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Quetiapine in Patients with Borderline Personality Disorder: An Open-Label Trial

ADITYANJEE, MD
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
and Northcoast Behavioral Healthcare, Northfield Campus, Northfield, OH

ANN ROMINE, RN
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

ERIC BROWN, MD
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA and Veterans Administration Medical Center, Minneapolis, MN

PAUL THURAS, PHD
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA and Veterans Administration Medical Center, Minneapolis, MN

SUSANNE LEE, PHD
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

S. CHARLES SCHULZ, MD
Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Background*: Quetiapine was assessed in patients diagnosed with borderline personality disorder (BPD) to examine its potential effect on symptoms and explore a tolerated dosing pattern.*
Method*: An open label case series with objective rating measures was undertaken. The study was of 8 weeks duration.*
Results*: Sixteen research subjects received quetiapine and completed at least one rating. Nine subjects completed the entire 8 week trial. In the LOCF and completer analyses, significant improvement was noted on GAF, SCL-90, BIS, and SIB. Specifically for the LOCF analysis, GAF increased from 57.7 to 64.6 ($p = 0.001$), SCL-90 decreased from 120.1 to 78.4 ($p = 0.004$), BIS improved from 73.4 to 59.9 ($p = 0.021$), and the SIB started at 267.8 and ended at 202.3 ($p < 0.001$).*

The average dose of quetiapine for LOCF analysis was 223.4 mg/d and was 286.1 mg/d for the completers. Common side-effects were similar to those seen in schizophrenic patients—sedation and increased appetite.
Conclusions*: Significant reductions in symptoms assessed by objective rating scales were observed in this pilot study of quetiapine administered to subjects with BPD. The dosing strategy in the study was well tolerated.*

Keywords Borderline personality disorder, Quetiapine, Outpatients, Dosing

Address correspondence to S. Charles Schulz, M.D., Professor and Head, Department of Psychiatry, University of Minnesota Medical School F282/2A West, 2450 Riverside Avenue, Minneapolis, MN 55454. E-mail: scs@umn.edu

INTRODUCTION

Quetiapine is a member of the atypical antipsychotic medication class and has been approved by the FDA for the treatment of schizophrenia as well as mania and bipolar depression based on substantial randomized controlled trials (1–4). Meta-analytic studies have assessed quetiapine for schizophrenia and affirmed its overall efficacy (5–7). Within the group of typical and atypical antipsychotic medications, quetiapine has been reported to have rates of extra-pyramidal side effects that are comparable to those observed on placebo and are not related to the dose of the compound (1). Quetiapine does not increase prolactin levels (1) and has an impact on weight in the middle range of results reported for atypical antipsychotic medications (8).

Borderline personality disorder (BPD) is a significant illness that occurs in 1% of the population (9). Symptoms of BPD are distressing to patients suffering from the disorder. Examination of symptoms listed as the criteria for the diagnosis of BPD in the DSM IV (10), such as affective instability, transient paranoid ideation, impulsivity, and intense anger are also seen in other psychiatric illnesses for which medication treatment has been useful. Clinicians generally regard BPD as difficult to treat yet in recent years psychosocial treatments such as Dialectical Behavior Therapy (DBT) (11) and Systems Training for Emotional Predictability and Problem Solving (12) have been shown to be efficacious.

Representatives of most classes of medications have been assessed in patients with BPD. Reports describing positive results have been published with regard to antidepressant SSRIs (13–16) and SNRIs (17), as well as the mood stabilizers valproic acid (18) and lamotrigine (19). A review of the emerging studies has tabulated and assessed the impact of medications on BPD and symptoms within the disorder (20).

Double-blind, placebo-controlled trials of traditional antipsychotic medications reported the efficacy of thiothixene (21) and haloperidol (22) two decades ago. Subsequent trials largely supported the efficacy of these medications but noted significant difficulty with side effects. With the advent of the atypical antipsychotic medications, clinical investigators began to examine the possibility that this new group of medications could lead to a reduction in symptoms with fewer side-effects—especially in the movement disorder area. Reports now include results of studies testing risperidone (23), olanzapine (24–26), and aripiprazole (27). As a group, these studies have been in a positive direction. One case series reporting on the use of quetiapine on impulsive symptoms of BPD has been published (28). Symptoms of impulsivity were significantly reduced in this trial.

Since the reports of Villenueve and Lemelin (28) and the two cases reported by Hilger and colleagues (29), four other European case series have reported on the use of quetiapine for borderline personality disorder. These case reports are quite useful in better understanding the potential role of quetiapine for BPD as they address different dosing and titration strategies and focus on a variety of clinical measures.

As quetiapine is an antipsychotic medication, Gruettert and Friege (30) discussed its effect on 12 female borderline outpatients who had psychotic symptoms (although not from schizophrenia or bipolar disorder). They aimed for quetiapine doses of 300–400 mg per day by day 4 of the study and then adjusted the dose to a range between 300–750 mg per day. They reported that all subjects completed the trial and that the average dose of quetiapine was 537 mg per day. Also, a positive correlation was noted between dose and improvement. The rating scales utilized, ranging from impulsivity to global functioning to psychoticism, showed significant improvement. The authors note that the medication was generally well tolerated, but reported two patients required a titration of 8–10 days because of somnolence.

Bellino and colleagues (31) noted the lack of data regarding quetiapine for BPD and reported on 14 outpatients who received quetiapine in an open label design for 12 weeks. Eleven of the 14 patients completed the study (2 discontinued secondary to somnolence) and received an average dose of 309 mg/d. The rating scale scores were significantly decreased across a broad range of symptoms.

Borderline personality disorder patients who were hospitalized were assessed in comparison to schizophrenic and drug-induced psychosis patients in an experiment by Mauri et al. (32). The BPD subjects were titrated to an average dose of 555 mg/d during the first 4–6 days of treatment—a dose that was similar across patient groups. All patient groups improved significantly and the BPD patients had a 58% response rate on PANSS (30% reduction of the total score). Twelve of the 13 patients completed the 12 week study. Of note was a positive correlation of quetiapine blood level and treatment response—underscoring the finding by Gruettert and Friege (30).

Most recently Perrella et al. (33) assessed the effect of quetiapine on 29 BPD outpatients over 12 weeks. After a medication washout patients were titrated to a dose of 150 mg/d by the third day and then upward as tolerated to an average dose of 543 mg/d. Twenty-three of the 29 subjects completed the study and significant improvement was seen on a broad range of rating scales. The major reason for discontinuation was sedation.

Therefore, recent open label studies of quetiapine which have included borderline personality disorder patients have shown improvement on objective rating scales which capture symptoms of BPD. Doses on these studies have ranged from 351 mg/d to 555 mg/d with generally good tolerability. The authors of these trials indicate that the data points to the need for randomized, controlled trials to assess quetiapine further.

The purpose of this study was to assess the effects of quetiapine on BPD using structured assessments completed either by patients (SCL-90) or investigators (BPRS and GAF) to examine the overall effect of the medication. Two other scales were administered to assess specific characteristics of BPD. The study utilized a flexible dosing strategy that was aimed at assisting in a determination of a useful and tolerated dose.

METHODS

Subjects

Research participants were sought by placing IRB approved ads in local newspapers describing the study goals. Subsequently, 29 candidates underwent a face-to-face interview, of which 20 subjects progressed to the baseline evaluation and received the initial starting medications. Of these 20, 16 returned for at least one rating and were included in the LOCF analysis. Nine research participants completed all 8 weeks of the study and were included in the observed cases analysis.

The subjects participating in the screening interview signed an approved consent form and underwent assessment by the Structured Clinical Interview for DSM-IV (SCID) and the Structured Clinical Interview for Personality Disorders (SCID-II). The subjects then underwent a history of medical illness and physical exam. Subjects were included if they met inclusion criteria of borderline personality disorder. Subjects may have been male or female and between 18 and 60 years of age. They may not have exclusion criteria of schizophrenia or bipolar disorder. They may have a history of major depression, but not within the last 12 weeks.

Assessment

In order to meet the goals of this study—to assess the effects of quetiapine on symptoms associated with BPD, patients completed the SCL-90 at baseline and at each weekly visit. The project coordinator administered the Brief Psychiatric Rating Scale (BPRS) (34) and GAF (35) at each visit as well. To address more specific domains of BPD, the Barratt Impulsivity Scale (BIS) (36) and the Schedule for Interviewing Borderlines (SIB) (37) were also administered.

Dosing

The study consisted of a washout of any psychiatric medication followed by an 8-week, open-label, dose finding trial. This enabled the investigators to determine the best general starting dose and dose increase strategy for this population. Symptoms and dosage were evaluated at each visit. Patients began treatment with a low dose (25 mg/daily) in the first week and then were raised incrementally, up to 300 mg/daily, if needed, within the first 4 weeks of the trial. Patients remained on the week four dosage without change for the rest of the study. For most patients, dosing reached 200–300 mg/daily by week four.

Statistical Analysis

The overall plan for analysis was to address the outcome of all subjects (N = 16) who completed at least one post-baseline assessment, an intent-to-treat analysis. In order to address the effect of quetiapine over the full 8 weeks of the study—both on symptoms and potential side-effects as well as quetiapine dosing, an observed cases (completers) analysis was performed. The total scores of three primary measures of outcomes were controlled for multiple assessments by setting significance at $p < 0.017$. Because there were statistically significant decreases in the total scores of the behavioral measures, subscales were analyzed to assess which specific symptoms changed over time.

Side effects were recorded at each visit and tabulated. Further, the reason for discontinuation was elicited and those reasons are reported. Subjects were assessed for movement disorders by the Simpson-Angus Scale (SAS). For the two exploratory measures, significance was set at $p < 0.05$. Baseline and endpoint scores were compared by t-test for by LOCF and completer samples.

RESULTS

The patients who were prescribed quetiapine and received at least one rating (N = 16) were included in the last observation carried forward (LOCF) analysis. The subjects were 33.7 + 11.3 years old. In this group, 2 were male and 14 female. An analysis of the subjects who completed the trial (N = 9) was also performed. The nine patients were 33.3 + 10.3 years old and 1 was male and 8 were female.

Table 1 displays the total scores at baseline and endpoint of the GAF, BPRS, and SCL-90, while Table 1a displays the BIS, and SIB. For scales that demonstrated a significant difference from baseline to last observation, the results for subscales are also listed. The results of the total scores of the rating scales reveal significant reductions in all scales except the BPRS. Within the rating scales, there were reductions in five of the nine subscales of the SCL-90, the non-plan scale of the BIS and 16 of the 21 subscales of the SIB, a scale addressing a number of schizotypal symptoms.

Table 2 displays the total scores of the same rating scales and the subscales of subjects who completed all 8 weeks of the study. Table 2a lists the results of the two exploratory measures—the BIS and SIB. For this analysis of the completers, the total scores showed statistically significant reductions from baseline to endpoint, except for the BPRS. A similar pattern of the subscales that changed significantly over time in the LCOF group was observed.

To address the potential clinical significance of quetiapine in this pilot study, effect sizes (Cohen's d) were calculated for the primary rating scales that were administered. The results are listed in Tables 1 and 2 and reveal substantial scores—for example the effect size for the GAF rating was 0.83 for the LOCF analysis and 0.99 for the observed cases analysis. There were relatively similar effect sizes observed for the SCL-90–0.74 for the LOCF analysis and 0.97 for the observed cases. These effect size values are considered to indicate substantial clinical significance.

Table 1 The Scales Administered to the LOCF Subjects are Tabulated with Mean Baseline and Last Rating. Statistical Significance is Listed for Each Overall Scale Comparison and Subscales. Statistically Significant Total Scores ($p < 0.017$) and Subscale Scores ($p < 0.05$) are Emboldened

	N	Week 1 Mean	LOCF Mean	T-statistic	Df	p-value	ES
GAF							
Total score	12	**57.67**	**64.58**	–4.342	11	**.001**	0.83
BPRS							
Total score	16	39.13	34.44	2.283	15	.037	0.62
SCL-90							
Total score	16	**126.13**	**78.44**	3.403	15	**.004**	0.74
S: somatization	14	0.94	1.09	–0.631	13	.539	0.21
OC: obsessive-compulsive	14	1.74	1.20	1.811	13	.093	0.49
IS: interpersonal sensitivity	14	**1.84**	**1.16**	2.771	13	**.016**	0.67
D: depression	14	**1.98**	**1.32**	2.677	13	**.019**	0.66
A: anxiety	14	1.34	0.91	1.584	13	.137	0.49
H: hostility	14	1.51	0.97	1.691	13	.115	0.55
PA: phobic anxiety	14	**0.91**	**0.42**	2.580	13	**.023**	0.65
PI: paranoid ideation	14	**1.59**	**1.08**	2.266	13	**.041**	0.49
P: psychoticism	14	**1.21**	**0.62**	3.132	13	**.008**	0.74
AI: additional items	14	**1.91**	**1.17**	2.780	13	**.016**	0.79
GSI: global severity index	14	**1.49**	**1.02**	2.542	13	**.025**	0.62
PSDI: positive symptom distress index	14	2.15	1.90	1.401	13	.185	0.33
PST: positive symptom total	14	**59.50**	**43.21**	2.952	13	**.011**	0.80

Note. Cohen's *d* was calculated for effect size (ES).

Table 1a Exploratory Scales Administered to the LOCF Subjects are Tabulated with Mean Baseline and Last Rating. Statistical Significance is Listed for Each Overall Scale Comparison and Subscales. Statistically Significant Assessments ($p < 0.05$) are Emboldened

	N	Baseline Mean	LOCF Mean	T-statistic	Df	Two-tailed p-value
Barratt Impulsivity Scale (BIS)						
Total Score	12	**73.42**	**59.92**	2.701	11	.021
INP (Non-Plan)	12	**28.50**	**23.25**	2.708	11	.020
IC (Cogn)	12	21.67	18.00	2.126	11	.057
IM (Motor)	12	23.25	18.67	2.058	11	.064
Schizotypal Rating Scale (SIB)						
Total Score	12	**267.83**	**202.33**	6.277	11	<.001
1. illusions	12	15.75	13.00	1.669	11	.123
2. deperson/dereal	12	**29.25**	**23.00**	3.773	11	.003
3. ideas of ref	12	**7.42**	**5.58**	3.051	11	.011
4. suspicious/paranoid	12	**24.42**	**18.92**	4.572	11	.001
5. mag thinking	12	**10.58**	**8.67**	3.727	11	.003
6. inadequate rapport	12	**14.92**	**13.00**	2.733	11	.019
7. odd communication	12	17.33	15.00	1.642	11	.129
8. social isolation	12	4.33	4.25	0.209	11	.838
9. social anxiety	12	**9.25**	**6.08**	4.490	11	.001
10. delus/halluc	12	**15.33**	**12.83**	2.887	11	.015
11. impulsivity	12	**38.42**	**26.33**	3.543	11	.005
12. phys damage bx	12	**12.58**	**8.33**	3.957	11	.002
13. unstable pers rshps	12	**11.00**	**8.08**	3.772	11	.003
14. compuls sociability	12	3.75	3.33	0.959	11	.358
15. affective instability	12	**9.25**	**6.33**	3.303	11	.007
16. inapprop ang-host	12	**7.17**	**4.75**	3.125	11	.010
17. emptiness/boredom	12	**7.33**	**4.75**	3.628	11	.004
18. free-float anxiety	12	**4.33**	**2.75**	2.370	11	.037
19. mood elevate praise	12	5.75	4.25	1.939	11	.079
20. reject sensitivity	12	**8.33**	**5.67**	2.305	11	.042
21. identity disturb	9	**15.11**	**9.89**	4.195	8	.003

Table 2 The Scales Administered to the Completer Subjects are Tabulated with Baseline and Last Rating Mean Values. Statistical Significance is Listed for Each Overall Scale Comparison and Subscales. Statistically Significant Total Scores ($p < 0.017$) and Subscale Scores ($p < 0.05$) are Emboldened

	N	Week 1 Mean	Week 8 Mean	T-statistic	Df	p-value	ES
GAF							
Total score	9	**57.33**	**66.11**	–5.789	8	**<.001**	0.99
BPRS							
Total score	9	38.22	31.78	2.161	8	.063	0.86
SCL-90							
Total score	9	**134.78**	**69.44**	3.684	8	**.006**	0.97
S: somatization	9	0.85	1.02	–0.533	8	.609	0.22
OC: obsessive-compulsive	9	1.82	0.92	2.294	8	.051	0.86
IS: interpersonal sensitivity	9	**2.01**	**1.02**	3.709	8	**.006**	0.97
D: depression	9	**2.11**	**1.16**	2.766	8	**.024**	0.94
A: anxiety	9	1.30	0.81	1.634	8	.141	0.52
H: hostility	9	1.61	0.78	2.019	8	.078	0.73
PA: phobic anxiety	9	**0.82**	**0.40**	3.169	8	**.013**	0.61
PI: paranoid ideation	9	**1.51**	**0.76**	3.268	8	**.011**	0.67
P: psychoticism	9	**1.34**	**0.62**	2.561	8	**.034**	0.82
AI: additional items	9	**2.08**	**1.06**	2.879	8	**.021**	1.06
GSI: global severity index	9	**1.55**	**0.88**	2.935	8	**.019**	0.83
PSDI: positive symptom distress index	9	2.24	1.83	1.624	8	.143	0.61
PST: positive symptom total	9	**59.11**	**35.89**	3.545	8	**.008**	1.06

Note. Cohen's *d* was calculated for effect size (ES).

Table 2a Exploratory Scales Administered to the Completer Subjects are Tabulated with Mean Baseline and Last Rating. Statistical Significance is Listed for Each Overall Scale Comparison and Subscales. Statistically Significant Assessments ($p < 0.05$) are Emboldened

	N	Baseline Mean	Week 8 Mean	T-statistic	Df	Two-tailed p-value
Barratt Impulsivity Scale (BIS)						
Total Score	9	**77.44**	**63.56**	2.500	8	.037
INP (Non-Plan)	9	**29.33**	**25.00**	2.335	8	.048
IC (Cogn)	9	23.56	18.89	2.228	8	.057
IM (Motor)	9	24.56	19.67	1.872	8	.098
Schizotypal Rating Scale (SIB)	9				8	
Total Score	9	**273.00**	**197.00**	6.588	8	<.001
1. illusions	9	16.00	13.11	1.360	8	.211
2. deperson/dereal	9	**31.00**	**22.67**	5.270	8	.001
3. ideas of ref	9	**7.78**	**5.78**	2.619	8	.031
4. suspicious/paranoid	9	**24.67**	**18.22**	4.651	8	.002
5. mag thinking	9	**11.67**	**9.11**	4.822	8	.001
6. inadequate rapport	9	13.33	11.89	1.696	8	.128
7. odd communication	9	17.33	14.33	2.107	8	.068
8. social isolation	9	3.89	3.89	.000	8	1.00
9. social anxiety	9	**9.00**	**5.78**	3.604	8	.007
10. delus/halluc	9	**15.78**	**12.78**	2.714	8	.027
11. impulsivity	9	**41.67**	**25.11**	5.062	8	.001
12. phys damage bx	9	**12.11**	**7.89**	2.990	8	.017
13. unstable pers rshps	9	**12.00**	**8.00**	5.657	8	<.001
14. compuls sociability	9	4.22	3.33	1.835	8	.104
15. affective instability	9	**9.33**	**6.22**	3.011	8	.017
16. inapprop ang-host	9	**6.78**	**4.33**	2.927	8	.019
17. emptiness/boredom	9	**7.44**	**4.89**	3.060	8	.016
18. free-float anxiety	9	4.56	2.89	2.041	8	.076
19. mood elevate praise	9	5.33	4.44	1.126	8	.293
20. reject sensitivity	9	**8.78**	**6.00**	2.273	8	.053
21. identity disturb	6	**15.50**	**9.50**	4.392	5	.007

Table 3 The Side-Effects Noted During Assessment Sessions are Tabulated in Order of Frequency. Nearly All Patients Reported Some Sedation at Some Point During the Trial

Seroquel BPD	Seroquel BPD
Adverse Event	**# of Subjects**
Sedation	15
Increased appetite	10
Dry Mouth	6
Weight Gain	6
Increased Irritability	4
Akathisia	3
Vivid Dreams	3
Confusion	2
Nasal Congestion	1
Tongue Edema	1

The doses of medications were 223.4 mg/d + 105.5 at the last visit for the LOCF group and 286.1 mg/d + 33.3 for the subjects who completed the 8 week study.

The side effects reported by the subjects were similar to the ones noted in studies of quetiapine for schizophrenia (1), mania (2), and depression in bipolar patients (3). The number of subjects who reported a side-effect is listed in Table 3. An assessment of the SAS ratings displayed in Table 4 revealed a small but nonsignificant increase for SAS ratings for both the LOCF and observed cases subjects.

DISCUSSION

The purpose of this study was to assess the effects of quetiapine on the symptoms of BPD using objective rating scales over an 8 week period. The scales selected were ones that included subscales so that the impact of symptom domains could be examined if the total scores were significantly different from baseline to endpoint. Because this is an early report of an objectively assessed case series utilizing quetiapine it was a goal to assess safety of the compound in the doses prescribed. Lastly, in this flexible dosing study, there was an opportunity to assess the doses utilized by the research team with the BPD subjects to guide further research and clinical use. Each of these goals will be discussed in turn.

An assessment of the total scores of the rating scales used in this study demonstrate a significant effect of quetiapine on behavioral scales and function assessed by GAF for the LOCF analysis. For the completer analysis, a similar pattern was seen. Statistically significant changes were not seen for BPRS rating, which may indicate that it is not a sensitive measure for BPD studies. Therefore, quetiapine had a substantial effect on both broad (SCL-90 and GAF) and more specific scales (BIS and SIB).

Because the total scores of the scales demonstrated statistically significant changes, an assessment of subscales is appropriate in order to examine affected symptom domains. An inspection of the two Tables reveals that for LOCF and completer analyses the subscales that were significantly changed were quite similar.

The SCL-90 is one of the most widely used scales for pharmacotherapy of BPD and the subscales that changed significantly—interpersonal sensitivity, depression, phobic anxiety, paranoia, and psychoticism—are scales seen to be changed in other antipsychotic medication trials (21,25). The same scales were reduced in the completers analysis. As in studies of other atypical antipsychotic medications (26,38), a broad number of symptoms were affected.

The first case series report on quetiapine focused on impulsivity and reported a decrease in this important symptom of 20% in 12 weeks (28). In this study, the BIS was reduced by 18.4% over 8 weeks. The subsequent case series generally show broad response to quetiapine (30–33), thus extending the findings of Villeneuve and Lemelin (28) and are consistent with the current report. Further studies may build on these studies to determine the types of symptoms affected. At this time, it appears that quetiapine effects aren't limited to psychosis-like symptoms.

A scale utilized by Goldberg and colleagues (21) in the first placebo controlled antipsychotic study was the Schedule for Interviewing Borderlines (37), which assesses a number of schizotypal symptoms was utilized in this study. There was a highly significant change in the SIB ($p < 0.001$) with a number of scales including depersonalization/derealization, suspicious/paranoid, magical thinking, social anxiety, and identity disturbance changing quite significantly. As these are symptoms that are commonly seen in BPD, their reduction is of great interest.

These symptom changes were accompanied by a significant increase in GAF ($p < 0.001$) in both analyses. This change in

Table 4 The Results of the SAS Exams for Both LOCF and Completer Groups are Displayed in this Table and Show Small, Non-Statistically Significant Increases Over the Study Period. Those Subjects Who had Both Ratings were Included

	N	Baseline Mean	Endpoint Mean	T-statistic	Df	Two-tailed p-value
LOCF analysis						
Simpson-Angus Scale						
Total Score	13	0.69	1.46	−1.690	12	.117
Completer analysis						
Simpson-Angus Scale						
Total Score	7	0.43	1.14	−1.508	6	.182

GAF indicates that not only did symptoms change in this study, but that functioning improved as well.

Regarding side-effects, Table 3 indicates that side-effects reported in trials of quetiapine for schizophrenia (1) were similar to those noted in the subjects who participated in this trial, with sedation and increased appetite being reported most frequently.

An important part of this study was to utilize a flexible dosing strategy to begin to determine a dose of quetiapine that was efficacious and well tolerated. Villeneuve and Lemelin (28) reported an average dose of 251 + 50 mg/d in their 12 week study. In this trial, the average dose in the LOCF analysis was 223.4 mg + 105.5, and 286.1 mg/d + 33.3 for the completers who all, obviously, completed 8 weeks of receiving quetiapine. For researchers, these results may assist in research design and for clinicians it will assist in determining an adequate trial of medication. It is of interest that the more recent trials have utilized higher doses. Next investigative steps may utilize fixed-dose strategies to determine the most appropriate dosing for an adequate trial of the medication.

In conclusion, quetiapine was tested with an open label design to assess its impact on symptoms of BPD and to examine side-effects and dosing. Significant reductions in multiple scales were noted and a broad group of symptoms changed. The side-effects were similar to those seen in quetiapine trials for other illnesses. Dosing results revealed that patients received doses of approximately one-half of that recommended for schizophrenia and equivalent to that of bipolar depression.

The results of this study need to be considered in light of the fact that it was an open trial with attendant concerns regarding the expectations of research subjects and clinicians. However, this report points in the direction of future research to assess quetiapine for BPD.

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