weight gain (N = 9), lack of effectiveness (N = 5), and persistent sedation (N = 2). Analysis of relative change in weight in those patients who were switched from another atypical antipsychotic to quetiapine was not possible due to insufficient weight data from the prior antipsychotic trial.

Analysis of CGI-S scores revealed a mean change in severity from markedly ill (5.1 ± 0.6; range, 4–6) to moderately ill (4.2 ± 1.1; range, 2–6) ($p = .002$). Although 8 (40%) of 20 patients were deemed responders by ratings of much improved (N = 6) or very much improved (N = 2) on the CGI-I, for the sample as a whole, the mean CGI-I score was only minimally improved (3.0 ± 1.1; range, 1–5). Regarding response between diagnostic subtypes, 7 (58.3%) of 12 patients with autistic disorder and 1 (12.5%) of 8 patients with PDD NOS were judged responders to quetiapine (Fisher exact test, $p = .07$). As a whole, 6 (46.2%) of 13 individuals with mental retardation and 2 (28.6%) of 7 without mental retardation responded to quetiapine (Fisher exact test, $p = .64$). In addition, further analyses found that neither dosage ($t = .42$, $df = 18$, $p = .68$) nor age ($t = –.99$, $df = 18$, $p = .34$) significantly affected response to the drug, whereas increased mean duration of treatment was associated with response ($t = 4.82$, $df = 18$, $p = .0001$).

Overall, adverse effects during treatment with quetiapine were recorded in 10 (50%) of 20 patients. These effects included weight gain (N = 5; 2.0 kg, 2.3 kg, 3.6 kg, 4.1 kg, 16.8 kg), persistent sedation (N = 2), TD (N = 1), insomnia (N = 1), and pain (N = 1). A mean increase in weight of 5.7 ± 5.8 kg (range, 0–16.8 kg) was found at the end of the quetiapine trial. In addition, 3 (60%) of 5 patients without prior exposure to another atypical antipsychotic drug experienced weight gain with quetiapine. At the time of data collection, 10 (50%) of 20 patients remained on quetiapine treatment. Among the other 10 patients, 3 discontinued quetiapine due to intolerable adverse effects (weight gain, N = 2; TD, N = 1), whereas 7 discontinued the drug secondary to a lack of effectiveness. A comprehensive summary of demographic data and results is presented in Table 1.

DISCUSSION

Data from this retrospective analysis suggest that quetiapine treatment is effective in a minority of patients based on a measure of global improvement that incorporates symptoms of aggression, self-injury, irritability, and hyperactivity associated with PDDs. Although 40% (N = 8) of patients in this study were deemed "responders," as measured by the CGI-I, it is notable that their overall level of illness severity was still rated as moderate at the end of the trial. Indeed, quetiapine was discontinued in approximately one third of the patients in this study due to persistent symptoms of aggression, self-injury, irritability, and hyperactivity. These findings are similar to previously described reports of quetiapine in subjects with PDDs.[15,17] In contrast, the aforementioned report by Jou and colleagues[16] found quetiapine more beneficial in the treatment of disruptive behavior in this diagnostic group. It may be that the higher dosages of quetiapine utilized in that study positively affected the treatment outcome.

Quetiapine was associated with adverse effects in 50% (N = 10) of the patients and resulted in drug discontinuation in 15% (N = 3) of the sample. This is similar to prior reports in which unfavorable tolerability profiles were described.[15,17] Whereas over half of the patients who had received a prior atypical antipsychotic trial discontinued that drug due to weight gain, in this study only 10% (2/20) of patients did so. This suggests that quetiapine may be an alternative agent for some patients when weight gain is of concern. It is noteworthy that a substantial mean increase in weight was recorded during treatment with quetiapine in this study of relatively long duration. Furthermore, 60% (3/5) of the patients who were not previously treated with an atypical antipsychotic experienced weight gain. However, a weight gain of 5 kg over 1 year in boys and girls at a mean age of 12 years falls in the 50th percentile according to the National Health and Nutrition Examination Survey U.S. growth charts.[21]

Table 1. Clinical Demographics and Treatment Response Data for 20 Patients With Pervasive Developmental Disorders (PDDs)

Patient No.	DSM-IV Diagnosis	Race/ Age (y)/Sex	Prior Atypical Antipsychotic and Effect	Target Symptom	Quetiapine Dose (mg/d)[a]	Duration of Treatment (wk)[b]	Concomitant Drugs	Treatment Response (CGI-I score)[c]	Adverse Effects
1	Autism Mental retardation–moderate	White/5/male	Olanzapine (weight gain, ineffective), risperidone (weight gain)	Aggression	50	148	None	1	None
2	PDD not otherwise specified Mental retardation–mild	White/6/male	None	Aggression	100	27	Guanfacine	3	Insomnia
3	Autism Mental retardation–severe	White/7/male	Risperidone (weight gain)	Aggression	550	180	None	2	None
4	Autism Mental retardation–moderate	White/7/male	Risperidone (weight gain, ineffective)	Aggression	50	4	Clonidine	5	None
5	Autism Mental retardation–moderate	White/7/male	None	Self-injurious behavior	600	50	None	4	None
6	Autism Mental retardation–moderate	Black/8/male	Risperidone (weight gain, ineffective)	Aggression	225	28	Clonidine	2	None
7	PDD not otherwise specified	Black/8/female	Risperidone (ineffective)	Impulsivity	75	30	None	3	None
8	Autism	White/8/male	Risperidone (ineffective)	Aggression	200	13	None	4	None
9	Autism Mental retardation–moderate	White/9/male	Risperidone (weight gain, rash, vomiting)	Aggression	150	10	None	3	None
10	Autism	White/9/male	Risperidone (ineffective)	Aggression	375	117	Sertraline	2	Tardive dyskinesia
11	Autism Mental retardation–moderate	Black/10/male	Ziprasidone (ineffective), risperidone (weight gain, ineffective)	Aggression	400	90	Fluoxetine	2	Weight gain
12	PDD not otherwise specified	White/11/male	Olanzapine (weight gain), risperidone (ineffective)	Aggression	400	126	None	2	None
13	PDD not otherwise specified Mental retardation–mild	White/11/male	Risperidone (sedation)	Hyperactivity	225	26	None	3	Sedation, weight gain
14	PDD not otherwise specified	White/12/male	Olanzapine (weight gain), risperidone (ineffective)	Aggression	50	13	None	3	Sedation
15	Autism Mental retardation–moderate	White/14/female	None	Self-injurious behavior	150	153	None	2	Weight gain
16	PDD not otherwise specified	Hispanic/15/male	Risperidone (sedation)	Aggression	600	52	None	3	None
17	Autism Mental retardation–severe	White/18/female	None	Aggression	25	32	None	2	Weight gain
18	Autism Mental retardation–moderate	Black/22/male	Risperidone (ineffective)	Aggression	500	54	None	4	None
19	PDD not otherwise specified	White/27/male	Risperidone (ineffective)	Impulsivity	50	9	None	5	Exacerbation of pain
20	PDD not otherwise specified Mental retardation–mild	White/28/female	None	Aggression	200	36	None	4	Weight gain

[a]Mean ± SD quetiapine dose = 248.7 ± 198.4 mg/d.
[b]Mean ± SD duration of treatment = 59.8 ± 55.1 wk.
[c]Mean ± SD treatment response (CGI-I score) = 3.0 ± 1.1. CGI-I score: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.
Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

Of concern, 1 subject in this study developed TD during treatment with quetiapine. This 9-year-old male had previously received a trial of risperidone that was effective for symptoms of aggression over a duration of 60 weeks, but then lost effectiveness and was discontinued. Quetiapine was subsequently initiated and titrated to a mean dosage of 375 mg/day. Although quetiapine was effective, TD emerged after 117 weeks of treatment and required discontinuation of the drug.

According to the clinical observations of Findling and colleagues,[22] quetiapine has been associated with a lower risk of EPS in the pediatric population. TD was not recorded during the aforementioned studies of the drug in youngsters with PDDs[15–17] or during 23-day and 88-week open-label extension trials of quetiapine in youth with psychotic disorders.[23,24] Indeed, there are no known prior reports of TD associated with quetiapine use in children and adolescents.[5]

Although drug dosage did not significantly affect treatment response, it is possible that the dosages of quetiapine used were inadequate and led to the reduced effectiveness observed. Moreover, because a majority of patients in this study had undergone treatment with at least one prior atypical antipsychotic, the group may be relatively treatment refractory and thus less likely to benefit significantly from a subsequent trial of another drug in this class. Finally, that an increased mean duration of treatment was significantly associated with response to quetiapine suggests that those patients who continued taking the drug for a longer period of time did so because they exhibited a positive treatment effect.

The results of this retrospective analysis should be weighed against its significant methodological limitations. The study's retrospective design is subject to observation and assessment bias. In addition, the small sample size is an important factor to consider. While diagnoses were made by board-certified child and adolescent psychiatrists experienced in treating this population, a criterion standard diagnostic instrument, such as the Autism Diagnostic Interview-Revised,[25] was not used. Finally, the design of this study limits the investigators' ability to determine whether adverse effects were clearly medication related.

CONCLUSION

In summary, overall, quetiapine was found to be modestly effective and somewhat poorly tolerated in children, adolescents, and young adults diagnosed with a PDD. On the other hand, quetiapine was effective for a number of individual patients in the study, many of whom continued taking the drug and had been unresponsive to other atypical antipsychotics. Given the limitations of this study, well-designed controlled research with a larger sample is needed.

Drug names: clonidine (Catapres, Duraclon, and others), fluoxetine (Prozac and others), guanfacine (Tenex and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

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