Efficacy and Tolerability of Quetiapine in the Treatment of Borderline Personality Disorder: A Pilot Study

Silvio Bellino, M.D.; Erika Paradiso, M.D.; and Filippo Bogetto, M.D.

Objective: Second-generation antipsychotics with a favorable tolerability profile have offered new treatment options for patients with borderline personality disorder. Sparse data are available on the use of quetiapine in treating this disorder. The aim of the present study is to investigate efficacy and tolerability of quetiapine in a group of patients with borderline personality disorder.

Method: Fourteen consecutive outpatients with a DSM-IV diagnosis of borderline personality disorder were treated for 12 weeks with open-label quetiapine at the dose of 200–400 mg/day. Patients were assessed at baseline, week 4, and week 12 with the Clinical Global Impressions (CGI) severity item, the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A), the Social and Occupational Functioning Assessment Scale (SOFAS), the Borderline Personality Disorder Severity Index (BPDSI), and the Barratt Impulsiveness Scale-version 11 (BIS-11). Adverse effects were evaluated using the Dosage Record and Treatment Emergent Symptom Scale. Statistical analysis was performed with the ANOVA for repeated measures. Significant p values were ≤ .05.

Results: Eleven patients completed the study. Three patients (21.4%) dropped out due to excessive somnolence or noncompliance. The mean ± SD dose of quetiapine was 309.09 ± 83.12 mg/day. A significant change was found for the scores of the following scales: CGI severity item, BPRS, HAM-A, SOFAS, BPDSI total score, BPDSI items "impulsivity" and "outbursts of anger," and BIS-11. Common adverse effects were mild-to-moderate somnolence, dry mouth, and dizziness.

Conclusion: Initial data suggest that quetiapine is efficacious and well tolerated in treating patients who have borderline personality disorder, particularly when impulsiveness/aggressiveness-related symptoms are prominent. At the moment, no reliable comparison is available in the literature. Double-blind controlled trials are needed to verify these findings.

(J Clin Psychiatry 2006;67:1042–1046)

Received Dec. 6, 2005; accepted Jan. 31, 2006. *From the Unit of Psychiatry, Department of Neuroscience, University of Turin, Turin, Italy.*

Drs. Bellino, Paradiso, and Bogetto report no financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Silvio Bellino, M.D., Unit of Psychiatry, Department of Neuroscience, University of Turin, via Cherasco 11, 10126 Turin, Italy (e-mail: silvio.bellino@unito.it).

Borderline personality disorder is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, and affects and marked impulsivity.[1] Although psychotherapy plays a significant role in the treatment of borderline patients, focusing on maladaptive personality traits and interpersonal relationship patterns,[2,3] pharmacotherapy is indicated by the guidelines of the American Psychiatric Association[4] to manage vulnerability traits, symptoms, and acute relapses.

Neuroleptics in low dosages are considered the first-line treatment for cognitive-perceptual distortions, such as transient psychotic or dissociative symptoms, that are a key element of borderline personality disorder. A recent review by Schulz[5] found that low doses of typical antipsychotics are efficacious in reducing anxiety, aggressiveness, and impulsiveness. However, adverse effects such as extrapyramidal symptoms (EPS), endocrinologic symptoms, sedation, and orthostatic dysregulation often lead to nonadherence or dropout, and the risk of tardive dyskinesia should be considered.

The introduction of second-generation antipsychotics with a favorable tolerability profile has offered new treatment options in the management of borderline personality disorder. In the opinion of a few authors, newer medications are superior to neuroleptics for patients with borderline and schizotypal personality disorders.[5] A small but growing body of literature supports the efficacy of second-generation antipsychotics on a broader spectrum of symptoms, probably due to their mechanism of action, combining both dopamine-2 (D_2) and serotonin-2 ($5\text{-}HT_2$) antagonism. Several studies[6–13] on the use of olanzapine and risperidone in patients with borderline personality disorder indicated the reduction of overall symptomatology, impulsiveness, aggressiveness, anxiety, and paranoid ideation. Clozapine was found to be effective on overall symptomatology, aggressiveness, and severe psychotic symptoms related to borderline personality disorder.[14–18] In fact, borderline patients treated with clozapine frequently had Axis I comorbidities and had been resistant to previous treatments.

Quetiapine is a dibenzothiazepine characterized by low affinity and fast dissociation from postsynaptic D_2 receptors, a profile that reduces the incidence of acute EPS, tardive dyskinesia, and neuroleptic malignant syndrome

  © Copyright 2006 Physicians Postgraduate Press, Inc.

and leads to no prolactin elevation and minimal weight gain.[19–22] To date, the sparse available data on the use of this novel antipsychotic in borderline patients derive from a case report[23] and preliminary results of an open-label study.[24] Hilger et al.[23] described the impact of quetiapine on 2 female patients with borderline personality disorder and severe self-mutilation and found the efficacy of the molecule on impulsive behavior and overall functioning. The first patient received 400 mg/day for 6 months, the second 800 mg/day for 8 months. In both cases, quetiapine was well tolerated. Adityanjee and Schulz (2002)[24] evaluated the efficacy of quetiapine (25 to 300 mg/day) in 10 borderline patients in an 8-week open-label trial. Preliminary findings of this study suggested a significant improvement in overall symptomatology, hostility, impulsivity, and global functioning. Two patients were discontinued due to positive toxicology screens, and 2 did not complete the trial.

In order to collect more data on this issue, the present investigation is a pilot open-label study concerning the efficacy and tolerability of quetiapine in the treatment of patients with borderline personality disorder.

METHOD

Fourteen consecutive outpatients aged 18 to 50 years who had a diagnosis of borderline personality disorder were included in this study. Patients attended the Service for Personality Disorders, Unit of Psychiatry, Department of Neuroscience, University of Turin, Turin, Italy. Diagnosis of borderline personality disorder was made by an experienced clinician (S.B.) using DSM-IV-TR criteria[4] and performing the Structured Clinical Interview for DSM-IV Axis II Disorders.[25]

Subjects were excluded if they had a current or previous record of delirium, dementia, amnestic disorder, or other cognitive disorders; schizophrenia or other psychotic disorders; or bipolar disorders. Patients were also excluded[1] if they had a current diagnosis of major depressive episode and/or substance abuse disorder[2] or if they had received psychotropic drugs and/or psychotherapy in the 3 months preceding the beginning of the study. Female patients of childbearing age were excluded if they were not using adequate birth control methods (according to the judgment of the clinician). Each patient participated voluntarily in the study after providing written informed consent. Declaration of Helsinki guidelines were followed.

Recruited patients were treated with open-label quetiapine. Medication was started at 25 mg/day and was increased up to a dose of 200–400 mg/day, supplied twice daily. Treatment was maintained for 12 weeks. No other psychotropic drug or psychological intervention was allowed during the trial.

Patients were repeatedly tested (at baseline, week 4, and week 12) using the following assessment instruments: the Clinical Global Impressions (CGI) severity item,[26] the Brief Psychiatric Rating Scale (BPRS),[27] the Hamilton Rating Scale for Depression (HAM-D),[28] the Hamilton Rating Scale for Anxiety (HAM-A),[29] the Social and Occupational Functioning Assessment Scale (SOFAS),[30] the Borderline Personality Disorder Severity Index (BPDSI),[31] and the Barratt Impulsiveness Scale-version 11 (BIS-11).[32]

The BPDSI is a semistructured clinical interview assessing the frequency and severity of manifestations of borderline personality disorder. The interview consists of 8 items scored on a 10-point frequency scale (0 = never; 10 = daily), including "abandonment," "interpersonal relationships," "impulsivity," "parasuicidal behavior," "affective instability," "emptiness," "outbursts of anger," "dissociation and paranoid ideation," and 1 item scored on a 4-point severity scale concerning "identity." The BPDSI showed excellent reliability coefficients and good validity indices in 2 studies performed by Arntz et al.[31]

The BIS-11 is a 30-item self-report questionnaire that assesses the personality trait of impulsivity.[33] The scale consists of 30 statements that are rated on a 4-point Likert scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always) without relation to any specific time period (a trait measure). Twelve items are reverse-scored, in order to avoid response sets. Higher scores for each item indicate higher levels of impulsivity. The BIS-11 showed adequate reliability and construct validity in both U.S.[34] and Italian[35] samples.

Assessment was performed by an investigator (E.P.) who was unaware of the dosing strategy. Prior to this study, the interviewer received training sessions on BPDSI. Adverse effects were assessed using the Dosage Record and Treatment Emergent Symptom Scale (DOTES).[36]

Statistics were performed on each rating scale by using the analysis of variance (ANOVA) for repeated measures (software system SPSS, version 12.0, SPSS Inc., Chicago, Ill.). p Values were considered significant when ≤ .05.

RESULTS

Fourteen subjects (mean ± SD age = 29.64 ± 5.5 years; 8 females and 6 males) were included. Three patients (21.4%) discontinued treatment in the first 4 weeks: 2 patients due to adverse effects (somnolence), 1 patient due to noncompliance. The 11 patients who completed the trial had a mean age of 30.55 ± 5.75 years; they were 6 females (54.5%) and 5 males (45.5%). The mean ± SD daily dose of quetiapine was 309.09 ± 83.12 mg/day.

Results of ANOVA applied to rating scales scores are reported in Tables 1 to 3. A statistically significant improvement was observed in the CGI severity item and BPRS mean scores (respectively, p = .003 and p = .002), HAM-A mean score (p = .002), SOFAS mean score (p = .009), BPDSI total score (p = .05), 2 BPDSI items,

Table 1. Results of Analysis of Variance for Repeated Measures Performed With Rating Scales for Borderline Personality Disorder–Related Symptoms and Social Functioning in Patients Treated With Quetiapine (N = 11)

	Score			
Measure	Baseline	Week 4	Week 12	p
CGI severity item				
Mean	4.55	4.18	3.82	.003
SD	0.52	0.41	0.41	
SE	0.157	0.122	0.122	
BPRS				
Mean	42.64	37.91	34.18	.002
SD	5.26	5.03	4.75	
SE	1.586	1.516	1.432	
HAM-A				
Mean	16.55	11.36	9.82	.002
SD	5.15	3.72	3.71	
SE	1.551	0.122	1.119	
HAM-D				
Mean	11.27	9.18	7.91	NS
SD	3.69	3.28	2.30	
SE	1.113	0.989	0.694	
SOFAS				
Mean	50.27	54.82	59.09	.009
SD	5.61	6.49	6.61	
SE	1.690	1.958	1.993	

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NS = not significant, SOFAS = Social and Occupational Functioning Assessment Scale.

Table 2. Results of Analysis of Variance for Repeated Measures Performed With Borderline Personality Disorder Severity Index (BPDSI) Total and Factor Scores in Patients Treated With Quetiapine (N = 11)

	Score			
BPDSI Measure	Baseline	Week 4	Week 12	p
Total				
Mean	50.02	46.28	44.72	.050
SD	5.55	4.90	4.36	
SE	1.673	1.476	1.313	
Abandonment				
Mean	6.78	6.40	6.40	NS
SD	1.43	1.47	1.47	
SE	0.430	0.443	0.444	
Interpersonal relationships				
Mean	6.84	6.33	6.07	NS
SD	1.94	1.82	1.78	
SE	0.585	0.548	0.535	
Identity				
Mean	2.60	2.57	2.55	NS
SD	0.98	0.95	0.94	
SE	0.303	0.296	0.284	
Impulsivity				
Mean	6.94	6.08	5.79	.028
SD	0.91	0.98	1.05	
SE	0.270	0.292	0.325	

Abbreviation: NS = not significant.

"impulsivity" (p = .028) and "outbursts of anger" (p = .009), and BIS-11 mean score (p = .025). On the contrary, there were no significant changes in HAM-D mean score and BPDSI items of "abandonment," "interpersonal relationships," "identity," "parasuicidal behavior," "affective instability," "emptiness," and "dissociation and paranoid ideation."

The most common adverse effects reported in the final sample of 11 patients were somnolence (5 patients, 45.5%) and dry mouth and dizziness (3 patients each, 27.3%). Other adverse effects included increased appetite and orthostasis (respectively, 2 patients (18.2%) and 1 patient, 9.1%). Nine patients (81.8%) reported at least 1 adverse effect, while 2 patients (18.2%) had no adverse effect. Adverse effects were mild to moderate in severity.

DISCUSSION

Results of this pilot study of quetiapine in the treatment of borderline patients indicate the efficacy of the antipsychotic drug as measured with the CGI severity item, BPRS, HAM-A, SOFAS, BPDSI total score, 2 BPDSI items ("impulsivity" and "outbursts of anger"), and Barratt Impulsiveness Scale.

The decrease of CGI, BPRS, HAM-A, and BPDSI mean scores and the increase of the SOFAS mean score suggest that quetiapine has effects on a broad spectrum of symptoms. The improvement of overall psychopathology and global functioning replicates previous findings concerning treatment of borderline personality disorder with atypical antipsychotics, such as olanzapine,[7,9,10,12,13] risperidone,[11] and clozapine.[14,17] Concerning previous quetiapine findings, only a case report[23] and preliminary results of a case series[24] are available: the efficacy on overall symptomatology was reported by Adityanjee and Schulz,[24] while the improvement in global functioning was found by both Adityanjee and Schulz[24] and Hilger et al.[23] As for HAM-A, the decrease of mean score was reported in 2 controlled studies of olanzapine,[9,13] but no data of quetiapine effects on anxious symptoms have been published yet.

When taking into account borderline personality disorder symptom dimensions, quetiapine seems to be selectively efficacious on impulsiveness and anger, as indicated by BPDSI items and by self-evaluation with BIS-11. The action of second-generation antipsychotics on impulsiveness has already been found by several investigations of olanzapine in borderline patients[7,12,13] and replicates sparse previous data on quetiapine.[23,24] The effects of quetiapine on the BPDSI item "outbursts of anger" indicate as well a modulation of behaviors related to the dimension impulsiveness/aggressiveness. Such effects on behavioral correlates of impulsivity have been outlined in cases treated with clozapine,[16] risperidone,[6,11] and olanzapine.[7,8,12,13]

Concerning tolerability, more common adverse effects in our patients were somnolence, dry mouth, and dizziness. Side effects were mild to moderate in most cases, but 2 patients discontinued treatment due to excessive somnolence. The pattern of adverse effects appears to be in

Table 3. Results of Analysis of Variance for Repeated Measures Performed With Borderline Personality Disorder Severity Index (BPDSI) Factor Scores and the Barratt Impulsiveness Scale-Version 11 (BIS-11) in Patients Treated With Quetiapine (N = 11)

	Score			
Measure	Baseline	Week 4	Week 12	p
BPDSI Factor				
Parasuicidal behavior				
Mean	2.68	2.49	2.33	NS
SD	2.54	2.28	2.00	
SE	0.766	0.687	0.603	
Affective instability				
Mean	6.14	5.48	5.22	NS
SD	1.61	1.21	1.08	
SE	0.484	0.365	0.325	
Emptiness				
Mean	6.30	6.17	6.20	NS
SD	1.96	1.82	0.81	
SE	0.592	0.550	0.547	
Outbursts of anger				
Mean	7.15	6.46	6.01	.009
SD	0.62	0.76	1.00	
SE	0.186	0.229	0.302	
Dissociation and paranoid ideation				
Mean	4.59	4.29	4.15	NS
SD	2.44	2.18	2.00	
SE	0.735	0.658	0.604	
BIS-11 score				
Mean	71.27	65.73	63.36	.025
SD	7.28	6.05	6.33	
SE	2.195	1.825	1.908	

Abbreviation: NS = not significant.

accordance with other investigations of quetiapine in patients with a diagnosis of schizophrenia or bipolar disorder,[37,38] although it cannot be compared with data collected in patients with borderline personality disorder. Hilger et al.[23] noticed only that quetiapine was well tolerated in their 2 cases, without specifying any side effect.

In conclusion, our results suggest that quetiapine can be considered as an effective antipsychotic treatment for patients with borderline personality disorder. In particular, it appears a good option when high levels of impulsiveness or aggressiveness are present. The good level of tolerability found in our sample and in other clinical populations is notable since patients with borderline personality disorder frequently present low levels of compliance and need long periods of drug therapy. However, lack of literature studies does not allow a reliable comparison of data concerning either efficacy or tolerability.

Limitations of our study are the small sample size and the lack of a control group. However, this pilot study is aimed to provide initial data on the use of quetiapine in borderline personality disorder and promote further investigations on this topic with a double-blind controlled design.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
2. Clarkin JF, Yeomans FE, Kernberg OF. Psychotherapy for borderline patients. New York, NY: John Wiley & Sons; 1999
3. Livesley WJ. A practical approach to the treatment of patients with borderline personality disorder. Psychiatr Clin North Am 2000;23:211–232
4. American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Borderline Personality Disorder. Washington, DC: American Psychiatric Association; 2001
5. Schulz SC. The promise of atypical antipsychotics for borderline disorders. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
6. Khouzam HR, Donnelly NJ. Remission of self-mutilation in a patient with borderline personality during risperidone therapy [case report]. J Nerv Ment Dis 1997;185:348–349
7. Schulz SC, Camlin KL, Berry SA, et al. Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. Biol Psychiatry 1999;46:1429–1435
8. Hough DW. Low-dose olanzapine for self-mutilation behavior in patients with borderline personality disorder [letter]. J Clin Psychiatry 2001;62: 296–297
9. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry 2001;62:849–854
10. Bogenschutz MP, Nurnberg GH. Olanzapine versus placebo in the treatment of borderline personality disorder. J Clin Psychiatry 2004; 65:104–109
11. Rocca P, Marchiaro L, Cocuzza E, et al. Treatment of borderline personality disorder with risperidone. J Clin Psychiatry 2002;63:241–244
12. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. J Clin Psychiatry 2004; 65:903–907
13. Soler J, Pascual JC, Campins J, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. Am J Psychiatry 2005;162:1221–1224
14. Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. Compr Psychiatry 1993;34:402–405
15. Chengappa KN, Baker RW, Sirri C. The successful use of clozapine in ameliorating severe self-mutilating in a patient with borderline personality disorder. J Personal Disord 1995;9:76–82
16. Chengappa KN, Ebeling T, Kang JS, et al. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. J Clin Psychiatry 1999;60:477–484
17. Benedetti F, Sforzini L, Colombo C, et al. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. J Clin Psychiatry 1998;59:103–107
18. Swinton M. Clozapine in severe borderline personality. J Forensic Psychiatry 2001;12:580–591
19. Kufferle B, Tauscher J, Asenbaum S, et al. IBZM SPECT imaging of striatal dopamine-2 receptors in psychotic patients treated with the novel antipsychotic substance quetiapine in comparison to clozapine and haloperidol. Psychopharmacology 1997;133:323–328
20. Hellewell JSE, Cameron Hands D, McKellar J. Seroquel: an effective atypical antipsychotic with no greater EPS than placebo across the full dose range. Schizophr Res 1998;29:154
21. Brecher M, Rak IW, Melvin K, et al. The long-term effect of quetiapine ("Seroquel") monotherapy on weight in patients with schizophrenia. Int J Psychiatry Clin Pract 2000;4:287–291
22. Kapur S, Zipursky R, Jones C, et al. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transient high dopamine D2 receptor occupancy. Arch Gen Psychiatry 2000;57:553–559
23. Hilger E, Barnas C, Kasper S. Quetiapine in the treatment of borderline personality disorder. World J Biol Psychiatry 2003;4:42–44
24. Adityanjee, Schulz SC. Clinical use of quetiapine in disease states other than schizophrenia. J Clin Psychiatry 2002;63(suppl 13):32–38
25. First MB, Gibbon M, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). Washington DC: American

Psychiatric Press; 1997
26. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
27. Ventura J, Green M, Shaner A, et al. Training and quality assurance with the Brief Psychiatric Rating Scale: "the drift busters." Int J Methods Psychiatr Res 1993;3:221
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
29. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
30. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149: 1148–1156
31. Arntz A, van den Hoorn M, Cornelis J, et al. Reliability and validity of the borderline personality disorder severity index. J Personal Disord 2003;17:45–59
32. Barratt ES. Factor analysis of some psychometric measures of impulsiveness and anxiety. Psychol Rep 1965;16:547–554
33. Barratt ES. Impulsiveness and aggression. In: Monahan J, Steadman HJ, eds. Violence and Mental Disorder: Developments in Risk Assessment. Chicago: University of Chicago Press; 1994:61–79
34. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 1995;51:768–774
35. Fossati A, Di Ceglie A, Acquarini E, et al. Psychometric properties of an Italian version of the Barratt Impulsiveness Scale-11 (BIS-11) in nonclinical subjects. J Clin Psychol 2001;57:815–828
36. Guy W. Dosage Record and Treatment Emergent Symptom scale (DOTES). In: ECDEU Assessment Manual for Psychopharmacology, Revised. Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:223–244
37. Conley RR, Kelly DL, Nelson MW, et al. Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. Clin Neuropharmacol 2005;28:163–168
38. Dunner DL. Safety and tolerability of emerging pharmacological treatments for bipolar disorder. Bipolar Disord 2005;7:307–325

