# Open-Label Study of Atypical Neuroleptic Quetiapine for Treatment of Borderline Personality Disorder: Impulsivity as Main Target

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***Background:*** Recent studies indicate that atypical neuroleptics may be safe and useful in treating many symptoms of borderline personality disorder (BPD), including impulsivity, which can constitute the core dimension of this pathology. This study aimed to evaluate the efficacy and safety of quetiapine in patients with well-defined BPD. It was hypothesized that quetiapine would reduce impulsivity (primary hypothesis) and also affective and micropsychotic symptoms, resulting in improved social and global functioning (secondary hypothesis).

***Method:*** Twenty-three outpatients with BPD according to DSM-IV criteria and the revised Diagnostic Interview for Borderlines completed a 12-week open-label study with quetiapine. The study was conducted from May 2001 to May 2003. The clinical efficacy was assessed using the following: Hamilton Rating Scales for Depression and Anxiety, Hopelessness Scale, Brief Psychiatric Rating Scale, Barratt Impulsivity Scale, Buss-Durkee Hostility Inventory, Temperament and Character Inventory, Social Adjustment Scale, and Global Assessment of Functioning.

***Results:*** The mean daily dose of quetiapine (251 ± 50 mg; range, 175–400 mg) was well tolerated. Impulsivity was significantly improved by quetiapine ($p = .0015$), as were most of our outcome measures: hostility, depression, anxiety, character dimensions, and social and global functioning ($p < .05$). In the small subgroup of patients with psychotic symptoms at baseline, there was a significant reduction in these symptoms ($N = 8$, $p = .018$).

***Conclusion:*** In a sample of patients with severe BPD without or with only few psychotic symptoms, a low dose of quetiapine was associated with a strong positive clinical impact, including improvement of impulsivity.

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The American Psychiatric Association (APA) guidelines[1] for the treatment of patients with borderline personality disorder (BPD) suggest that "most patients with BPD will need extended psychotherapy to attain and maintain lasting improvement in their personality, interpersonal problems, and overall functioning. Pharmacotherapy often has an important adjunctive role, especially for diminution of symptoms such as affective instability, impulsivity, micropsychotic symptoms, and self-destructive behavior."[1(p4)] A pharmacologic approach to the treatment of BPD is based upon evidence that some dimensions of the pathophysiology appear to be mediated by dysregulation of neurotransmitter physiology and are responsive to medication. It is also recommended that pharmacotherapy be used for treating state symptoms during periods of acute decompensation as well as for treating trait vulnerabilities.

A wide variety of medication classes have been used in BPD: anticonvulsants, psychostimulants, β-adrenergic antagonists, benzodiazepines, antidepressants, and neuroleptics. A recent review by Soloff[2] showed that antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), neuroleptics, and mood stabilizers, were the most effective drugs for BPD. In addition, Soloff[2] concluded that the efficacy of a medication mainly depends on its "ability" to reduce impulsivity.

Impulsivity constitutes a core dimension of BPD and may be the key symptom target of its treatment. First, many manifestations of BPD include behavioral problems: impulsive aggression, suicide attempts, self-mutilation, and self-damaging behaviors (e.g., promiscuous sex, substance abuse, reckless spending). Second, Links et al.[3] showed that, of the 4 main symptom domains associated with BPD (affective symptoms, micropsychotic symptoms, impulsive behaviors, and interpersonal problems), impulsive behaviors could explain more than 24% of the total variance of the pathology. Finally, in a 7-year follow-up study, this group[3] also concluded that impulsivity is the best predictor of BPD diagnosis stability.

Conventional antipsychotics are probably the best-studied psychotropic medications for BPD, but noncompliance is often due to their severe side effects. The introduction of the atypical neuroleptics increases clinicians' options for treating BPD. Zanarini[4] recently reviewed



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all open-label and placebo-controlled trials of atypical neuroleptics studied in samples of well-defined BPD. Zanarini[4] reported 2 open-label studies of clozapine, 1 open-label study and 1 placebo-controlled study of olanzapine, and, finally, 1 open-label study and 1 placebo-controlled study of risperidone. In all studies, atypical neuroleptics were associated with an overall functioning improvement and a reduction of impulsivity level.[4]

Quetiapine is another atypical neuroleptic that is increasingly used to treat BPD in clinical practice.[5,6] According to clinicians, quetiapine is a very interesting pharmacologic treatment, because it is effective, well tolerated (only moderate weight gain), and safe (less risky than clozapine).

### Objective and Hypothesis

This study aims to evaluate efficacy and tolerability of quetiapine in patients with BPD. Our primary hypothesis was that quetiapine would reduce the impulsivity of BPD. Our secondary hypothesis was that quetiapine would reduce the affective and micropsychotic symptoms of BPD, resulting in improved social and global functioning. This study should be considered as a pilot study permitting the development of a future randomized comparative study.

## METHOD

### Subjects

Outpatients of either sex, aged between 18 and 60 years, with a diagnosis of BPD according to DSM-IV criteria and the revised Diagnostic Interview for Borderlines[7,8] were recruited from the Clinique Le Faubourg St-Jean, Québec, Québec, Canada. In order to participate in this study, patients had to have a total score of less than 55 on the Global Assessment of Functioning (GAF),[9] indicating the presence of marked symptoms or severe disturbances in vocational or social functioning. Patients were excluded if they had a current DSM-IV diagnosis of a major depressive episode or substance dependence within the last 6 months or a past or ongoing DSM-IV diagnosis of major psychotic disorder or type I bipolar disorder. Also excluded were patients suffering from any major medical or neurologic illness and women who were pregnant or lactating or of childbearing age and not taking adequate contraceptive measures. The study was conducted from May 2001 to May 2003. The protocol was approved by the institutional review board, and the subjects gave their informed, written consent to participate. Demographic and clinical characteristics of these patients are shown in Table 1.

**Table 1. Demographic and Clinical Characteristics of 34 Patients With Borderline Personality Disorder**

| Variable | Value |
|---|---|
| Sex, N (men/women) | 9/25 |
| Age, mean ± SD, y | 33.65 ± 6.36 |
| Education, mean ± SD, y | 12.06 ± 4.95 |
| DSM-IV Axis II codiagnosis, N (%) | |
| Antisocial personality disorder | 4 (12) |
| Narcissistic personality disorder | 3 (9) |
| Histrionic personality disorder | 3 (9) |
| Dependent personality disorder | 1 (3) |
| Avoidant personality disorder | 2 (6) |
| DSM-IV Axis I codiagnosis, N (%) | |
| Dysthymia | 6 (18) |
| Social phobia | 7 (21) |
| Specific phobia | 3 (9) |
| Generalized anxiety disorder | 5 (15) |
| Panic disorder | 1 (3) |
| Posttraumatic stress disorder | 4 (12) |
| Obsessive-compulsive disorder | 1 (3) |
| Pathological gambling | 1 (3) |
| Eating disorders | 1 (3) |
| Alcohol abuse | 4 (12) |
| Drug abuse | 6 (18) |
| Hospitalization days in previous 2 months, mean ± SD | 0.32 ± 0.88 |
| Parasuicidal acts in previous 2 months, mean ± SD, no | 0.44 ± 0.75 |
| Suicidal acts in previous 2 months, mean ± SD, no | 0.21 ± 0.41 |

### Procedure

The study began with a 2-week washout period. Patients stopped their psychotropic medication, which constituted antidepressants (N = 27), benzodiazepines (N = 19), mood stabilizers (N = 4), atypical neuroleptics (N = 4), and classical neuroleptics (N = 1).

Patients were treated with open-label quetiapine for 12 weeks. Quetiapine was administered orally twice daily starting at 50 mg/day. The dose was increased to 250 mg/day by the end of week 2, and then to a maximum of 400 mg/day according to patient tolerability and until the patient responded clinically. During the 2-week washout period and the first week of treatment, long-acting benzodiazepines were permitted for agitation. If necessary, it was possible to maintain this medication throughout the study. No other psychotropic drugs were permitted during the study.

Patients were seen weekly or every 2 weeks as follows: baseline, week 1 (after 1 week of treatment), week 2, week 3, week 4, week 6, week 8, week 10, and week 12. Parasuicidal, suicidal, and heteroaggressive gestures were recorded at each visit. Side effects were evaluated using the UKU Side Effect Rating Scale (UKU)[10] and the Extrapyramidal Symptom Rating Scale (ESRS)[11] starting with the week 1 visit.

The primary efficacy variable was the mean change from baseline to endpoints in the Barratt Impulsivity Scale-Version 10 (BIS-10)[12,13] total score. The secondary efficacy variables included the mean change from baseline to endpoints in various measures presented in Table 2. Adverse events, dropout rates, and reasons for dropping out were recorded throughout the study.

### Analysis

Changes in clinical outcome measures from baseline to the last rating (week 12) were compared using random-

Table 2. Measures Used to Assess Changes in Patients With Borderline Personality Disorder Treated With Quetiapine

| Measure | Type | Dimension |
|---|---|---|
| Barratt Impulsivity Scale[12,13] | Self-reported | Impulsivity |
| Buss-Durkee Hostility Inventory[14] | Self-reported | Hostility |
| Hopelessness Scale[15] | Self-reported | Hopelessness |
| Hamilton Rating Scale for Depression[16] | Clinician-rated | Depression |
| Hamilton Rating Scale for Anxiety[17] | Clinician-rated | Anxiety |
| Brief Psychiatric Rating Scale[18] | Clinician-rated | Micropsychotic symptoms |
| Temperament and Character Inventory[19] | Self-reported | Personality dimensions |
| Social Adjustment Scale[20] | Self-reported | Social functioning |
| Global Assessment of Functioning[9] | Clinician-rated | Global functioning |

effects regression modeling with repeated measures. All significance tests were subjected to Bonferroni correction, where required, to maintain an overall p = .05 level.

## RESULTS

A total of 34 outpatients (9 men and 25 women) entered the study. Twenty-three patients completed the entire 12 weeks of the study. Among patients who dropped out, 4 of 11 patients left due to circumstances out of their control: 2 patients left following our instructions because of serious physical conditions (1 for moderate neutrophil reduction and 1 for suspected malignant neuroleptic syndrome), 1 patient was imprisoned for an offense committed before the beginning of this study, and 1 patient went into closed therapy to avoid relapse of substance abuse. The other 7 dropout patients evoked different motives to quit the trial, but it seems to us that the main reason was a lack of motivation: 5 patients complained about fatigue and sleep disturbances, 1 patient reported muscle pain, and 1 patient was not able to tolerate his performance anxiety.

We compared clinical scale scores at baseline of the 11 dropout patients to the 23 patients who completed the trial to see if there were any differences in their clinical profiles before quetiapine treatment. t Tests for independent samples were performed on total scores of every clinical scale presented in Table 2. Interestingly, only 1 comparison showed a statistically significant difference between groups, and it was the mean perseverance score of the Temperament and Character Inventory (TCI)[19] (23 who completed = 5.39 vs. 11 who dropped out = 3.36; t = 2.833, p = .008). According to the TCI model, a low score for perseverance indicates that the individual tends to give up a goal because of fatigue or obstacles. This supports our hypothesis of a lower level of motivation in our dropout group.

The final mean ± SD quetiapine dose was 251 ± 50 mg (range, 175–400 mg). During the trial, 4 patients took bromazepam (3 mg), and 7 patients took oxazepam (from 15 to 60 mg).

### Adverse Events

The weight gain of patients was not statistically significant during the trial (baseline = 67.20 ± 3.48 kg, endpoint = 69.08 ± 3.08 kg; analysis of variance [ANOVA] with repeated measures: F = 0.757, df = 10, not significant). The body mass index also did not significantly vary during the trial (baseline = 25.64 ± 1.37 kg/m$^2$, endpoint = 26.39 ± 1.24 kg/m$^2$; ANOVA with repeated measures: F = 0.788, df = 10, not significant).

Information collected with the UKU indicated that quetiapine was rarely associated with severe side effects. Actually, only 1 patient presented with severe but transient symptoms, namely gastrointestinal problems at week 3 and week 6. However, these symptoms were present prior to the trial. Only 2 patients experienced extrapyramidal symptoms as assessed by the ESRS. One patient presented with mild dystonia affecting the lower jaw, and another patient presented with very mild parkinsonism (tremor of hands, muscular contractions). Moreover, these manifestations were transient.

### Clinical Outcome Measures

Changes in outcome measures within the study period are displayed in Table 3. Analysis of the mean score for both clinician-rated and self-rated scales revealed a significant improvement during the period of quetiapine administration.

The primary outcome measure, the BIS-10 total score, was statistically significantly better during quetiapine treatment, with a mean decrease of 20% from the baseline evaluation to the final endpoint (p = .0015).

Depressive and anxiety symptoms were significantly reduced by quetiapine (p = .0015), with a mean decrease of 63% and 68% on the Hamilton Rating Scales for Depression (HAM-D)[16] and Anxiety (HAM-A),[17] respectively. However, we did not find significant reduction on the Hopelessness Scale score (23%, p = .06, not significant).

The thought disorder factor of the Brief Psychiatric Rating Scale (BPRS)[18] was used to evaluate evolution of micropsychotic symptoms during the trial. Because of low baseline scores, the reduction in score did not reach statistical significance (19%, p = .1). Actually, 15 of 23 patients had a score of 4, which corresponds to "absence of symptom." The other 8 patients presented with clinically significant micropsychotic symptoms at baseline. This 8-patient subgroup showed a significant reduction of thought disorder BPRS score during the trial (baseline = 8.13, last rating = 4.63; nonparametric Wilcoxon test, p = .018).

Table 3. Changes in Outcome Measures Among Patients With Borderline Personality Disorder Treated With Quetiapine

| Measure | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 | Week 1 Versus Week 12 Mean Change, % ± SD | p Value for Change From Baseline[a] | p Value for Change in Time[b] |
|---|---|---|---|---|---|---|---|---|
| Hamilton Rating Scale for Depression score | 18.78 | 10.82 | 9.18 | 7.57 | 6.87 | 63 ± 18 | .0015 | .0001 |
| Hamilton Rating Scale for Anxiety score | 20.61 | 11.86 | 10.09 | 7.43 | 6.57 | 68 ± 25 | .0015 | .0001 |
| Hopelessness Scale score | 11.74 | – | – | – | 9.09 | 23 ± 178 | NS | .060 |
| Brief Psychiatric Rating Scale (thought disorder) score | 5.43 | 4.91 | 4.82 | 4.61 | 4.39 | 19 ± 28 | NS | .099 |
| Social Adjustment Scale total score | 2.67 | – | – | – | 1.48 | 45 ± 14 | .003 | .0002 |
| Barratt Impulsivity Scale total score | 67.48 | 60.41 | 60.14 | 53.91 | 54.13 | 20 ± 16 | .0015 | .0001 |
| Buss-Durkee Hostility Inventory total score | 44.22 | 40.91 | 38.68 | 35.09 | 36.83 | 17 ± 17 | .003 | .0002 |
| Global Assessment of Functioning score | 48.91 | – | – | – | 61.04 | 25 ± 9 | .0015 | .0001 |
| Temperament and Character Inventory score | | | | | | | | |
| Novelty seeking | 21.22 | – | – | – | 20.74 | 2 ± 84 | NS | .67 |
| Harm avoidance | 26.43 | – | – | – | 25.39 | 4 ± 56 | NS | .54 |
| Reward dependence | 14.65 | – | – | – | 15.91 | 9 ± 30 | NS | .055 |
| Persistence | 5.39 | – | – | – | 5.22 | 3 ± 71 | NS | .57 |
| Self-directed | 16.74 | – | – | – | 23.26 | 39 ± 82 | .015 | .001 |
| Cooperation | 25.52 | – | – | – | 30.83 | 21 ± 48 | .015 | .001 |
| Self-transcendence | 14.87 | – | – | – | 11.48 | 23 ± 45 | NS | .055 |

[a]Bonferroni adjusted.
[b]Repeated-measures analysis.
Abbreviation: NS = not significant. Symbol: – = no data available.

There was a reduction of hostility during quetiapine treatment as indicated by a decrease in Buss-Durkee Hostility Inventory[14] total score from baseline to last rating (p = .003).

Changes observed on the TCI suggest that all 3 character dimensions tend to normalize with treatment. There was an increase of self-directedness and cooperativeness scores (p = .015) and a trend toward a decrease of self-transcendence score (p = .055, before Bonferroni adjustment). Temperament dimensions did not significantly vary under quetiapine treatment.

Quetiapine also appears to have an impact on social adaptation since a significant reduction of Social Adjustment Scale[20] total score was observed during the trial (45%, p = .003). Interestingly, compared to normalized data,[21] our patients exhibited a normal level of social functioning at the last rating (t = 47).

In addition to improvement in symptomatology, substantial changes in global assessment of functioning were observed, with a 12-point increase in the mean GAF score (p = .0015).

## DISCUSSION

In a sample of patients with severe BPD without or with only few psychotic symptoms, a low dose of quetiapine (251 ± 50 mg, range, 175–400 mg) was associated with a positive clinical impact. In accordance with our primary hypothesis, quetiapine reduced impulsivity of patients with BPD as assessed by the BIS-10. The present results also support our secondary hypothesis that quetiapine improves affective and micropsychotic symptoms and social and global functioning. This first open-label study with quetiapine in patients with BPD corroborates data of previous open-label studies with other atypical antipsychotics showing improvement in symptomatology and global functioning.

Despite that atypical neuroleptics have been reserved as add-ons to anticonvulsants or SSRIs,[1] this study suggests that they can be used alone as first-line treatment in patients with BPD, even in those without severe psychotic symptoms. Quetiapine, which was selected specifically for its favorable side effect profile, induced very few and only mild side effects in the present study. This is a very important aspect in this population of patients who showed weak tolerance to frustration and annoyance. Before starting quetiapine, the most frequent warnings given by patients were about weight gain, insomnia, and anxiety. To alleviate sleep disturbance, which is a relatively frequent effect, we prescribed the main dose in the evening, using the sleepiness side effect as therapeutic benefit. For some of our patients, this positive effect on sleep was an important adherence factor. We did not note a statistical difference in weight of patients before and after quetiapine treatment, nor in their body mass index. It is also important to underscore that 22 of 23 patients who completed the study chose to continue quetiapine after the trial.

As hypothesized, impulsivity measures indicated that quetiapine reduces impulsiveness of patients with BPD. Behaviors linked to impulsivity, such as pathological gambling and substance abuse, were also attenuated during the trial. These results also concur with subjective reports of the effect of quetiapine by the patients. Many patients with BPD actually described the main drug impact as follows: quetiapine would allow them to inhibit their first impulsive reaction, to achieve more elaborate information processing that led to a more appropriate and less impulsive response.

It is interesting to observe that quetiapine reduced impulsivity by 20%, while it reduced anxiety and depression by more than 60%. Anxiety and depression were measured by the HAM-A and -D, respectively, and correspond with the pathologic symptoms, which are expected to disappear with treatment. On the other hand, impulsivity is a temperament trait. We would expect that, even with treatment, people with BPD will still have a high level of impulsivity. Nevertheless, any reduction of their impulsivity will produce a positive effect on cognitive processing, allowing patients to solve difficulties more easily or to better plan their life situations. Impulsivity becomes less dysfunctional, resulting in less problematic behaviors and consequences. Like many subjects without BPD, these patients who show improvement of their BPD would still exhibit high levels of impulsivity that could be qualified as functional impulsivity.[22]

Personality dimensions, as assessed by the TCI, take an interesting course under quetiapine treatment. There was no significant modification on temperament dimensions but a move toward normalization for all 3 character dimensions. According to Cloninger's personality model,[19] character dimensions discriminate individuals with and without a personality disorder.[23] Thus, quetiapine tends to attenuate the personality disorder of patients with BPD.

Although they are promising, our results should be considered only as preliminary. First, we used an open-label design that limited conclusions about treatment impact. Many placebo-controlled studies actually reported a positive placebo effect in patients with BPD.[24,25] Second, data need to be confirmed in a larger number of patients. Third, long-term studies are needed to assess persistence of quetiapine positive impact in this patient population.

This study provides interesting data, however, regarding elaboration of future randomized comparative studies using quetiapine in patients with BPD. This study first suggests a good risk-to-benefit ratio and also indicates that a quetiapine dose of 250 mg could be effective. Moreover, this study suggests that significant clinical improvement occurred after 2 weeks of treatment on clinician-rated scales and after 8 weeks of treatment on self-reported questionnaires. A treatment duration of at least 8 weeks is then necessary to demonstrate therapeutic benefits of quetiapine in patients with BPD.

## CONCLUSION

This was an open-label trial of quetiapine in patients with well-defined severe BPD. These patients, even though they had no or only few micropsychotic symptoms, exhibited statistical and clinical improvement with a low dose of quetiapine; their whole symptomatology was reduced, including impulsivity, which can constitute the key treatment symptom. This study must be considered as a preliminary one, because it (1) is the first published quetiapine trial with BPD, (2) includes a relatively small sample size, and (3) has an open-label design. Our results do not support APA guidelines, which recommend the use of atypical antipsychotics only as adjuvant to SSRIs or to mood stabilizers, especially when patients present with psychotic symptoms. Further research is needed, in particular, double-blind controlled studies comparing the effects of atypical neuroleptics and other well-studied and frequently prescribed medications against impulsivity in BPD. It also would be highly interesting to examine cognitive processes underlying impulsivity so that we can specify the biological path through which quetiapine acts to reduce impulsivity of patients with BPD.

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

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