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Efficacy and tolerability of asenapine compared with olanzapine in borderline personality disorder: an open label randomized controlled trial

Running title: Asenapine compared with olanzapine in borderline personality disorder

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Abstract

Background

Asenapine is a new second generation antipsychotic, that is understudied in borderline personality disorder (BPD). Only one study investigating the use of the drug in this indication (an open-label pilot study) has been conducted to date.

Objective

The present open label randomised controlled trial aimed to evaluate the efficacy and tolerability of asenapine in comparison with olanzapine, the most broadly studied antispychotic in BPD.

Methods

51 outpatients aged between 18 and 50 years, with a diagnosis of BPD based on DSM-5 criteria were assigned for 12 weeks to: (1) asenapine (5-10 mg/day) or (2) olanzapine (5-10 mg/day). Participants were assessed at baseline and after 12 weeks with: Clinical Global Impression Scale, Severity item (CGI-S), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Social Occupational Functioning Assessment Scale (SOFAS), Borderline Personality Disorder Severity Index (BPDSI), Barratt Impulsiveness Scale, version 11 (BIS-11), Modified Overt Aggression Scale (MOAS), Self Harm Inventory (SHI), and Dosage Record and Treatment Emergent Symptom Scale (DOTES).

Analysis of variance repeated measures was performed. Intention to treat analysis with last observation carried forward was conducted.

Results

Drop-outs were 11 (21.57%): six patients taking asenapine and five patients receiving olanzapine. Two patients who received asenapine stopped the drug, one due to oral hypoesthesia and the other due to moderate anxiety. Two patients receiving olanzapine discontinued the treatment for a significant weight gain ($\geq$ 3 Kg). The remaining seven drop-outs resulted from the lack of compliance with the trial prescription. Forty out of the 51 patients (78%) completed the trial: 19

patients received asenapine, while 21 patients received olanzapine.We found a significant within-subjects effect (trial duration) for all rating scales, except from the HAM-D, the MOAS, and two items of the BPDSI: namely, “identity disturbance” and “parasuicidal behaviors”. A significant effect between subjects was found for the two items of the BPDSI: “affective instability” and “dissociation/paranoid ideation”. Asenapine was found superior to olanzapine in reducing the affective instability score (P = 0.001), whereas olanzapine was found superior to asenapine in reducing dissociation/paranoid ideation (P = 0.012). However, the study was found to be underpowered to detect a difference between the drugs on the dissociation/paranoid ideation item of the BPDSI. Two patients receiving asenapine experienced akathisia and another two restlessness/anxiety, while three patients receiving olanzapine reported somnolence and two fatigue.

Conclusions

Asenapine and olanzapine were demonstrated to have a similar efficacy. While asenapine was found to be more efficacious than olanzapine in treating affective instability, olanzapine was superior to asenapine in treating paranoid ideation and dissociation. However, the study was underpowered to detect a difference between groups on the dissociation/paranoid ideation item. Both medications were well tolerated, with asenapine being related to a higher frequency of oral hypoaestesia and akathisia, and olanzapine being prone to induce weight gain.

The open label study design, lack of a placebo group, and small sample size constituted major limitations of this trial. Our findings require to be replicated in further studies.

The trial was registered in the Australian New Zealand Clinical Trials Registry (code: ACTRN12614000551695).

Key points: The new antipsychotic asenapine had the same global efficacy as olanzapine in treating borderline personality disorder. It had better results on affective instability, while olanzapine was more effective on cognitive-perceptual symptoms. However, the study was found

to be underpowered to detect a difference between the drugs on the dissociation/paranoid ideation item.

Adverse effects were mild but different between drugs, with oral dysesthesia more common with asenapine and weight gain more common with olanzapine.

These results are useful to guide clinicians'choice of treatment for BPD.

1. Introduction

Treatment of borderline personality disorder (BPD) is very complex, mainly due to the heterogeneity of clinical manifestations and poor adherence of patients to therapeutic interventions. Although many drugs were investigated across studies generating promising findings, firm conclusions regarding efficacy cannot be drawn due to methodological limitations. Furthermore, clinicians are often faced with an even more challenging situation, as recommendations provided in treatment guidelines are somewhat discordant. In particular, the UK National Institute for Health and Clinical Excellence [1] guidelines suggested psychotherapeutic interventions as the treatment of choice for BPD, thereby confining the pharmacological tools to a secondary role. On the other hand, the American Psychiatric Association [2,3] put forward a treatment approach that is based on a symptom-oriented pharmacotherapy.

In the last years, results of meta-analyses [4] and findings of systematic reviews [5,6] have induced a noticeable shift of experts' opinions and clinical practice from the use of antidepressants to mood-stabilizers, omega-3 fatty acids, and second generation antipsychotics in the treatment of BPD. Therapeutic effects of antipsychotic drugs were demonstrated across a wide range of symptoms. Whilst their action is primarily directed at alleviating cognitive-perceptual symptoms such as transient paranoid ideation or dissociative symptoms, these agents were further reported to induce significant improvements across other psychopathological domains including mood instability, anxiety, impulsiveness, and aggression [7-9].

Among novel antipsychotics olanzapine is the most extensively studied across case-reports [10], open-label studies [11,12] and double-blind controlled trials (RCT) of patients with a diagnosis of BPD [13-21]. Antipsychotic drugs may owe their therapeutic efficacy to actions at D2-D4 and 5HT-2A receptors, while adverse effects are believed to be induced by antagonist activity at H1, M1-M5, and α1 receptors [22].

To date, ten RCTs have been conducted in samples with BPD to assess the efficacy of olanzapine versus placebo [13,16,23,19,21], versus active drugs [14,17,20], or versus placebo in a combined treatment with psychotherapy (dialectical behavioral therapy) [15,18]. The majority of accumulated evidence suggests that olanzapine is efficacious in treating cognitive-perceptual symptoms (psychotic-like symptoms), and in producing significant reduction in mood instability and impulsive behavioral dyscontrol.

Asenapine is the most recent compound approved for the acute treatment of schizophrenia and mania associated to bipolar disorder. This drug is available as a sublingual tablet formulation and acts as an antagonist at serotonin, dopamine, histamine and α-2 adrenergic receptors, with almost no binding affinity for muscarinic receptors [24]. A considerable number of randomized controlled trials were performed to test the efficacy of asenapine in comparison with placebo [25-27] or active drugs [28,29] in schizophrenia. Other studies evaluated the efficacy and tolerability of this drug in treating manic or mixed episodes of bipolar disorder, either in monotherapy or in adjunction to lithium or valproate [30-32]. Only one open-label study tested the efficacy of asenapine in 12 borderline personality disorder [33], and found that after 8 weeks of treatment with asenapine (5-20 mg/day) it was efficacious, not only against BPD general symptomatology, but more specifically affective instability, impulsivity, and cognitive symptoms.

With regard to tolerability, novel antipsychotics present a more favorable tolerability profile over traditional neuroleptics. Indeed, the former are associated with fewer and milder extrapyramidal adverse effects, a lower risk for developing tardive dyskinesia, as well as the possibility of enhancing cognitive functions [34].

Nevertheless, several adverse effects have been recorded for both olanzapine and asenapine, with some differences between the two drugs. In particular, the most frequent side effects that may be caused by olanzapine are somnolence, fatigue, hyperprolactinaemia, increase in metabolic parameters (glucose, triglycerides, cholesterol) and a significant weight gain [35,18]. Although asenapine may also cause somnolence, glucose increase, and weight gain, recent systematic reviews of data from asenapine placebo- or olanzapine-controlled clinical trials showed that asenapine was less likely than olanzapine to induce weight gain and change the levels of glucose, triglycerides, and cholesterol [36-38,29]. Among adverse effects most frequently related to asenapine are anxiety, several extra-pyramidal symptoms, in particular akathisia, and dysgeusia/oral hypoesthesia [36].

The present randomized controlled trial set out to compare the efficacy and tolerability of asenapine and olanzapine in the treatment of BPD patients, in order to elucidate the relevant efficacy and tolerability profile of asenapine across specific symptom clusters.

2. Methods

A sample of 51 consecutive outpatients, aged between 18 and 50 years, with a diagnosis of BPD based on DSM-5 criteria [39] were recruited in the study between June 2014 and February 2016. Patients attended the Centre for Personality Disorders of the Psychiatric Clinic, Department of Neuroscience, University of Turin, Italy. The psychiatric diagnosis was made by an expert clinician and confirmed with the Structured Clinical Interview for DSM-IV Axis I and II Disorders [40,41]. Exclusion criteria were: (1) a diagnosis of dementia or other cognitive disorders, schizophrenia or other psychotic disorders, or bipolar disorders, (2) a co-occurring major depressive episode and/or substance abuse, (3) and the administration of psychotropic medications and/or psychotherapy in the two months preceding the beginning of the study. Female patients who did not use an adequate birth control method were also excluded. Each patient participated voluntarily in the study after providing written informed consent. The study

was conducted in compliance with the Declaration of Helsinki guidelines. Approval was obtained from the ethics committee of the University Hospital "Città della Salute e della Scienza – Ospedale dell'Ordine Mauriziano" of Turin. The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR), and allocated the following code: ACTRN12614000551695.

Patients were randomly assigned to two arms of treatment for 12 weeks: (1) asenapine (dose range: 5-10 mg/day); (2) olanzapine (dose range: 5-10 mg/day). Research Randomizer (Urbaniak and Plous, Social Psychology Network Wesleyan University, Middletown, CT), a free web-based service for randomization, was used. All drugs were titrated (for the first five days at the dose of 5 mg/day and after at the dose of 10 mg/day, if the drug was well tolerated). We administered low doses of both drugs as suggested by the American Psychiatric Association guidelines (3). Concerning previous investigations, the only study of asenapine in BPD patients (33) used a broad dose range of 5-20 mg/day. As for olanzapine, several studies (12, 13, 17, 21) chose the same dose range of 5-10 mg/day used in our study.

Patients were assessed at baseline and after 12 weeks with the following assessment instruments:

1) the Clinical Global Impression Scale, Severity item (CGI-S) [42],
2) the Hamilton Depression Rating Scale (HAM-D) [43],
3) the Hamilton Anxiety Rating Scale (HAM-A) [44],
4) the Social Occupational Functioning Assessment Scale (SOFAS) [45],
5) the Borderline Personality Disorder Severity Index (BPDSI) [46],
6) the Barratt Impulsiveness Scale, version 11 (BIS-11) [47],
7) the Modified Overt Aggression Scale (MOAS) [48],
8) the Self Harm Inventory (SHI) [49].

Adverse effects of the two drugs were assessed with the Dosage Record and Treatment Emergent Symptom Scale (DOTES) [50].

The CGI is a clinician-rated instrument to make global assessment of illness and it consists of

three different measures: severity of illness, global improvement, and efficacy index. In this study severity of illness was considered and measured with the seven-point scale ranging from 1 (normal) to 7 (extremely ill).

The HAM-D is a clinician-rated scale that scores severity of 21 depressive symptoms in the last week. Items are variably scored 0-2, 0-3, or 0-4, with a total score ranging from 0 to 64. The HAM-A is a clinician-rated scale scoring severity of 14 symptoms of anxiety in the last week. Item are all scored 0-4, with a total score ranging from 0 to 56.

The SOFAS is a clinician-rated scale developed to measure a patient's impairment in social and occupational domains. It is independent of the severity of patients' symptoms. The scores range between 0 to 100 with higher scores indicative of a better functioning.

The BPDSI is a semi-structured clinical interview assessing frequency and severity of BPD related symptoms. The interview consists of eight items scored on 10-point frequency scales (0=never; 10=daily), including 'abandonment', 'interpersonal relationships', 'impulsivity', 'parasuicidal behavior', 'affective instability', 'emptiness', 'outbursts of anger', 'dissociation and paranoid ideation', and of one item scored on a 4-point severity scale, concerning 'identity'.

The BIS-11 is a 30-item self-report questionnaire used to measure the trait of impulsivity on a 4-point Likert scale. Higher scores for each item indicate higher levels of impulsivity. Twelve items are reverse-scored, in order to avoid response sets.

The MOAS is a clinician-rated scale consisting of four subscales for different types of aggression (verbal aggression, aggression against objects, aggression against others, and self-aggression). The subscales are rated on a 5-point scale (score 0-4) [48].

The SHI is a brief, self-report instrument which provides data on clinically relevant self-harm behaviors. The scoring of the instrument is easily determined by counting the number of endorsed self-harm behaviors.

The DOTES is a rating scale to measure the presence and intensity of side effects induced by psychotropic medications. It consists of a broad range of 41 parameters including items on

posture and movement, alertness, and cardiovascular, oral, nasal, bowel, and dermatological problems.

Assessment was performed by an investigator (P.B.) who had received a training session on psychometric instruments prior to the study.

Statistical analysis were performed both in the group of patients who completed the trial and in the whole group of patients who were randomized including drop-outs. In the second group, intention to treat (ITT) analysis was performed with the last observation carried forward (LOCF). Baseline mean scores of rating scales were compared between the two treatment groups with one-way analysis of variance (ANOVA). Comparison of score change at the end of the trial between the two groups was calculated for each rating scale with the analysis of variance (ANOVA) repeated measures. Bonferroni correction was applied to correct for multiple comparisons. Effect size was calculated as eta square.

Software system SPSS 22.0 (IBM Corporation, 2013) was used for calculations. P values were considered significant at ≤ 0.05.

3. Results

Fifty-one patients were randomly assigned to (1) asenapine (N=25) or to (2) olanzapine (N=26). Forty out of the 51 patients (78%) completed 12 weeks of the trial: 19 patients (47.5% of the completers) received asenapine, while 21 patients (52.5%) received olanzapine. Eleven patients (21.57%) discontinued the treatment at the fourth week: six taking asenapine and five receiving olanzapine. The final sample resulted in 40 patients with the mean age of 24.7 ± 5.3 years; they were 15 males (37.5%) and 25 females (62.5%).

Results of the ANOVA calculated for baseline mean scores of rating scales are reported in Table 1 and Table 2. No significant differences between groups were found at baseline between the two treatment arms.

The ITT-LOCF analysis was performed on the entire sample of 51 patients recruited. Results of

the ANOVA repeated measures of the effects of trial duration (within-subjects effect) and treatment modality (between-subjects effect) on the score changes after 12 weeks are reported in Table 3, Table 5, and Table 7.

We found a significant within- subjects effect (trial duration) for all rating scales (P ranged from 0.001 to 0.012; η^2 ranged from 0.53 to 0.25), except from the HAM-D (P = 0.862; η^2 = 0.01), the MOAS (P = 0.119; η^2 = 0.1); and two items of the BPDSI: namely, "identity disturbance" (P = 0.541; η^2 = 0.02) and "parasuicidal behaviors" (P = 0.092; η^2 = 0.14). Furthermore, a significant effect between subjects (treatment modality) was found for two items of the BPDSI: "affective instability" (P = 0.001, η^2 = 0.53), and "dissociation/paranoid ideation" (P = 0.021; η^2 = 0.21). In particular, asenapine was found superior to olanzapine in reducing the affective instability score, whereas olanzapine was found superior to asenapine in reducing dissociation/paranoid ideation.

We performed a post-hoc power calculation using the software tool ClinCalc.com (ClinCalc LLC, 2017). As the main objective of our study was to detect the differences between the drugs concerning specific symptom clusters, we applied the post-hoc power calculation to the two BPDSI items with a significant difference between groups: "affective instability" and "dissociation/paranoid ideation". We obtained a power of 100% for "affective instability", but only of 39% for "dissociation/paranoid ideation". These results demonstrated that the study was underpowered to detect a difference between the drugs on the "dissociation/paranoid ideation" item of the BPDSI.

Results of the analysis performed on the sample of 40 completers are reported in Table 4, Table 6, and Table 8. The significant effects found in the group of completers were not different from those found in the entire sample of 51 patients recruited. In particular, a significant effect within subjects (trial duration) was confirmed for all rating scales (P ranged from 0.001 to 0.013; η^2 ranged from 0.53 to 0.24) except from the HAM-D (P = 0.775; η^2 = 0.01), the MOAS (P = 0.119; η^2 = 0.1), and the two items of BPDSI: "identity disturbance" (P = 0.437; η^2 = 0.02) and "parasuicidal behaviors" (P = 0.086; η^2 = 0.14). The significant effect between subjects

(treatment modality) was confirmed for two items of BPDSI: "affective instability" (P = 0.001; η^2 = 0.53), and "dissociation/paranoid ideation" (P = 0.012; η^2 = 0.25).

Out of the eleven subjects who discontinued treatment, five (three taking asenapine and two taking olanzapine) dropped-out due to adverse effects. Specifically, two patients who received asenapine stopped the drug, one due to oral hypoesthesia and the other due to moderate anxiety. Two patients receiving olanzapine discontinued the treatment after experiencing a significant weight gain (≥ 3 Kg). The remaining seven drop-outs resulted from the lack of compliance with the trial prescription. The overall side effects reported in the two arms of treatments were mild to moderate. In the asenapine treatment arm two patients experienced akathisia and other two restlessness/anxiety, while in the olanzapine group somnolence was observed in three patients and fatigue in two.

4. Discussion

The present randomized controlled study tested the efficacy and tolerability of asenapine in comparison with olanzapine in patients affected by BPD. The aim was to investigate whether the two drugs had different effects on specific symptom clusters and profiles of tolerability. As no prior efficacy trials of asenapine versus olanzapine in BPD are available in the literature, our findings are interpreted in the light of results from head to head comparisons of these two drugs in schizophrenia and in bipolar disorder, as well as studies testing the efficacy of asenapine and olanzapine separately in BPD samples.

In our trial we found that the overall efficacy of asenapine was not different from olanzapine regarding global symptoms assessed with the CGI-S score, anxiety measured with the HAM-A score, and social and occupational functioning assessed with the SOFAS score. Our finding of no difference in the efficacy of asenapine and olanzapine in improving global symptomatology is consistent with reports of meta-analysis [51] of data collected from patients with schizophrenia,

and with results from clinical trials [30] of patients affected by bipolar disorder. More specifically, Szegedi and colleagues [51] concluded that in acute schizophrenia the reduction of global symptomatology, as measured with the Positive and Negative Symptoms Scale (PANSS), did not reach a statistically significant difference between treatments with asenapine and olanzapine. Moreover, a double-blind trial of patients with bipolar disorder showed non-inferiority of asenapine relative to olanzapine in extended treatment of bipolar patients during a manic episode [30].

Furthermore, we observed that, neither asenapine nor olanzapine led to significant decrease of depressive symptoms in our sample. This result is substantially in accordance with preliminary evidence provided by Buchanan and colleagues [28], who found only a minimal effect of both asenapine and olanzapine on depressive symptoms in schizophrenic patients. In addition, this lack of positive effect of asenapine on depressive symptoms in BPD has already been demonstrated in an open-label study published by Martin-Blanco and colleagues [33]. These trends are inconsistent with results of other two clinical trials of subjects with bipolar disorder [52], where asenapine was found superior to olanzapine in improving depressive symptoms during manic or mixed episodes. A possible reason for this inconsistency may be that, whilst in our sample HAM-D scores at baseline were rather low (with a mean lower than 13) as patients with concomitant major depression had been excluded, in the other two studies of bipolar disorder patients [52] depressive symptoms were rated as “clinically relevant”.

In our study we found that neither drug significantly improved aggressive symtpoms. This finding did not confirm previous data obtained by Amon and colleagues (53) in a group of inpatients with aggressiveness measured with the MOAS. In that study, the Authors showed a significant reduction of physical aggressiveness in the group that received asenapine versus usual management. The discrepancy with our results may be due to a number of factors. Baseline MOAS total score (Mean ± SD = 19 ± 9.80) in patients enrolled by Amon and colleagues was significantly higher than baseline MOAS score (Mean ± SD = 5.50 ± 2.59) registered in our

sample. Moreover, patients enrolled by Amon and colleagues (53) were not BPD patients but inpatients with schizophrenia and bipolar disorders. In the only previous investigation performed by Martin-Blanco and colleagues (33) with asenapine in BPD subjects the symptom of aggressiveness was not considered. So, we cannot compare with other investigations our finding of the lack of effect of asenapine on aggressive symptoms. Concerning the effects of olanzapine on aggression in BPD there is not an overall agreement among the Authors who conducted previous studies. Cochrane systematic reviews on pharmacological treatment for BPD (5,6) concluded that olanzapine induced significant decreases in affective instability, anxiety, anger, and psychotic paranoid symptoms. Aggressiveness was not listed among these effects.

With regard to the role of asenapine and olanzapine in treating specific BPD symptoms, we found that the two antipsychotics produced non-different effects on BPD related psychopathology, impulsivity, and self-injury, measured with the BPDSI total score, the BIS-11 score and with BPDSI item "impulsivity" score, and with the SHI score respectively.

On the other hand, significant differences of effect between the two drugs were found on measures of two core BPD symptom domains, namely affective instability and cognitive perceptual symptoms measured with BPDSI specific items. More specifically, asenapine was found significantly superior to olanzapine in reducing the severity of affective instability. This finding supports the evidence provided by Martin-Blanco and colleagues [33] of a significant effect of asenapine on affect dysregulation in BPD patients.

Furthermore, we found that olanzapine was more efficacious than asenapine against cognitive-perceptual symptoms. It must be acknowledged that this finding has a limited value, as our study was found to be underpowered to detect a difference between the drugs on the dissociation/paranoid ideation item of the BPDSI. However, the effect of olanzapine on this symptom domain in BPD patients has been widely reported in previous open-label and controlled studies. Thus, Schultz and colleagues [12] demonstrated a significant reduction of psychoticism in BPD patients treated with olanzapine. Moreover, Zanarini and Frankenburg [19] reported a

significant improvement of paranoid ideation in BPD subjects treated with olanzapine versus placebo. More recently, this trend was confirmed in a study involving a larger BPD sample by the same research group [21], which specified that the improvement in cognitive-perceptual symptoms (paranoid ideation and dissociation) was observed in BPD patients treated with a moderate dose of olanzapine, ranging from 5 to 10 mg/day. Noteworthy, the dose used in our study is within this range.

Different conclusions on this topic were drawn by Jariani and colleagues [14], who compared olanzapine with sertraline in BPD subjects and did not find any significant differences between the two medications on this type of symptoms. However, in this study the diagnosis of BPD was not supported by any standardized assessment instrument, and the effects of olanzapine and sertraline were measured in a group of heroin-dependent patients on methadone maintenance therapy.

With regard to tolerability, both treatment modalities were rather well tolerated, with only mild to moderate adverse effects reported in our sample. Nevertheless, some differences between asenapine and olanzapine were identified, with mild akathisia and restlessness/anxiety more commonly reported by patients receiving asenapine. Moreover, only three drop-outs among subjects treated with asenapine were due to adverse effects: two experienced oral hypoesthesia, and one moderate anxiety. Olanzapine instead was responsible for mild somnolence and fatigue reported in our BPD patients. Two patients treated with olanzapine discontinued the drug due to a significant weight gain (≥ 3Kg).

Our finding of several detectable differences in adverse effects between asenapine and olanzapine is overall consistent with data published in previous studies. Typically, asenapine was associated with a lower incidence of weight gain than olanzapine, more common extrapyramidal symptoms (akathisia) and oral hypoaesthesia [36- 38, 29].

Study limitations

The open label design, the lack of a placebo group, and a rather small sample size constituted

major limitations of this trial. A further possible limitation was the exclusion of subjects with co-occurring major depression, substance abuse or dependence in order to avoid their confounding effect on the outcome of the study. Given that these are common psychiatric comorbidities, the study sample may present clinical features that are partially different from those typically found in clinical practice, thereby compromising generalisability of our findings to the target population. Another limit is that we used the individual items of BPDSI as outcome measures of several BPD symptom domains, in particular of affective instability and paranoid ideation. More specific instruments would provide more reliable results and are needed to replicate our findings. A further limitation is that data on pharmacotherapies and psychotherapies received by our patients prior to entering the study had not been collected and compared between the two treatment arms. This, however, was partially corrected by excluding patients who had received pharmacological and psychotherapeutic interventions in the 2 months before enrollment in the study. Another limitation of the study is that it was not powered to detect a difference between the drugs on the dissociation/paranoid ideation item of the BPDSI. It should be noticed that obtaining large enough samples for trials of BPD has historically proven difficult.

We had a rather high drop-out rate in our study (21.7%), but this appears to be a common trend across the majority of preceding trials involving BPD patients, who are prone to poor adherence. However, intention to treat analysis with last observation carried forward was performed to analyze data in the whole group of patients who entered the trial, and the significant effects of the two drugs found with the ANOVA were the same obtained in the group of completers.

5. Conclusions

In conclusion, our findings indicated that asenapine was not different from olanzapine with regard to overall measures of efficacy and general level of tolerability. Effect size, eta square, calculated for the effect within subjects (treatment duration) ranged from 0.25 to 0.53. These are high values of size effect indicating a high level of efficacy of both medications. Moreover,

some differences in therapeutic effect on specific symptom clusters were identified. Also, the type of adverse effects was partially different between the two drugs. The open label study design, lack of a placebo group, and small sample size constituted major limitations of this trial. Another limitation was that the study was not powered to detect a difference between the drugs on the dissociation/paranoid ideation item of the BPDSI. Research in this field has major clinical implications, contributing to identify which antipsychotic is more useful to treat specific symptom domains in BPD patients. Further investigations are required to replicate our findings in larger samples.

Compliance with Ethical Standards

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This research received no sources of funding to assist with conducting the study and preparing the manuscript.

Conflict of interest

The four Authors, Paola Bozzatello, Paola Rocca, Maria Uscinska, and Silvio Bellino, declare that they have no conflicts of interest.

Informed Consent and Ethics approval

Each patient participated voluntarily in the study after providing written informed consent. Declaration of Helsinki guidelines (1964) were followed. Ethical approval was obtained from the ethics committee of University Hospital "Città della Salute e della Scienza - Ospedale Ordine Mauriziano" of Turin.

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Table 1. Comparison of the baseline values of symptoms and functioning rating scales between the asenapine and olanzapine treated groups.

Scale	Asenapine (N=21) Mean ± SD	Olanzapine (N=19) Mean ± SD	ANOVA *P*
CGI-S	4.00 ± 0.816	4.20 ± 0.789	0.584
HAM-A	17.30 ± 4.923	18.50 ±3.951	0.555
HAM-D	12.90 ± 3.784	15.70 ± 3.945	0.123
BIS-11	70.40 ± 9.454	75.30 ± 12.544	0.337
MOAS	5.50 ± 2.593	5.20 ± 3.190	0.820
SHI	7.90 ± 5.021	4.029 ± 1.274	0.254
SOFAS	60.10 ± 7.015	55.50 ± 9.265	0.227

SD=standard deviation; ANOVA=analysis of variance; CGI-S=Clinical Global Impression scale – Severity item; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; SOFAS=Social Occupational Functioning Assessment Scale; BIS-11=Barrett Impulsiveness Scale – version 11; MOAS=Modified Overt Aggression Scale; SHI=Self Harm Inventory.

Table 2. Comparison of baseline values of BPDSI total score and single items between the asenapine and olanzapine treated groups.

Scale	Asenapine (N=21) Mean ± SD	Olanzapine (N=19) Mean ± SD	ANOVA *P*
BPDSI total score	55.59 ± 9.245	53.37 ± 10.961	0.630
Abandonment	7.55 ± 1.41	7.24 ± 1.32	0.322
Interpersonal relationships	7.59 ± 0.63	7.68 ± 1.23	0.811
Identity	4.80 ± 1.47	5.51 ± 1.22	0.203
Impulsivity	8.31 ± 1.30	7.71 ± 1.31	0.232
Parasuicidal behaviors	1.50 ± 1.60	1.82 ± 1.08	0.251
Affective instability	8.21 ± 0.38	7.54 ± 1.78	0.201
Outbursts of anger	6.91 ± 1.45	7.88 ± 1.23	0.153
Emptiness	6.60 ± 1.85	5.82 ± 1.27	0.172
Dissociation/paranoid ideation	2.37 ± 1.58	2.49 ± 1.87	0.554

SD=standard deviation; ANOVA=analysis of variance; BPDSI=borderline personality disorder severity index.

Table 3. Results of ITT-LOCF analysis for the CGI-S, HAM-A, HAM-D, and SOFAS scales.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
CGI-S	Asenapine olanzapine	4.00 ± 0.82 4.20 ± 0.79	3.70 ± 0.82 3.90 ± 0.74	P=0.012 η^2=0.25	P=0.561 η^2=0.02
HAM-A	Asenapine olanzapine	17.30 ± 4.92 18.50 ± 3.95	17.00 ± 4.27 16.40 ± 4.35	P=0.004 η^2=0.3	P=0.878 η^2=0.01
HAM-D	Asenapine olanzapine	12.90 ± 3.78 15.70 ± 3.95	12.80 ± 4.02 15.70 ± 3.27	P=0.862 η^2=0.01	P=0.103 η^2=0.12
SOFAS	Asenapine olanzapine	60.10 ± 7.06 55.50 ± 9.27	61.00 ± 6.58 58.30 ± 10.06	P=0.004 η^2=0.3	P=0.337 η^2=0.03

Table 4. Results of ANOVA repeated measures to compare the changes of the CGI-S, HAM-A, HAM-D, and SOFAS scores between treatment groups.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
CGI-S	Asenapine olanzapine	4.00±0.74 4.15±0.80	3.75±0.75 3.92±0.76	P=0.013 η^2=0.24	P=0.582 η^2=0.01
HAM-A	Asenapine olanzapine	16.50 ± 4.83 18.38 ± 3.91	16.25 ± 4.25 16.77 ± 4.26	P=0.007 η^2=0.28	P=0.486 η^2=0.02
HAM-D	Asenapine olanzapine	13.17 ± 3.49 15.31 ± 3.79	13.08 ± 3.70 15.54 ± 3.04	P=0.775 η^2=0.01	P=0.110 η^2=0.11
SOFAS	Asenapine olanzapine	59.25 ± 6.98 55.38 ± 8.28	60.00 ± 6.74 57.54 ± 9.06	P=0.006 η^2=0.29	P=0.320 η^2=0.04

ANOVA=analysis of variance; SD=standard deviation; CGI-S=Clinical Global Impression scale – Severity item; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; SOFAS=Social Occupational Functioning Assessment Scale; η^2=Eta square

Table 5. Results of ITT-LOCF analysis for the MOAS, BIS-11, and SHI scales.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
MOAS	asenapine olanzapine	5.50 ± 2.59 5.20 ± 3.19	5.20 ± 2.90 4.80 ± 3.26	P=0.119 η^2=0.1	P=0.794 η^2=0.01
BIS-11	asenapine olanzapine	70.40 ± 9.45 75.30 ± 12.54	64.70 ± 11.19 72.90 ± 13.71	P=0.005 η^2=0.3	P=0.219 η^2=0.07
SHI	asenapine olanzapine	7.90 ± 5.02 10.30 ± 4.03	6.90 ± 5.32 8.80 ± 3.65	P=0.004 η^2=0.3	P=0.297 η^2=0.05

Table 6. Results of ANOVA repeated measures to compare the changes of the MOAS, BIS-11, and SHI scores between treatment groups.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
MOAS	asenapine olanzapine	5.50 ± 2.43 5.00 ± 3.08	5.25 ± 2.70 4.69 ± 3.12	P=0.119 η^2=0.1	P=0.645 η^2=0.01
BIS-11	asenapine olanzapine	71.50 ± 8.93 75.23 ± 11.45	66.75 ± 11.20 73.38 ± 12.45	P=0.005 η^2=0.3	P=0.243 η^2=0.06
SHI	asenapine olanzapine	8.83 ± 5.12 11.15 ± 3.91	8.00 ± 5.56 10.00 ± 3.96	P=0.005 η^2=0.29	P=0.253 η^2=0.06

ANOVA=analysis of variance; SD=standard deviation; MOAS=Modified Overt Aggression Scale; BIS-11=Barrett Impulsiveness Scale – version 11; SHI=Self Harm Inventory; η^2=Eta square

Table 7. Results of ITT-LOCF analysis for the BPDSI total score and single items.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
BPDSI total score	asenapine olanzapine	55.59 ± 9.25 53.37 ± 10.96	51.35 ± 9.33 49.12 ± 11.73	P=0.001 η^2=0.53	P=0.634 η^2=0.01
Abandonment	asenapine olanzapine	7.55 ± 1.41 7.24 ± 1.32	7.09 ± 1.32 6.69 ± 1.12	P=0.001 η^2=0.53	P=0.732 η^2=0.01
Interpersonal relationships	asenapine olanzapine	7.59 ± 0.63 7.68 ± 1.23	6.89 ± 1.32 7.29 ± 1.40	P=0.001 η^2=0.53	P=0.565 η^2=0.02
Identity disturbance	asenapine olanzapine	4.80 ± 1.47 5.51 ± 1.22	4.72 ± 1.61 5.40 ± 1.29	P=0.541 η^2=0.02	P=0.256 η^2=0.06
Impulsivity	asenapine olanzapine	8.31 ± 1.30 7.71 ± 1.31	7.78 ± 1.36 7.00 ± 1.58	P=0.001 η^2=0.53	P=0.301 η^2=0.04
Parasuicidal behaviors	asenapine olanzapine	1.50 ± 1.60 1.82 ± 1.08	1.46 ± 1.52 1.67 ± 1.33	P=0.092 η^2=0.14	P=0.682 η^2=0.01
Affective instability	asenapine olanzapine	8.21 ± 0.38 7.54 ± 1.78	4.58 ± 1.1 6.86 ± 1.67	P=0.001 η^2=0.53	P=0.001 η^2=0.53
Outbursts of anger	asenapine olanzapine	6.91 ± 1.45 7.88 ± 1.23	6.05 ± 1.15 7.19 ± 1.82	P=0.001 η^2=0.53	P=0.312 η^2=0.04
Emptiness	asenapine olanzapine	6.60 ± 1.85 5.82 ± 1.27	5.81 ± 1.58 5.27 ± 1.11	P=0.001 η^2=0.53	P=0.630 η^2=0.01
Dissociation/paranoid ideation	asenapine olanzapine	2.37 ± 1.58 2.49 ± 1.87	2.36 ± 1.15 1.67 ± 1.83	P=0.001 η^2=0.53	P=0.021 η^2=0.21

ANOVA=analysis of variance; SD=standard deviation; BPDSI=borderline personality disorder severity index; η^2=Eta square

Table 8. Results of ANOVA repeated measures to compare the BPDSI total score and single items between treatment groups.

Scale	Treatment	Baseline Mean ± SD	12 weeks Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
BPDSI total score	asenapine olanzapine	55.05 ± 8.50 52.65 ± 9.95	51.52 ± 8.50 49.38 ± 10.51	P=0.001 η^2=0.53	P=0.548 η^2=0.02
Abandonment	asenapine olanzapine	7.59 ± 1.45 7.27 ± 1.38	7.06 ± 1.34 6.67 ± 1.21	P=0.001 η^2=0.53	P=0.682 η^2=0.01
Interpersonal relationships	asenapine olanzapine	7.63 ± 0.82 7.70 ± 1.42	6.84 ± 1.28 7.31 ± 1.30	P=0.001 η^2=0.53	P=0.672 η^2=0.01
Identity disturbance	asenapine olanzapine	4.81 ± 1.65 5.53 ± 1.18	4.62 ± 1.72 5.31 ± 1.43	P=0.437 η^2=0.02	P=0.186 η^2=0.07
Impulsivity	asenapine olanzapine	8.36 ± 1.51 7.71 ± 1.45	7.78 ± 1.39 6.96 ± 1.47	P=0.001 η^2=0.53	P=0.230 η^2=0.06
Parasuicidal behaviors	asenapine olanzapine	1.52 ± 1.70 1.80 ± 1.12	1.45 ± 1.73 1.67 ± 1.31	P=0.086 η^2=0.14	P=0.631 η^2=0.01
Affective instability	asenapine olanzapine	8.27 ± 0.47 7.55 ± 1.68	4.54 ± 1.52 6.85 ± 1.47	P=0.001 η^2=0.53	P=0.001 η^2=0.53
Outbursts of anger	asenapine olanzapine	6.94 ± 1.56 7.84 ± 1.51	6.02 ± 1.27 7.17 ± 1.71	P=0.001 η^2=0.53	P=0.295 η^2=0.05
Emptiness	asenapine olanzapine	6.65 ± 1.96 5.83 ± 1.22	5.80 ± 1.85 5.23 ± 1.32	P=0.001 η^2=0.53	P=0.525 η^2=0.03
Dissociation/paranoid ideation	asenapine olanzapine	2.38 ± 1.75 2.51 ± 1.99	2.35 ± 1.32 1.61 ± 1.62	P=0.001 η^2=0.53	P=0.012 η^2=0.25

ANOVA=analysis of variance; SD=standard deviation; BPDSI=borderline personality disorder severity index; η^2=Eta square