

Clinical Use of Quetiapine in Disease States Other Than Schizophrenia

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Although quetiapine was introduced as an atypical antipsychotic drug with clinical efficacy in schizophrenia patients, it has been used in a variety of disease states over the last 5 years. The most common conditions have included mood and anxiety disorders, obsessive-compulsive disorder, aggression, hostility, posttraumatic stress disorder, borderline personality disorder, delirium, and comorbid substance abuse. Considering its efficacy in a wide variety of neuropsychiatric conditions and its excellent tolerability profile, quetiapine could emerge as a broad-spectrum psychotropic medication that may be helpful in psychiatry across various diagnostic categories. Traditionally, studies on the predictive validity of psychiatric disorders help with nosologic issues and controversies. Assessing quetiapine's tolerability and its overall treatment response might help tease out the predictive validity of various psychiatric syndromes (based currently on an atheoretical descriptive approach) and may shape psychiatric nosology in the future. Quetiapine's low affinity and fast dissociation from postsynaptic dopamine-2 receptors give the least risk of producing acute extrapyramidal side effects, tardive dyskinesia, and neuroleptic malignant syndrome. These factors suggest that the clinical utility of quetiapine in psychiatric conditions other than schizophrenia has not been fully exploited thus far.

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Quetiapine is a novel antipsychotic drug that was approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of patients with schizophrenia. It is a dibenzothiazepine with both dopamine-2 (D_2) receptor and serotonin-2 ($5-HT_2$) receptor antagonism but with a much higher level of occupancy of $5-HT_2$ receptors.¹ In addition to the high $5-HT_2:D_2$ receptor binding ratio, quetiapine has affinity for $5-HT_{1A}$, $5-HT_6$, histamine-1 (H_1), α_1 -adrenergic, and α_2 -adrenergic receptors. It also demonstrates moderate serotonin reuptake inhibition.² Quetiapine's unique chemical profile is believed to be responsible for its low affinity for and fast dissociation from postsynaptic D_2 receptors.³ Its favorable toler-

ability profile includes no greater incidence of extrapyramidal symptoms (EPS) than placebo across the entire dosage range (50-750 mg/day) in pivotal studies of schizophrenia, no sustained prolactin elevation, and minimal weight gain.⁴⁻⁶ Clinical experience thus far suggests that quetiapine is not a risk factor for tardive dyskinesia, tardive dystonia, akathisia, and neuroleptic malignant syndrome. Due to its excellent tolerability profile, it has been tried across multiple diagnostic categories. For example, several recent studies have demonstrated quetiapine's clinical benefits in patients with bipolar and other mood disorders, anxiety disorders, impulsivity, aggression, and comorbid substance abuse disorders.⁷⁻⁹

MATERIALS AND METHODS

In 2002, 4 separate MEDLINE searches (English language) were performed for the period between January 1997 to April 2002 using key words denoting atypical antipsychotics and nonpsychotic disorders. The first search of atypical antipsychotics in patients with anxiety disorders, including obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and panic disorders, revealed 60 articles published since 1997 (when quetiapine was approved for marketing by the FDA). A second search on atypical antipsychotics and mood disorders, including bipolar disorder and depression, resulted in 64 articles. A third search on atypical antipsychotics in comorbid substance abuse resulted in 12 articles. Lastly, a search on use

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of atypical antipsychotics in aggression and hostility revealed 64 English-language articles published since 1997. Out of these searches, we selectively identified publications on quetiapine. We also looked for cross-references in the published articles, obtained data-on-file information from AstraZeneca Pharmaceuticals L.P., and included abstracts presented at conferences. Furthermore, results presented at recent meetings and our own ongoing work assessing quetiapine in borderline personality disorder were included in the review.

Mood Disorders

Antipsychotics are commonly added to the treatment regimen for patients with psychotic mood disorders.^{10,11} However, use of antipsychotics in such populations may be associated with emergence of EPS, possible worsening of depression, and functional impairment.^{12,13} Atypical antipsychotics have been found to be beneficial in the treatment of depressive symptoms in patients with schizophrenia.¹⁴ Compared with typical antipsychotics, atypical agents may have superior efficacy in treating schizophrenia patients with mood symptoms.¹⁵

Mania

Atypical antipsychotics have been used successfully in the treatment of patients with acute mania. Olanzapine was recently approved by the FDA for the treatment of mania on the basis of 2 pivotal placebo-controlled trials evaluating its clinical efficacy in acute mania.^{16,17} Additionally, a placebo-controlled augmentation study has assessed the efficacy of risperidone in patients with acute mania and found it to be effective.¹⁸ There is also a small, single monotherapy study that found risperidone to have equal efficacy compared with lithium, but this trial was not placebo-controlled.¹⁹

In an open-label, retrospective case series of 6 patients, Ghaemi and Katzow⁷ report improvement with quetiapine in 2 of the 6 treatment-refractory bipolar type I patients who met criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*). The mean dose of quetiapine was 100 ± 82.2 mg/day (range, 25–200 mg/day), and duration was 8.3 ± 6.5 weeks (range, 1–16 weeks). In a larger, open-label series of 16 neuroleptic-dependent bipolar and schizoaffective patients who received add-on quetiapine (154.7 mg/day for 10.8 weeks) with standard mood stabilizers, Sajatovic and colleagues²⁰ found improvement in prospectively assessed standard mood rating scales. Hamilton Rating Scale for Depression (HAM-D) scores improved from approximately 16 to 8; Young Mania Rating Scale (YMRS) scores improved from approximately 9 to 4.

In a naturalistic, retrospective chart review, Zarate et al.²¹ assessed response to quetiapine and associated factors in 145 consecutive patients in a private, academic, psychiatric hospital. These patients had received a discharge

diagnosis of bipolar disorder, major depression with psychotic features, schizophrenia, schizoaffective disorder, delusional disorder, or psychosis not otherwise specified, according to DSM-IV criteria. Of 145 patients treated with quetiapine, 37% (N = 53) had previously discontinued risperidone, 43% (N = 62) had discontinued olanzapine, and 17% (N = 25) had discontinued clozapine because of either nonresponse or treatment intolerance. Of 145 patients, 76% (N = 110) subsequently responded to quetiapine. Logistic regression analysis indicated that a diagnosis of major depression with psychotic features and longer duration of illness were associated with a lower chance of treatment response. The response rate for schizophrenia in this study was 74%, which is substantially higher than the 51% response rate reported by Arvanitis and Miller.²²

In a retrospective chart review of acutely ill, hospitalized patients (N = 7) with bipolar disorder, manic or mixed episode with psychotic features who received quetiapine monotherapy or quetiapine with mood stabilizers, Dunayevich et al.²³ reported that 71% (N = 5) of the patients were “much” or “very much” improved on the Clinical Global Impressions (CGI) scale modified for bipolar disorder (CGI-BP). YMRS and CGI-BP scores at discharge were significantly reduced compared with those at admission. No worsening of manic symptoms was seen in this group of patients. In a larger retrospective study of 45 bipolar patients, Chisholm et al.²⁴ evaluated effectiveness and tolerability of quetiapine as an adjunctive treatment (dose range, 25–400 mg/day). Response to quetiapine was assessed over a minimum of 2 weeks and up to 6 months using YMRS, CGI-BP, and inventory of depressive symptoms. Fifty-eight percent (N = 26) of the patients were excluded due to insufficient data, substance abuse, or inadequate exposure to quetiapine. Patients received monthly prospective ratings for symptoms of bipolar disorder. Overall, patients treated with quetiapine had substantial reduction of symptoms and reported few somatic complaints, with sedation as the most commonly reported side effect.

In a 12-week, open-label study, Brown et al.²⁵ assessed 12 outpatients (mean age = 35.4 ± 8.2 years) with bipolar disorder and cocaine dependence using the HAM-D, YMRS, Brief Psychiatric Rating Scale (BPRS), Cocaine Craving Questionnaire, urine toxicology screening, and self-report of drug use including dollar amount expended. Mean maximum dose of quetiapine was 312.5 ± 95.6 mg/day. Last-observation-carried-forward (LOCF) analysis showed significant improvement from baseline to exit in HAM-D, YMRS, and BPRS scores, and cravings on the Cocaine Craving Questionnaire. There was no significant reduction in the dollar amount spent on drugs or percentage of positive urine drug screens during the study in the LOCF analysis. However, 8 patients who completed the study showed an 87% reduction in the dollar amount spent

on cocaine. Quetiapine was well tolerated, and no patients dropped out due to side effects.

In an open-label, prospective, add-on trial of quetiapine in rapid-cycling bipolar disorder, Ghaemi et al.²⁶ reported data on 41 recruited patients, 19 of whom received quetiapine monotherapy. For the patients receiving quetiapine treatment, the mean dosage of quetiapine was 171.0 ± 173.3 mg/day, for an average duration of 16.0 ± 16.6 weeks. For the patients receiving quetiapine monotherapy, the mean dosage of quetiapine was 148.0 ± 128.6 mg/day for an average duration of 11.6 ± 13.5 weeks. Analyses at weeks 2 through 52 indicated improvement in HAM-D and YMRS ratings, with the reductions statistically significant for weeks 2 through 16. CGI-BP ratings indicated improvement in both manic and depressive symptoms from week 2 onward. Improvement similarly occurred in HAM-D, YMRS, and CGI-BP scores for the patients who received quetiapine monotherapy. Weight change was minimal, with a mean amount of 2.7 lb (1.2 kg) lost at the endpoint. These results strongly suggest that quetiapine improves rapid-cycling bipolar disorder.

DelBello et al.²⁷ evaluated the efficacy, tolerability, and safety of quetiapine as adjunctive therapy to valproate in adolescents (aged 12 to 18 years) with bipolar disorders who were hospitalized for mixed or manic episode. Thirty patients received an initial valproic acid (VPA) dose of 20 mg/kg and were randomly assigned to quetiapine ($N = 15$) or placebo ($N = 15$) for 6 weeks. The mean dosage of quetiapine was 432 mg/day, and mean VPA levels were 106 and 93 mg/mL in the VPA plus placebo and VPA plus quetiapine groups, respectively. Repeated analysis of variance measures of completers ($N = 22$) indicated better overall response for reducing depressive, manic, and psychotic symptoms in the VPA plus quetiapine group compared with the VPA plus placebo group. There was a significantly greater response rate (defined by $\geq 50\%$ reduction in YMRS scores from baseline) in the VPA plus quetiapine group (87%) compared with the VPA plus placebo group (53%).

Reimherr²⁸ studied the benefits of open-label, variable-dose quetiapine (doses of 75 to 600 mg/day) in a series of 10 child and adolescent patients diagnosed with bipolar disorder and/or attention-deficit/hyperactivity disorder (ADHD) who had exhibited limited response to previous standard medications. These patients experienced substantial relief in their psychotic symptoms; hallucinations and delusions disappeared predictably, mania and reality testing stabilized, and depression and aggressive behavior improved markedly. Although this was not a controlled study and the diagnostic criteria were not stringent, quetiapine may have efficacy in bipolar and ADHD patients.

In summary, preliminary data suggest that quetiapine has beneficial effects in the treatment of patients with acute mania. These studies need to be followed up by placebo-controlled, double-blind, clinical trials with larger groups of patients.

Depressive Symptoms

In a 4-month, multicenter, open-label trial, Sajatovic et al.²⁹ compared the efficacy of quetiapine with risperidone in reducing depressive symptoms in psychotic outpatients with DSM-IV diagnoses of schizophreniform disorder, schizoaffective disorder, bipolar disorder, major depressive disorder, delusional disorder, Alzheimer's dementia, and vascular dementia. Efficacy was measured using the Positive and Negative Syndrome Scale (PANSS), the CGI scale, and the HAM-D. A total of 554 patients were randomly assigned to quetiapine and 175 to risperidone. The mean dose at 16 weeks was 317 mg/day for quetiapine and 4.5 mg/day for risperidone. Although both agents caused reductions in mean HAM-D scores, quetiapine produced a greater reduction than risperidone in all patients ($p = .0015$). There was also a lower incidence of EPS in quetiapine-treated patients than in those taking risperidone. These results suggest that quetiapine may be a useful agent in the management of depressive symptoms in patients with psychotic disorders.

Anxiety and Depressive Symptoms

In an open-label, variable-dose, 10-week trial of adjunctive quetiapine, Adson et al.³⁰ assessed patients treated with a selective serotonin reuptake inhibitor (SSRI) for depression or dysthymia ($N = 10$; mean age = 50.5 ± 9.5 years) who had persistent anxiety symptoms. Each patient had a Hamilton Rating Scale for Anxiety (HAM-A) score of 16 or greater at baseline. The mean quetiapine dosage was 180 mg/day at week 6. As predicted, there was a statistically significant reduction in HAM-A scores and Mini-Mental State Examination (MMSE) anxiety inventory scores. There was also a reduction in depressive symptoms, as shown on the HAM-D, and no patients required or asked for adjunctive benzodiazepine treatment. This pilot study suggests that quetiapine may be effective as adjunctive therapy with SSRIs in treating patients with anxiety and depressive symptoms.

Obsessive-Compulsive Disorder

Though SSRIs are the first-line agents for treatment of OCD,^{31,32} they are effective in only 50% to 60% of OCD patients. Growing evidence shows that augmentation of an SSRI by dopamine blockers in treatment-resistant OCD can lead to further symptom reduction.³³⁻³⁵ A recent study by Denys et al.³⁶ examined 10 patients with OCD who had not responded to at least 3 previous SSRI treatments at maximum dose and duration. Following 8 weeks of treatment with quetiapine in addition to an SSRI, 7 patients responded, and the overall mean reduction in the Yale-Brown Obsessive Compulsive Scale was 35.4%. In a retrospective chart review, Mohr et al.⁹ report results of quetiapine augmentation in 8 patients refractory to SSRI treatment. Four of these 8 patients were responders (CGI reduced by 1 or 2 points) within 4 weeks. Quetiapine was

also well tolerated in the responders. These results are consistent with growing evidence⁹ suggesting that approximately 50% of OCD patients resistant to treatment with SSRIs may respond to augmentation with an atypical antipsychotic. Although there are anecdotal, single case reports of emergence or exacerbation of OCD symptoms by atypical antipsychotics,³⁷⁻³⁹ including one with quetiapine,⁴⁰ there was no worsening of OCD symptoms in this series. These anecdotal case reports of negative effects of atypical antipsychotics on OCD symptoms are not likely to be substantiated in larger, controlled studies. Since patients with schizophrenia do manifest obsessive-compulsive symptoms and since schizo-obsessive disorder is increasingly being recognized as a subtype of schizophrenia, future clinical trials in this schizophrenia subpopulation are needed. Further controlled studies of quetiapine augmentation in patients with treatment-resistant OCD and related disorders are warranted.

Posttraumatic Stress Disorder

Currently, the only FDA-approved treatments for PTSD are sertraline and paroxetine, and none of the currently available atypical antipsychotics are indicated for PTSD. On the basis of its clinical efficacy and tolerability profile, quetiapine could help ameliorate PTSD symptoms. Hamner et al.⁴¹ reported the efficacy of quetiapine in reducing PTSD symptoms in a 6-week, open-label, add-on trial of combat veterans (N = 20) who did not show adequate response to antidepressant treatment. The primary outcome measure was the Clinician Administered PTSD Scale (CAPS). The secondary efficacy measures were the PANSS, CGI, and HAM-D. The average dose of quetiapine was 100 ± 70 mg/day, with a range of 25 to 300 mg/day. Sixty-three percent of the patients met the criteria for a clinically significant response on the CAPS, defined as a 20% or greater reduction in composite scores. A significant decline in CAPS ratings was evident at week 2 and week 4 evaluations, with continued improvement noted at week 6. PANSS positive, negative, and general psychopathology symptoms showed a significant decline, and 58% of the patients met the criteria for CGI improvement (change of 2 or 3 points). Larger, randomized, double-blind, controlled studies are needed to better define the potential role of quetiapine in the treatment of patients with PTSD.

Aggression and Hostility

There is a vast clinical literature suggesting a specific antiaggressive effect of clozapine in patients with psychotic disorders.^{42,43} Citrome et al.⁴⁴ compared the specific antiaggressive effect of clozapine with olanzapine, risperidone, and haloperidol using PANSS and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE). Patients differed in their treatment response as measured by the hostility item on the PANSS, with the patients taking

clozapine showing significantly greater improvement than the patients taking haloperidol or risperidone. The effect of hostility appeared to be independent of the antipsychotic effect of clozapine on other PANSS items that reflect delusional thinking, a formal thought disorder, or hallucinations and independent of sedation as measured by the NOSIE. Neither risperidone nor olanzapine showed superiority to haloperidol. The authors concluded that clozapine has a relative advantage over other antipsychotics as a specific antihostility agent. The effect of atypical antipsychotics on hostility and aggression, therefore, does not seem to be a class effect with differential response rates for individual medication. Although this study did not have a quetiapine arm for comparison, Citrome et al.⁴⁵ have reported antiaggressive effects of quetiapine in a case report of a patient with schizoaffective disorder.

In a case series of 4 patients, Thomas et al.⁴⁶ observed good improvement with open-label quetiapine in behavioral aspects of antisocial personality disorder in a maximum-security inpatient forensic facility. Quetiapine, in a dosage range of 600 to 800 mg/day, decreased symptoms of irritability, impulsivity, and aggression and was well tolerated and accepted by the patients. Though preliminary results are encouraging, there is a need for larger, double-blind, controlled studies using objective measures of aggression, irritability, and impulsivity in this population.

Goldstein⁴⁷ reports reduction in hostility and aggression with quetiapine in hospitalized patients with acute schizophrenia in a 6-week, placebo-controlled, double-blind, randomized trial (N = 361). The trial evaluated 5 fixed doses of quetiapine (75, 150, 300, 600, 750 mg/day) and a single dose of haloperidol (12 mg/day). Aggression and hostility were assessed using the BPRS Factor V score (mean of hostility, excitement, suspiciousness, and uncooperativeness), the BPRS hostility item, and a BPRS hostility cluster score (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness, and excitement). Response was defined as a decrease in score of ≥ 2 for the BPRS hostility cluster and the BPRS hostility item, and ≥ 2.5 for the BPRS positive symptoms cluster and the BPRS Factor V. The evaluated population included patients with a baseline and 1 postbaseline BPRS evaluation and at least 2 weeks of treatment (N = 301). Changes from baseline in BPRS scores were analyzed using analysis of covariance with baseline score, treatment, and center included in the model. The proportion of patients responding in each treatment group was compared using Cochran-Mantel-Haenszel chi-square tests, controlling for center. Quetiapine and haloperidol were both superior to placebo in reducing the positive symptoms; however, only quetiapine (at a dosage of 600 mg/day) was superior to placebo on all 3 measures of aggression and hostility. Haloperidol treatment was not associated with greater improvement in hostility and aggression than placebo. Quetiapine treatment resulted in greater improvements in hostility mea-

tures than haloperidol, although the differences were not statistically significant. Furthermore, relative to haloperidol, quetiapine treatment appeared to have direct effects on hostility, which were independent of the reduction in psychotic symptoms.

Since the use of clozapine is limited by its serious adverse effect profile, quetiapine may emerge as a good replacement for clozapine in patients with aggression and hostility due to its much improved safety and tolerability profile.

Borderline Personality Disorder

Although the treatment of choice for patients with borderline personality disorder is psychotherapy, optimal response is frequently obtained by adding pharmacologic treatment to psychotherapy. Schulz⁴⁸ recently reviewed several studies that involved strategies using low doses of typical antipsychotic medications (i.e., haloperidol, thiothixene, loxapine, thioridazine, trifluoperazine). Partial improvement was found in terms of decreased symptoms of anxiety, impulsivity, and psychotic symptoms in those patients who were able to tolerate the treatment. However, the typical antipsychotics were poorly tolerated due to the high incidence of EPS in this patient population.

More recent studies have suggested that newer atypical antipsychotic medications are superior to typical antipsychotics for patients with borderline personality disorder and schizotypal personality disorder.⁴⁸ Early reports with clozapine and olanzapine have noted a decrease in impulsivity and aggression in borderline personality disorder and schizotypal personality disorder patients.⁴⁹ Clozapine, at dosages of 25 to 100 mg/day, was well tolerated and effective in reducing "psychotic-like" symptoms, impulsivity, and affective symptoms in patients with borderline personality disorder. Short-term trials of risperidone at dosages of 1.0 to 2.5 mg/day and olanzapine at a dosage of 6 mg/day were also performed with promising results.^{49,50}

We are studying the safety and efficacy of quetiapine (25 to 300 mg/day) in patients with DSM-IV diagnoses of borderline personality disorder in an 8-week, open-label, dose-ranging trial [A. and S.C.S., unpublished data]. The patients received a variable dose for the first 4 weeks and a fixed dose for the second 4 weeks. The following assessment measures were conducted on a weekly basis: (1) BPRS, (2) Buss-Durkee Hostility Inventory, (3) Barratt Impulsivity Scale, (4) Hopkin's Symptom Checklist 90 (SCL-90), (5) Global Assessment of Functioning (GAF), (6) Modified Schedule for Interview of Borderlines, (7) Temperament and Character Inventory, and (8) Simpson-Angus Scale for monitoring EPS. Neuropsychological scoring assessments were administered pretreatment and posttreatment. To date, 10 patients entered the study, and 6 patients completed the study. Two patients were discontinued because of positive toxicology screens, and 2 did not complete the study. Demographic data of evaluable pa-

tients included the following: age (range, 29–50 years; mean = 38 years), race (white, 83%; African American, 17%), and sex (female, 83%; male, 17%). The results of SCL-90, GAF, and BPRS scores for these patients at baseline visit and the week 8 visit were compared. Using the LOCF approach, preliminary findings suggest a clinically significant improvement in all the measures studied.

Delirium

Traditionally, haloperidol has been the drug of choice for management of medically ill patients with delirium. Most intensive care units have used either haloperidol or droperidol for calming down agitated or psychotic delirious patients.⁵¹ In a retrospective study, Schwartz and Masand⁵² evaluated the efficacy and tolerability of quetiapine compared with haloperidol in medically ill patients with delirium. There were no significant differences at baseline between the patients treated with haloperidol or quetiapine with regard to age, sex, or Delirium Rating Scale scores. Fourteen of 15 patients in the quetiapine group and 12 of 15 patients in the haloperidol group had a greater than 50% improvement in Delirium Rating Scale Scores. Although there was no difference in onset of symptom resolution, duration of treatment, and overall clinical improvement between the 2 groups, quetiapine was better tolerated in these medically ill patients, with a lower incidence of EPS and a lower discontinuation rate.

An open-label study was conducted by Kim⁵³ in 12 hospitalized patients who met DSM-IV criteria for delirium. Patients were given a starting dose of quetiapine 25 mg twice daily. The dosage was then increased until patients were maximally stabilized. Patients were discharged on the stabilizing dose of quetiapine. Patients had follow-up visits at the first month and the third month of therapy. At the first-month visit, quetiapine was tapered off when the patients were considered stable. The assessments administered at each visit were the MMSE, Delirium Rating Scale, and CGI. The mean duration required for maximal stabilization of patients was 5.9 ± 2.2 days, and the mean dosage of quetiapine was 93.8 ± 23.3 mg/day. All measures showed statistically significant improvement at all time points. Furthermore, the Delirium Rating Scale and MMSE scores continued to improve from the baseline to the third month. None of the 12 patients developed EPS, and the rates of other side effects were considered minimal. Larger, controlled studies are needed to confirm the safety and efficacy of quetiapine in the treatment of patients with delirium.

Comorbid Substance Abuse

There are very few drug treatment options for patients with psychotic illnesses and comorbid substance abuse. Brown et al.⁵⁴ in 2 pilot studies report that quetiapine may be associated with improvement in psychiatric symptoms and a reduction in stimulant cravings in patients with

psychiatric illnesses. The first study included patients (N = 29; mean age = 37 ± 8 years) with bipolar disorder (N = 15), schizophrenia (N = 4), schizoaffective disorder (N = 7), major depressive disorder (N = 3), and cocaine/amphetamine-related disorders confirmed by the Structured Clinical Interview for DSM-IV. Patients were receiving chronic neuroleptic therapy (mean = 331 mg/day chlorpromazine equivalents) at baseline. The patients were randomly assigned to either continue (N = 17) or discontinue (N = 12) neuroleptics. Patients in the discontinuation group who had psychotic symptoms (N = 8) were given quetiapine (exit dose = 394 mg/day), while non-psychotic patients received no antipsychotics. Significant reductions of modified Cocaine Craving Questionnaire and BPRS scores were seen in the group that discontinued neuroleptics. Significant decreases in HAM-D, BPRS, and Cocaine Craving Questionnaire scores were found in quetiapine-treated patients compared with patients who continued to receive neuroleptics.

In the second study, the use of open-label, add-on therapy for 12 weeks was examined in patients (N = 17, mean age = 36 ± 7 years) with psychotic disorders and comorbid substance abuse. Significant reductions in HAM-D, YMRS, BPRS, and Cocaine Craving Questionnaire scores were seen from baseline to exit using an LOCF analysis of all patients enrolled; however, the decrease in drug use did not reach statistical significance.

Cruz⁵⁵ reports quetiapine to be efficacious in treating the symptoms of schizophrenia in 1 patient who abused alcohol or other drugs. In this case, quetiapine was more effective than typical antipsychotics and markedly reduced the patient's psychotic and addictive symptoms, allowing him to return to work, to meet social responsibilities, and to volunteer for work in a Narcotics Anonymous program.

Quetiapine may be associated with improvement in psychiatric symptoms and reduction in stimulant cravings in psychiatric patients. However, the long-term utility of quetiapine in substance-induced or complicated psychotic disorder management warrants further investigation in larger, controlled studies.

PREDICTIONS FOR THE FUTURE

Quetiapine has been used in clinical settings as an anti-manic agent and a mood stabilizer and has anti-anxiety and anti-aggressive activity. It effectively reduces impulsivity and appears to have craving-reducing properties as well. Its serotonin transport reuptake inhibitor action profile may give it antidepressant activity. Its effect on suicidal behavior has not been studied in controlled trials. Quetiapine is known to enhance cognition in schizophrenia patients,⁵⁶ and its tolerability and safety profile is excellent. Long-term treatment results in minimal weight gain. Its lack of associated EPS and prolactin elevation is probably

related to low affinity and fast dissociation from postsynaptic D₂ receptors.³ Since it does not cause EPS, it is unlikely to cause tardive dyskinesia.⁵⁷⁻⁵⁹ Its effectiveness in neuroleptic-induced movement disorders like tardive dyskinesia and dystonia is clinically appreciated, although no controlled clinical trials have been conducted. However, based on its clinical profile and a unique mechanism of action, it is likely to emerge as a broad-spectrum psychotropic medication that may be helpful in psychiatry across current diagnostic categories. These clinical leads suggest the need for conducting randomized, controlled clinical trials in various diagnostic categories so that quetiapine could be used as first-line therapy for the treatment of psychiatric conditions other than schizophrenia.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), droperidol (Inapsine and others), haloperidol (Haldol and others), loxapine (Loxitane), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril and others), thiothixene (Navane and others), trifluoperazine (Stelazine and others), valproic acid (Depakene and others).

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