

## Second-generation antipsychotic use in borderline personality disorder: What are we targeting?

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### Abstract

**Introduction:** Borderline personality disorder (BPD) is a personality disorder plagued with high rates of psychotropic polypharmacy. Estimates show that second-generation antipsychotics (SGAs) are used in most of these patients; however, they are being prescribed off label.

**Methods:** A literature review was conducted via PubMed in search for studies evaluating SGA use in BPD.

**Results:** There are available data investigating 8 of 11 SGAs and their use in BPD. Of N = 269 potential articles, N = 34 evaluating the use of SGAs in BPD were included.

**Discussion:** Strong evidence supporting SGAs in BPD is lacking. Potential target symptoms in which a SGA may be useful include depression, anxiety, anger, impulsivity, and paranoia/dissociative behavior.

**Keywords:** second-generation antipsychotics, borderline personality disorder, off-label uses

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### Introduction

Borderline personality disorder (BPD) is characterized by affective instability, instable interpersonal relationships, and self-image, as well as marked impulsivity.<sup>1</sup> Frequently, there is much difficulty encountered in treating patients with a diagnosis of BPD because there are currently no medications indicated for its treatment, causing clinicians to use medications off label.<sup>2</sup> Furthermore, patients with BPD may present with a variety of symptoms, including impulsivity, suicidal behavior, affective instability, and intense anger, making each treatment regimen patient specific.

Treatment guidelines are consistent in supporting and recommending dialectical behavior therapy as first-line

treatment of BPD.<sup>3-6</sup> Guidelines differ, however, on recommendations pertaining to pharmacotherapy. Specific to second-generation antipsychotic (SGA) use, the 2001 American Psychiatric Association guidelines, the oldest of available guidelines, recommend a low-dose antipsychotic for management of cognitive-perceptual symptoms.<sup>3</sup> The 2007 World Federation of Societies of Biological Psychiatry guidelines state that moderate evidence is available supporting the use of SGAs for treatment of cognitive-perceptual symptoms, and impulse behavior control.<sup>4</sup> The 2012 National Health and Medical Research Council guidelines, which are the most recent guidelines, argue that there is a lack of sufficient reliable evidence to formulate an evidence-based recommendation to support the use of a particular agent to target specific outcomes.<sup>5</sup> The 2009 National Institute for Clinical Excellence guidelines recommend against any medications used specifically for BPD, in an attempt to decrease possible polypharmacy.<sup>6</sup> Therefore, it can be inferred from guideline variations that a level of uncertainty exists within this treatment realm.

Many individuals with BPD will receive pharmacologic treatments. In fact, nearly 90% of BPD patients are

medicated with psychotropic drugs.<sup>7-9</sup> A major concern is that despite this high medication use, there is currently no single medication available with a labeled indication for treatment of BPD, nor is there any medication that will achieve remission of BPD symptoms.<sup>10</sup> Additional psychotropics tend to be added to existing regimens in efforts to augment existing regimens, perpetuating psychotropic polypharmacy in this patient population.<sup>2,10</sup> Studies have shown rates of 40% to 57% of BPD patients taking 3 or more standing psychotropic medications, illustrating that psychotropic polypharmacy is a serious issue in this population.<sup>7-9</sup> However, psychotropic polypharmacy is not supported by evidence and should be avoided whenever possible.<sup>11</sup>

A clear understanding for the rationale of antipsychotics may help reduce unguided psychotropic polypharmacy. The objective of this review article is to clarify which antipsychotics have the most evidence in treatment of BPD, and for which specific symptoms.

## Methods

Clinical studies and trials were located using PubMed with the following search terms: *borderline personality disorder AND antipsychotic*. A search was also conducted for each SGA. Initially, there were N=269 potential articles identified for possible inclusion in this review. All original studies written in English, evaluating the use of SGAs in BPD patients were included.

## Results

A total of 34 studies were included in this review. Data were found evaluating the use of 8 different SGAs: clozapine (n=6), olanzapine (n=9), quetiapine (n=9), risperidone (n=3), aripiprazole (n=3), ziprasidone (n=2), paliperidone (n=1), and asenapine (n=1). Presentation of the findings of each antipsychotic is in the Table, as well as summarized below.

### Clozapine

To date there are no large-scale studies on the effect of clozapine on the symptoms of BPD.<sup>12</sup> Existing data comprise case reports, retrospective chart reviews, and open-label trials using mean doses of 43 to 421 mg. Available evidence suggests that clozapine may be beneficial on an individual basis for the management of self-injurious behavior and aggression to others in BPD.<sup>13-15</sup> Further improvements noted are total scores of Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scale, as well as decreased hospitalization lengths of stay.<sup>13-18</sup> The most pronounced changes appear to occur within the first 6 months of clozapine

treatment. With the lack of high-quality evidence, it is difficult to formulate a strong recommendation advocating for the use of clozapine.

### Olanzapine

There have been several double-blind, placebo-controlled studies conducted that assess olanzapine's efficacy in the treatment of BPD symptoms.<sup>19-24</sup> Available studies have evaluated mean dosages of 4.46 to 8.83 mg/d. The most frequently improved target symptoms were depression and anger/hostility/aggressiveness.<sup>12,21,23-27</sup> Furthermore, there may be evidence to suggest that olanzapine may alleviate anxiety and paranoia/psychoticism.<sup>21,23,25,26</sup> The largest available studies evaluated individual symptom relief via the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD), an 8-item screening tool comprising yes/no evaluations of core BPD symptoms.

In a double-blind, placebo-controlled study (N=314), participants were given olanzapine (mean dosage, 7.09 mg/d) or placebo and were evaluated on a biweekly basis for 12 weeks.<sup>19</sup> The study found a significant decrease in mean ZAN-BPD scores in both groups, but no significant difference between olanzapine and placebo.<sup>19,28</sup> In a separate double blind, placebo-controlled study (N=451), moderate dosages of olanzapine (5-10 mg/d), but not low dosages, were superior to placebo in reducing mean ZAN-BPD scores. Both dosages of olanzapine demonstrated a significant reduction in intense anger, affective instability, suicidal and self-mutilating behavior, and paranoia/dissociation on the ZAN-BPD.<sup>20</sup> This discrepancy in trial results raises doubts regarding olanzapine's efficacy in managing BPD patients.

### Quetiapine

A cross-sectional study from the European Drug Safety Arzneimittelsicherheit in der Psychiatrie analyzed prescriptions of 2195 inpatients with BPD and revealed that quetiapine was the single most prescribed psychotropic—up to 22% of BPD patients.<sup>7</sup> In the only available double-blind, placebo-controlled study (N=95), participants who were taking 150 mg or 300 mg of quetiapine ER showed measurable improvement in BPD symptoms using the ZAN-BPD, with less adverse effects reported in the 150 mg/d group.<sup>29</sup> Open-label studies have also evaluated quetiapine at mean dosages of 251 to 540 mg/d. Quetiapine appeared to have a significant improvement on aggression/hostility, anxiety, and depression.<sup>29-35</sup> Further open-label studies have also demonstrated general symptom improvements as measured by various rating scales, including ZAN-BPD, CGI, BPRS, the Social and Occupational Functioning Assessment Scale, the Borderline Personality Disorder Severity Index (BPDSI), and the Symptom Checklist (SCL-90-R).<sup>29,30,32,34,36,37</sup>

**TABLE:** Summary of second-generation antipsychotics (SGAs) in borderline personality disorder (BPD) studies

Study, y	Design; Duration, wk	Sample Size	Dosage of SGA, mg/d, Mean (Range)	Evaluated Outcomes
<b>Clozapine</b>				
Frogley et al, <sup>13</sup> 2013 <sup>a</sup>	Case series; 18	22	N/A (N/A)	General symptom severity, count of aggressive incidents, self-directed aggression, days spent in enhanced observation, decreased use of additional as-needed antipsychotic and anxiolytic medication
Ferreri et al, <sup>14</sup> 2004 <sup>a</sup>	Case report; 4	1	300 (N/A)	Anxiety, self-mutilation, duration of hospitalization
Chengappa et al, <sup>15</sup> 1999	Retrospective chart review; maximum of 52	7	421 (300-550)	Incidence of seclusion/restraint interventions, global functioning, decreased use of additional as-needed anxiolytic medication, aggression to others, duration of hospitalization
Parker, <sup>16</sup> 2002 <sup>a</sup>	Retrospective; varied	8	334 (175-550)	Duration of hospitalization
Frankenburg and Zanarini, <sup>17</sup> 1993	OLS; 8-36	15	253.3 (75-550)	General BPRS mean score, nonspecific symptom severity as measured by CGI
Benedetti et al, <sup>18</sup> 1998	OLS; 16	12	43.8 (25-100)	General BPRS score, psychoticlike symptoms, depression, increase in global functioning
<b>Olanzapine</b>				
Schulz et al, <sup>19</sup> 2008	DBPC; 12	314	7.09 (2.5-20)	General symptom severity as measured by ZAN-BPD
Zanarini et al, <sup>20</sup> 2011	DBPC; 12	451	N/A (2.5-10)	Intense anger, paranoia or dissociation, suicidal ideation, self-injurious behavior, affective instability
Zanarini and Frankenburg, <sup>21</sup> 2001	DBPC; 31	28	5.33 (N/A)	Anxiety, anger, paranoia, interpersonal sensitivity
Bogenschutz and Nurnberg, <sup>22</sup> 2004	DBPC; 12	40	6.9 (2.5-20)	Depression, general symptom severity as measured by CGI-BPD
Soler et al, <sup>23</sup> 2005	DBPC; 12	60	8.83 (5-20)	Anxiety, depression, impulsivity/aggressive behavior
Linehan et al, <sup>24</sup> 2008	DBPC; 31	24	4.46 (2.5-15)	Irritability, aggression, depression, self-injury
Schulz et al, <sup>25</sup> 1999	OLS; 8	11	7.73 (2.5-10)	Psychoticism, depression, interpersonal sensitivity, anger
Shoja-Shafti, <sup>26</sup> 2006	OLS; 8	20	4.86 (2.5-10)	Tension, anxiety, hostility, suspiciousness, excitement, depressive mood, increase in global functioning
Zanarini et al, <sup>27</sup> 2012	OLS; 12	444	6.01 (2.5-15)	General symptom severity as measured by ZAN-BPD
<b>Quetiapine</b>				
Black et al, <sup>29</sup> 2014	DBPC; 8	95	150 mg 300 mg	Affective disturbances, cognitive disturbances, disturbed relationships, aggression, general symptom severity as measured by Zanarini scale, SCL-90, and Sheehan Disability scale
Altamura et al, <sup>30</sup> 2012	Observational; 12	41	350.21 (50-800)	Anxiety, general symptom severity as measured by BPRS
Villeneuve and Lemelin, <sup>31</sup> 2005	OLS; 12	34	251 (175-400)	Anxiety, depression, hostility, impulsivity, social and global functioning
Bellino et al, <sup>32</sup> 2006	OLS; 12	14	309.09 (200-400)	Anxiety, impulsivity, anger, general symptom severity as measured by CGI, BPRS, SOFAS, and BPDSI

**TABLE:** Summary of second-generation antipsychotics (SGAs) in borderline personality disorder (BPD) studies (continued)

Study, y	Design; Duration, wk	Sample Size	Dosage of SGA, mg/d, Mean (Range)	Evaluated Outcomes
Roepke et al, <sup>33</sup> 2008	OLS; 8	15	400 (400)	Depression
Perrella et al, <sup>34</sup> 2007	OLS; 12	29	540 (400-800)	Depression, hostility, suspiciousness, aggression, global functioning, general symptom severity as measured by CGI
Van den Eynde et al, <sup>35</sup> 2008	OLS; 12	41	Flexible (100-800)	Impulsivity, hostility, affective lability, depression, anxiety, anger
Romine et al, <sup>36</sup> 2008	OLS; 8	16	286.1 (25-300)	Global functioning, general symptom severity as measured by SCL-90, impulsivity
Van den Eynde et al, <sup>37</sup> 2009	OLS; 12	41	412.5 (100-800)	Executive functioning in neurocognitive tasks
<b>Risperidone</b>				
Friedel et al, <sup>38</sup> 2008	OLS; 8	18	1.8 (0.25-2)	Anxiety, depression, hostility, impulsivity, cognitive-perceptual impairment
Carrasco et al, <sup>39</sup> 2012	OLS; 24	49	N/A (37.5-50 intramuscularly/ 2 wk)	Aggression, anxiety, global functioning
Rocca et al, <sup>40</sup> 2002	OLS; 8	15	3.27 (1-4)	Aggression, depression, global functioning, general symptom severity as measured by BPRS
<b>Aripiprazole</b>				
Nickel et al, <sup>41</sup> 2006	DBPC; 8	52	15 (N/A)	Anxiety, depression, obsessive-compulsive, insecurity in social contacts, aggressiveness/hostility, paranoia, psychoticism
Nickel et al, <sup>42</sup> 2007	OLS; 72	26	15 (N/A)	Anxiety, depression, hostility, psychoticism, obsessive-compulsive, somatization, interpersonal sensitivity, paranoia
Bellino et al, <sup>43</sup> 2008	OLS; 12	21	13.1 (10-15)	Impulsivity, dissociation, paranoia, general symptom severity as measured by CGI-Severity and BPRS
<b>Ziprasidone</b>				
Pascual et al, <sup>45</sup> 2008	DBPC; 12	60	84.1 (40-200)	No statistically significant improvements
Pascual et al, <sup>44</sup> 2004	OLS; 2	12	102.7 (40-160)	Anxiety, depression, general symptom severity as measured by CGI-Severity and BPRS
<b>Asenapine</b>				
Martín-Blanco et al, <sup>46</sup> 2014	OLS; 8	12	9.2 (5-20)	Impulsivity, affect instability, general symptom severity as measured by CGI-BPD and BPRS
<b>Paliperidone</b>				
Bellino et al, <sup>47</sup> 2011	OLS; 12	18	4.8 (3-6)	Impulsivity, outbursts of anger, dissociative symptoms, general symptom severity as measured by CGI, SOFA, BPDSI, and BPRS

BPDSI = Borderline Personality Disorder Severity Index; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; DBPC = double-blind, placebo-controlled study; N/A = not applicable; OLS = open-label study; SCL-90-R = Symptom Checklist-90 Revised; SOFAS = social and occupational functioning assessment scale; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

<sup>a</sup>Study presented outcomes but made no mention of statistical significance. All other outcomes presented in the above table achieved statistical significance in their respective studies.

Conflicting reports exist on how effective quetiapine is at controlling impulsive symptoms of BPD. Four open-label studies have demonstrated marked improvement in impulsivity.<sup>31,32,35,36</sup> However, an additional open-label study and double-blind, placebo-controlled study were unable to show a significant improvement in impulsivity compared with placebo.<sup>29,33</sup> The data available for quetiapine only present small-scale studies, with fewer than 50 patients, with the exception of one randomized, placebo-controlled trial. Once again, the scarcity of large trials makes it difficult to extrapolate results from this limited evidence.

## Risperidone

Current data have suggested that many symptoms of BPD may be ameliorated with risperidone.<sup>38-40</sup> In an open-label study (N = 15), risperidone (final mean dosage, 3.27 mg/d) had a statistically significant 21% decrease in BPRS scores from baseline after 8 weeks. A statistically significant decrease in the areas of hostility and suspicion (30% change from baseline), depression, and anergia (18% and 15% change from baseline, respectively) was also observed.<sup>40</sup> Similar results have been demonstrated, indicating potential for risperidone in controlling symptoms of aggression and anxiety.<sup>38,39</sup> These results are drawn from open-label studies because there are no randomized, placebo-controlled studies available. Furthermore, studied sample sizes were small, making it difficult to apply observed trends.

## Aripiprazole

A double-blind, placebo-controlled study (N = 52), found that 15 mg/d during an 8-week period significantly improved BPD symptoms as measured by the SCL-90-R, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, and State-Trait Anger Expression Inventory. Symptoms of obsessive-compulsive traits, depression, anxiety, aggression/hostility, social insecurity, paranoid thinking, and psychoticism showed particular improvement.<sup>41</sup> Two follow-up studies demonstrated that improvements remained consistent across all scales in the aripiprazole group versus the placebo group, as well as augmentation therapy to sertraline.<sup>42,43</sup> Aripiprazole may be a viable option, given the favorable results of these initial smaller studies.

## Ziprasidone

Early studies yielded preliminary data potentially indicating that ziprasidone may have a role in the treatment of BPD symptoms.<sup>44</sup> Unfortunately, initial promising results could not be replicated in a double-blind, placebo-controlled study (N = 60) evaluating a mean dosage of

84.1 mg/d, which raised doubts regarding the utility of ziprasidone.<sup>45</sup>

## Asenapine

An open-label study (N = 12) found that there was a significant improvement in CGI-BPD and BPRS scores in participants treated with asenapine (mean dosage, 9.2 mg/d) during 8 weeks.<sup>46</sup> The study also found that symptoms of impulsivity, affect instability, and emptiness had significant improvement, whereas depressive symptoms did not. It is important to note that at the time of study, only 1 patient received asenapine as monotherapy. A total of 11 patients received asenapine as augmentation therapy to preexisting psychotropic regimens, making it difficult to attribute clinical improvement specifically to asenapine.

## Paliperidone

To date, paliperidone has not been comprehensively evaluated as a treatment for BPD. In a pilot study (N = 18), paliperidone ER (mean dosage, 4.8 mg/d) was administered during a 12-week period, statistically significant improvements were found in the mean scores for impulsivity, anger, and dissociative symptoms, as well as overall improvement of symptoms measured by CGI-Severity, BPRS, Barratt Impulsiveness Scale, and BPDSI scales.<sup>47</sup>

## Discussion

Of 11 SGAs available in the United States, 8 have been investigated in some capacity in the BPD population. The scant supportive evidence available raises concerns of SGA clinical utility. Inconsistencies in the available studies included variations in rating scales used to evaluate symptom response, as well as variations in participants' non-SGA medication regimens. The lack of sufficient high-quality evidence made it difficult to soundly recommend an SGA for management of BPD, although available evidence suggested that SGAs might have a role. Key possible target symptoms identified included depression, anxiety, anger/aggression, impulsivity, and paranoia. Another limitation, however, is that SGAs failed to consistently improve these identified symptoms. Olanzapine is the most well-studied SGA in the BPD population, but efficacy data still remain questionable.

Patients with BPD are at increased risk of psychotropic polypharmacy and are less likely to have their medication profiles reviewed within the last year, particularly regarding tolerability.<sup>48</sup> This is concerning given the high likelihood that BPD patients may be placed on an SGA, and the potential adverse effects, such as metabolic and



extrapyramidal side effects, that may occur. Caution should be advised in recommending the addition of an SGA for the treatment of BPD because there is a lack of strong supportive evidence.

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