Asenapine in the management of impulsivity and aggressiveness in bipolar disorder and comorbid borderline personality disorder: an open-label uncontrolled study

Andrea Aguglia[a,b], Ludovico Mineo[c], Alessandro Rodolico[c], Maria S. Signorelli[c] and Eugenio Aguglia[c]

Borderline personality disorder (BPD) often co-occurres with bipolar disorder (BD). Impulsivity and aggressiveness represent core shared features and their pharmacological management is mainly based on mood stabilizers and antipsychotics, although scarce evidence is available for this context of comorbidity. The aim of the present study was to evaluate the role of Asenapine as an adjunctive drug for reducing aggressiveness and impulsivity in a sample of Italian BD type I outpatients with or without a comorbid BPD. This was an observational 12-week open-label uncontrolled clinical study carried out from April to October 2014 in two psychiatric clinics in Sicily. Each patient was treated with asenapine at two dose options, 5 mg (twice daily) or 10 mg (twice daily), and concomitant ongoing medications were not discontinued. We measured impulsivity using the Barratt Impulsiveness Scale (BIS) and aggressiveness using the Aggressive Questionnaire (AQ). For the analysis of our outcomes, patients were divided into two groups: with or without comorbid BPD. Adjunctive therapy was associated with a significant decrease of BIS and AQ overall scores in the entire bipolar sample. Yet, there was no significant difference in BIS and AQ reductions between subgroups. Using a regression model, we observed that concomitant BPD played a negative role on the Hostility subscale and overall AQ score variations; otherwise, borderline co-diagnosis was related positively to the reduction of physical aggression. According to our post-hoc analysis, global aggressiveness scores are less prone to decrease in patients with a dual diagnosis, whereas physical aggressiveness appears to be more responsive to the add-on therapy in patients with comorbidity. *Int Clin Psychopharmacol* 33:121–130 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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[a]Department of Neuroscience, Rehabilitation, Opthalmology, Genetics, Maternal and Child Health, University of Genoa, Section of Psychiatry, IRCCS Policlinico San Martino Hospital, Genoa, [b]'Rita Levi Montalcini' Department of Neuroscience, University of Turin, Turin and [c]Department of Experimental and Clinical Medicine, Psychiatric Clinic University Hospital 'Gaspare Rodolico', University of Catania, Catania, Italy

Correspondence to Alessandro Rodolico, MD, Department of Experimental and Clinical Medicine, Psychiatric Clinic University Hospital 'Gaspare Rodolico', University of Catania, Via Santa Sofia, 78, Catania 95123, Italy
Tel/fax: +39 095 378 2470; e-mail: alessandro.rodolico@me.com

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Introduction

Bipolar disorder (BD) is a chronic mental illness with a relapsing and remitting course often characterized by comorbid psychopathological conditions. The US National Comorbidity Survey Replication found that almost 93% of respondents with BD fulfilled the criteria for at least another Axis I *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) diagnosis (Merikangas *et al.*, 2007), with higher rates for anxiety and impulse control disorders. Analogously, cluster B personality disorder features are evident in about one-third of bipolar patients, with a greater prevalence of borderline personality traits (Garno *et al.*, 2005).

Borderline personality disorder (BPD) is a severe personality dysfunction characterized by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image (Leichsenring *et al.*, 2011).

A recent meta-analysis among 42 studies showed a wide range of rates of comorbidity of these conditions (i.e. 0–62.5% of BPD in BD and 0–62.5% of BD in BPD), eventually quantifying the prevalence of BPD in patients with a primary diagnosis of BD at 21.6% (95% confidence interval: 17.0–27.1) and the converse at 18.5% (95% confidence interval: 12.7–26.1) (Fornaro *et al.*, 2016).

These high rates of comorbidity, together with the relevant heterogeneity of the data obtained by the available prevalence studies, may be partially linked to errors in the clinical assessment of both conditions and consequent misdiagnosis. Differentiation of BD from BPD in fact represents a diagnostic challenge because of the overlapping of phenomenological and clinical features such as emotional dysregulation, mood instability, aggressiveness, impulsivity, unstable interpersonal relationships, repeated self-injury, and suicidal attempts. The relationship between these nosological entities

is still a matter of academic debate, with some authors questioning the possibility of a real comorbidity, considering it as a 'nosographic artifact' and placing the borderline syndrome under the bipolar spectrum (Akiskal, 2004; MacKinnon and Pies, 2006; Perugi *et al.*, 2013). In contrast, psychiatrists who strongly advocate the categorization of BPD among personality disorders underline specific psychopathological features compared with BD spectrum subtypes, and warn clinicians about the necessity of diagnostic evaluations able to detect precise features in the phenomenology of shared symptoms by integrating clinical practice with appropriate testing methods (Paris, 2004; Fulford *et al.*, 2015; Vöhringer *et al.*, 2016; Bayes and Parker, 2017; di Giacomo *et al.*, 2017). Moreover, differences in the course and longitudinal trajectories of these conditions, patients' family history, and response to medication should be taken into account (Hatchett, 2010; Renaud *et al.*, 2012).

A considerable part of the overlapping symptoms pertains to the dimension of impulsivity, although different phenomenological aspects of this domain have been described in the two disorders.

Impulsivity in potentially self-damaging areas is listed in DSM-V (American Psychiatric Association, 2013) as a diagnostic criterion for BPD and represents a clinical hallmark in patients affected; it has been evaluated as extremely stable over time and highly predictive of borderline psychopathology (Moeller *et al.*, 2001; DeShong and Kurtz, 2013). In BD, instead, impulsivity is believed to have a more episodic course than in BPD (Swann, 2010), although higher levels of impulsivity are recorded frequently during the interepisode phase (Swann *et al.*, 2004; Powers *et al.*, 2013).

Furthermore, from a neuropsychological prospective, differential patterns of impulsivity have been described for depressive and manic episodes in BD with a prevalence of motor impulsivity (tendency to act on the spur of the moment) related to mania and nonplanning impulsivity (difficulty with planning actions carefully and thinking about the consequences of actions) related to depression. This latter component of impulsivity also seems to be prevailing in BPD (Swann *et al.*, 2004; Flory *et al.*, 2006; Wilson *et al.*, 2007).

Impulsivity-related symptoms appear to be closely linked to mood lability and they often manifest as inappropriate sexual behaviors in both BD and BPD, although impulsivity may also consist of physical, financial, binge eating-related, or aggressive acts (Ghaemi *et al.*, 2014; Fornaro *et al.*, 2016). In fact, impulsivity is considered the main psychopathological mediator of aggressiveness in both conditions (Goodman and New, 2000; Wilson *et al.*, 2007; Látalová, 2009; Barker *et al.*, 2015).

Aggressiveness against self or against others is one of the core components of BPD accounting for a significant proportion of morbidity and mortality associated with this disorder (Goodman *et al.*, 2010). In BPD, aggressiveness is mainly of the impulsive type, driven by lack of behavioral inhibition and generally triggered by environmental overstimulation and stress (Wilson *et al.*, 2007; Latalova and Prasko, 2010).

Similarly, in BD, most of the aggressiveness is apparently impulsive, occurring largely during acute episodes, independent of psychosis. However, aggressive behaviors may also be present in euthymic phases, suggesting that impulsive aggressiveness is not only state related but also a trait component of BD (Grunebaum *et al.*, 2006; Najt *et al.*, 2007; Látalová, 2009).

Comorbidity between BD and BPD has already been described as an adjunctive detrimental factor for the clinical course and evolution of both disorders; patients with BD and comorbid BPD present an earlier onset of disease, higher self-harming behavior and suicidality, greater hostility, lower rates of stabilization and treatment adherence, and a more remarkable risk of substance use in comparison with BD alone (Vieta *et al.*, 2001; Swartz *et al.*, 2005; Goldberg and Garno, 2009; Latalova *et al.*, 2013; McDermid *et al.*, 2015).

To date, only a few studies have investigated the potential contribution of cluster B disorders to impulsivity/aggressiveness in mood disorders (including BDs) converging on higher levels of impulsivity/aggressiveness in comorbid patients compared with those with only a mood disorder diagnosis (Henry *et al.*, 2001; Wilson *et al.*, 2007; Garno *et al.*, 2008).

Undoubtedly, in this subgroup of patients, control of impulsive–aggressive behaviors is a therapeutic priority, particularly to prevent risks of self-injuries or harm to others.

On the basis of the available data for each single disorder (Prado-Lima, 2009; Kendall *et al.*, 2010; Lieb *et al.*, 2010; Leichsenring *et al.*, 2011), some mood stabilizers (especially lithium carbonate, divalproex sodium and valproate, carbamazepine, lamotrigine) and second-generation antipsychotics (SGAs) (risperidone, olanzapine, quetiapine) may be considered suitable pharmacotherapeutic options targeting these shared symptom dimensions, even with different degrees of evidence.

Antagonism to 5-HT_{2A} receptors in mitigating aggressive–impulsive behaviors (Blake and Grafman, 2004; Siever, 2008) makes SGAs a valid alternative in this subgroup of patients as the use of other available drugs (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors), interfering with the serotoninergic system in the modulation of aggressiveness-impulsivity neural circuitry, is not generally recommended.

The proven efficacy and tolerability of asenapine in the treatment of acute mania in BD (Samalin *et al.*, 2013; Scheidemantel *et al.*, 2015), along with some promising evidences of its efficacy in BPD (Martín-Blanco *et al.*, 2014; Bozzatello *et al.*, 2017), led us to speculate about the

potential utility of this new antipsychotic as a drug option for patients with BPD alone or in comorbidity with BD.

Recently approved by the US Food and Drug Administration for the treatment of schizophrenia and BD, asenapine presents a peculiar receptor binding profile with a 5-HT_{2A} : D2 affinity ratio similar to other SGA, but a higher affinity for serotonergic, $\alpha_{1,2}$ adrenergic receptors (Weber and McCormack, 2009; Timpe and Chopra, 2010). Together with clozapine, asenapine is the unique antipsychotic presenting a D4/D2 affinity ratio of more than 1 that has been purported to confer an antiaggression effect (El-Mallakh and McKenzie, 2013). This latter hypothesis was proposed in the light of the proven superiority of clozapine – in both open and randomized trials (Frogley *et al.*, 2012) – over other antipsychotic comparators.

Finally, asenapine has shown a more favorable tolerability profile with a lower propensity to cause weight gain, prolactin elevation, or QTc prolongation compared with most SGA (Gonzalez *et al.*, 2011; Citrome, 2014).

The aim of this study was to evaluate the efficacy of asenapine as an adjunctive drug for reducing aggressiveness and impulsivity in a group of Italian outpatients with BD type I with or without a comorbid BPD.

Patients and methods

Population

This was an observational, 12-week open-label uncontrolled clinical study, carried out from April to October 2014. Patients, aged between 18 and 75 years with a previous diagnosis of BD type I, were recruited into the adult psychiatric outpatient services of Catania University Hospital and Siracusa City Hospital. All patients included in the study underwent assessment with the Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.*, 2002) and the Italian version of the Mood Disorder Questionnaire (Hirschfeld, 2002) to confirm their past diagnosis of BD type I by means of two different screening instruments.

To evaluate the comorbidity with BPD, we used the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First *et al.*, 1997) and the Borderline Syndrome Index (BSI), a 52-item, yes–no, self-report questionnaire used widely by clinicians as a rapidly administered and scored instrument for assessing borderline psychopathology. Consistent with the available literature data, we set a BSI cutoff score at 25 to differentiate the two groups (Conte *et al.*, 1980; Edell, 1984).

Exclusion criteria were as follows: current episode of BD (depressive, manic, mixed), occurrence of severe physical conditions (i.e. neurological disease, mental deficiency, and other neurological conditions), a past or current schizophrenia spectrum disorder or other psychotic disorder; a past or current mental disorder because of a medical condition; current mental retardation or other significant neurocognitive disturbances; current severe physical illness; and concurrent alcohol and/or other substance abuse/dependence history of mental disorders because of a medical condition. Pregnant and sexually active women unwilling to use an effective means of contraception were also excluded.

Design and measures

The sample selected for this study included 50 patients with a primary diagnosis of BD type I in the euthymic phase. Recruitment of patients was performed on a consecutive basis. After the assessment for the borderline traits, they were divided into two groups: patients with a diagnosis of BD type I and patients with BD type I and BPD (BSI > 25).

Each patient was treated with asenapine at two dose options, 5 mg (twice daily) or 10 mg (twice daily), according to the clinical judgment of the investigator evaluating the clinical course for a 12-week period. Concomitant medications started before inclusion in the study could be continued by the patients. Psychiatric interviews, clinical examination, scale administration, and assessment of medical history were performed by a trained psychiatric resident with at least 5 years of postgraduate clinical experience in the outpatient clinical setting.

Body weight, height, and waist circumference were also measured. Weight of the undressed patients was measured in fasting condition; height was measured barefoot. To evaluate central adiposity, waist circumference was measured between the inferior margin of the ribs and the superior border of the iliac crest, at minimal respiration. BMI, defined as the ratio of body weight (in kg) and height (in m^2), was calculated.

Aggressiveness was evaluated using the Italian version (Fossati *et al.*, 2003) of the Aggression Questionnaire (AQ) (Buss and Perry, 1992). This is a four-factor model questionnaire consisting of 29 items scored on a five-point Likert scale, from extremely uncharacteristic of me = 1 to extremely characteristic of me = 5 (with some items scored in reverse), that provides a global measure of aggressiveness and four subscales: Physical Aggressiveness (PA, nine items), Verbal Aggressiveness (VA, five items), Anger (A, seven items), and Hostility (H, eight items).

Impulsivity was evaluated using he Italian version of the BIS-11 (Patton *et al.*, 1995; Fossati *et al.*, 2001). This self-report questionnaire consists of 30 items, scored on a four-point Likert scale (rarely/never – 1, occasionally – 2, often – 3, almost always/always – 4). To minimize the risk of response bias, 10 of the items are scored reversely (rarely/never – 4, occasionally – 3, often – 2, almost always/always – 1). The scale measures the three subdimensions of impulsivity: attentional (eight items; inattention and cognitive instability), motor (11 items; motor impulsivity, and lack of perseverance), and nonplanning (11 items; lack of self-control and intolerance of cognitive complexity).

Aggressiveness and impulsivity levels were assessed at baseline (V0) and at 12 weeks (V1). A telephone number was provided to each patient to report any possible side effects or to provide any useful information about the course of the illness at any time: if a patient had shown any significant clinical symptom, he or she would have been immediately visited. In any case, at 6 weeks, a psychiatric visit was planned to evaluate the course of illness and tolerability.

The study was carried out according to the principles of the Declaration of Helsinki. Participants did not receive any compensation for the study. Patients expressed their willingness to participate in the study by signing a written consent, after being thoroughly informed about the aim and procedures of the study. The study design was reviewed by the local ethic committee.

Safety

Adverse events were recorded on the basis of spontaneous report or investigator observations. We considered an adverse event as treatment-emergent adverse event if it was newly reported after open-label baseline or reported to have worsened in severity since open-label baseline.

Predefined treatment-emergent adverse events of interest in the study were dizziness, insomnia, somnolence/hypersomnia/sedation combined, oral hypoesthesia/dysgeusia, extra-pyramidal symptoms (EPS), and incidence of clinically significant weight increase defined by an increase superior 7% from baseline. EPS were assessed using a clinician-administered Abnormal Involuntary Movement Scale (Munetz and Benjamin, 1988), the Barnes Akathisia Scale (Barnes, 2003), and the Simpson-Angus Scale (Simpson *et al.*, 1970).

Statistical analysis

Descriptive data were summarized as number of patients and percentage (%) or mean ± SD. Comparisons within groups were performed using a paired-samples *t*-test. Comparisons between groups (with or without BD) were performed using an independent-samples *t*-test (continuous variables: score AQ-PA, AQ-VA, AQ-A, AQ-H, AQ-total, BIS) or the χ^2-test (dichotomous variables: percentage of patients who improved). To determine factors significantly related to the changes of the different scores, general linear models were applied: correlation testing was performed using analysis of covariance models with sex, education level, borderline personality diagnosis, and Mood Disorder Questionnaire score as fixed factors and age, SCID-II score, BSI score, and baseline scores for each subscale (AQ-PA, AQ-VA, AQ-A, AQ-H) as covariates. A significance level of 0.05 was used for each test. For all the analyses, IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, New York, USA), was used.

Results

Fifty BD type I patients were included in the study; 35 (70%) had BPD comorbidity (BD-I/BPD patients) and 15 (30%) patients had only BD type I diagnosis (BD patients). Clinical and sociodemographic characteristics of the recruited patients are reported in Table 1.

At the beginning of the study, only three (6%) patients were drug-free, 30 (60%) patients were receiving mood stabilizers (lithium or valproic acid at therapeutic range), 14 (28%) patients were receiving mood stabilizers plus benzodiazepines, one patient was receiving mood stabilizers (lithium 600 mg and carbamazepine 400 mg) and serotonin norepinephrine reuptake inhibitors (venlafaxine at 75 mg), and two patients were receiving mood stabilizers with selective serotonin reuptake inhibitors (lithium 750 mg plus escitalopram 10 mg and valproic acid 1000 mg plus sertraline 75 mg) and benzodiazepines. Lack of efficacy of previous medications in modulating impulsive–aggressive behaviors was reported as the main reason for starting therapy. The mean daily dose of asenapine at T0 was 14.8 mg/day (SD = 2.5) for the group BD type I/BPD and 15.3 mg/day (SD = 2.3) for the group BD. All patients completed the study and no medication regimen changes were made during the trial.

A significant reduction in the AQ and BIS overall score was found in the total sample ($P < 0.001$) and for each subgroup (BD type I $P < 0.001$ and BD type I/BPD $P < 0.001$). This finding was also obtained for all AQ subscales (PA, VA, A, and H subscales) at paired *t*-test analysis at T1 score versus baseline.

No significant differences in the AQ-total and subscales (AQ-total PA, VA, A, H) score variations from baseline to T1 were found between groups as shown in Table 2.

Some subscales scores differed significantly between groups at baseline as shown in Table 3.

It should be noted that the difference in the baseline levels of impulsivity between the two groups (BD type I vs. BD type I/BPD) was not significant ($P = 0.563$), whereas AQ-total score and two subscales scores (AQ-H, AQ-A) were different between groups (BD type I vs. BD type I\BPD). Considering the statistically significant difference of various baseline scores, it was not possible to compare row values of AQ and BIS scales and subscales. Thus, it was more reasonable to compare the scores difference before and after the treatment. To assess the role of candidate predictors in scores' reduction, we investigated whether any baseline variable could play a role in modulating a decrease in scores with an analysis of covariance model, which is presented in Table 4. The borderline concomitant diagnosis seems to play a negative role in the H subscale variation, $F(1,39) = 12.067$, $P = 0.001$, and on overall AQ score variation, $F(1,39) = 13.683$, $P = 0.001$. Indeed, the reduction of these is more relevant in BD patients without BPD comorbidity. Otherwise, even if not strictly significant ($P = 0.053$), borderline co-diagnosis might be related positively to PA reduction in patients treated with asenapine, considering a more relevant decrease in its subscale scores in comorbid patients (80.0 vs. 97.1%, $P = 0.041$).

Table 1 Demographic and clinical data for the study sample

	BD only ($N=15$)	BD and BPD ($N=35$)	Total ($N=50$)	P value
Sex [*n* (%)]				
Female	8 (53.3)	15 (42.9)	23 (46.0)	0.496
Male	7 (46.7)	20 (57.1)	27 (54.0)	
Age (years)				
Mean (SD)	43.1 (14.04)	47.6 (13.08)	46.2 (13.40)	0.277
Median	45	50	48	
Minimum–maximum	20–68	21–72	20–72	
Education [*n* (%)]				
Elementary school	–	2 (5.7)	2 (4.0)	0.462
Middle school	–	3 (8.6)	3 (6.0)	
High school	8 (53.3)	18 (51.40)	26 (52.0)	
Graduatiom	7 (46.7)	12 (34.3)	19 (38.0)	
Most recent episode [*n* (%)]				
Depressive	–	4 (11.4)	4 (8.0)	0.069
Depressive with mixed features	1 (6.7)	9 (25.7)	10 (20.0)	
Mania	5 (33.3)	12 (37.1)	18 (36.0)	
Mania with mixed features	9 (60.0)	9 (25.7)	18 (36.0)	
Concomitant therapy with asenapine				
No concomitant therapy	1 (6.7)	2 (5.7)	3 (6.0)	0.831
Mood stabilizer	10 (66.7)	20 (57.1)	30 (60.0)	
Mood stabilizer + BDZ	4 (26.7)	10 (28.6)	14 (28)	
Mood stabilizer + SNRI	–	1 (2.9)	1 (2.0)	
Mood stabilizer + SSRI + BDZ	–	2 (5.7)	2 (4.0)	
Previous substance abuse [*n* (%)]	6	11	17	0.746

BD, bipolar disorder; BDZ, benzodiazepines; BPD, borderline peronality disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors.

Table 2 Impulsivity and aggression score variations: differences between BD and BD/BPD

	BD only ($N=15$)	BD and BPD ($N=35$)	P value (two-sided t-test)
ΔAQ-PA	−7.1 (7.72)	−7.0 (4.02)	0.962
ΔAQ-VA	−5.9 (5.08)	−4.3 (3.99)	0.287
ΔAQ-A	−4.8 (4.16)	−6.8 (3.94)	0.121
ΔAQ-H	−7.2 (6.98)	−7.2 (5.55)	1
ΔAQ	−24.9 (16.57)	−25.3 (11.37)	0.933
ΔBIS	−15.7 (11.06)	−13.6 (11.47)	0.544

AQ, Aggression Questionnaire; AQ-A, Aggression Questionnaire-Anger; AQ-H, Aggression Questionnaire-Hostility; AQ-PA, Aggression Questionnaire-Physical Aggression; AQ-VA, Aggression Questionnaire-Verbal Aggression; BD, bipolar disorder; BIS, Barratt Impulsiveness Scale; BPD, borderline peronality disorder.

Side effects

No serious adverse effect was recorded and there was no discontinuation of treatment. Nineteen (38%) patients reported increased somnolence/sedation, 14 (28%) reported oral hypoesthesia, 10 (20%) reported dysgeusia, and eight (16%) patients reported sporadic dizziness. No movement disorder was spontaneously reported or detected after clinical evaluation with dedicated scales. At T1, we did not find any significant weight variation, $t(49)=0.884$, $P=0.381$, two tails. The mean BMI at baseline was 28.6 (2.4), whereas at 12 weeks; it was slightly reduced, 28.3 (3.2).

Discussion

To the best of our knowledge, this open-label trial is the first prospective study on pharmacological management of impulsivity and aggressiveness in patients affected by BD type I and comorbid BPD. Furthermore, although there are already two studies that have investigated the efficacy and tolerability of asenapine in BPD (Martín-Blanco *et al.*, 2014; Bozzatello *et al.*, 2017), the present work is the only one available on the use of asenapine as an adjunctive drug in pharmacotherapy of BP patients with BPD.

In our sample, we observed a 70% rate of BPD diagnosis among patients with BD type I. This is quite a high rate compared with the mean percentage of this comorbidity reported by the most recent meta-analysis on this topic (Fornaro *et al.*, 2016). However, in some hospital-based studies included in that work, BD/BPD comorbidity prevalence reaches percentages as high as ours (Zimmerman and Mattia, 1999; Benazzi, 2000; Wilson *et al.*, 2007). Finally, differences in assessment instruments used, a small sample size, and missing long-term follow-up for the diagnostic validation of both conditions may account for this discrepancy. Moreover, we hypothesize that a further reason behind this difference might be the method of patient recruitment. Patients were recruited on a consecutive basis and this might have led to selection bias. To partially overcome this issue, statistical evaluations were performed by correcting scores of scales for BPD diagnosis.

The co-occurrence of BD and BPD appears to be bidirectional in nature, irrespective of the index population studied (BPD with BD or vice-versa) (Garno *et al.*, 2005; Paris *et al.*, 2007) and, along with the high rate of overlapping symptoms, continues to foster the debate on the underlying nature of the relationship between these conditions. However, most recent trends in the psychopathological literature tend to consider BD and BPD as two separate nosographic entities with distinguishable clinical and diagnostic features (Paris *et al.*, 2007; Bassett, 2012; Ghaemi *et al.*, 2014). In particular, quality and

Table 3 Baseline scores of impulsivity and aggressiveness in BD and BD/BPD

	BD only ($N=15$)	BD and BPD ($N=35$)	Total ($N=50$)	P value (two-sided t-test)
SCID-II				
Mean (SD)	9.8 (1.82)	10.6 (1.67)	10.4 (1.74)	0.137
Median	10	11	11	
Minimum–maximum	5–13	7–13	5–13	
BSI				
Mean (SD)	16.2 (8.09)	37.9 (7.08)	31.4 (12.42)	<0.001*
Median	20	40	33	
Minimum–maximum	4–25	26–50	4–50	
MDQ [n (%)]				
Negative	6 (40.0)	2 (5.7)	8 (16.0)	0.002*
Positive	9 (60.0)	33 (94.3)	42 (84.0)	
AQ-PA				
Mean (SD)	23.7 (8.41)	29.5 (6.49)	27.8 (7.52)	0.012*
Median	23	32	30.5	
Minimum–maximum	13–36	14–43	13–43	
AQ-VA				
Mean (SD)	17.3 (7.48)	19.3 (3.83)	18.7 (5.20)	0.22
Median	19	20	20	
Minimum–maximum	5–28	10–28	5–28	
AQ-A				
Mean (SD)	21.5 (5.77)	25.6 (4.05)	24.4 (4.94)	0.007*
Median	21	27	25.5	
Minimum–maximum	13–32	14–34	13–34	
AQ-H				
Mean (SD)	21.2 (6.92)	27.0 (5.16)	25.3 (6.28)	0.002*
Median	20	28	25.5	
Minimum–maximum	8–31	18–35	8–35	
AQ-total				
Mean (SD)	83.8 (22.23)	101.4 (14.09)	96.1 (18.58)	0.001*
Median	89	104	101	
Minimum–maximum	43–114	66–129	43–129	
BIS				
Mean (SD)	67.2 (10.27)	69.2 (11.45)	68.6 (11.04)	0.563
Median	64	71	69	
Minimum–maximum	56–92	44–84	44–92	

AQ-A, Aggression Questionnair-Anger; AQ-H, Aggression Questionnaire-Hostility; AQ-PA, Aggression Questionnaire-Physical Aggression; AQ-VA, Aggression Questionnaire-Verbal Aggression; BD, bipolar disorder; BIS, Barratt Impulsiveness scale; BPD, borderline peronality disorder; BSI, Brief Symptom Inventory; MDQ, Mood Disorder Questionnaire; SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders.
*P value indicates significant.

Table 4 ANCOVA model of AQ total score variation

	Sum of squares	$d.f.$	Mean of squares	F	Significance	η^2
Corrected model	5627.573	55	562.757	8.393	0.000	0.683
Intercept	1410.541	1	1410.541	21.037	0.000	0.350
Age	132.139	1	132.139	1.971	0.168	0.048
Sex	152.895	1	152.895	2.280	0.139	0.055
Education	153.379	3	917.459	0.762	0.522	0.055
Borderline personality disorder	917.459	1	917.459	13.683	0.001	0.260
MDQ	44.945	1	44.945	0.670	0.418	0.017
SCID-II	54.827	1	54.827	0.818	0.371	0.021
BSI	102.646	1	102.646	1.531	0.223	0.038
AQ-total score	2807.590	1	2807.590	41.872	0.000	0.518
Error	2615.007	39	67.051	–	–	–
Total	40 045.000	50	–	–	–	–
Corrected total	8242.580	49	–	–	–	–
$R^2=0.683$ (corrected $R^2=0.601$)						

AQ, Aggression Questionnaire; BSI, Brief Symptom Inventory; MDQ, Mood Disorder Questionnaire; SCID-II, Structured Clinical Interview for DSM-II.

temporal pattern of mood swing episodes, types and trigger factors of impulsive behaviors, psychotic dimension, and longitudinal course (onset and prognosis) of disease have been targeted as the main parameters useful to distinguish the two diagnoses (Hatchett, 2010; Biskin and Paris, 2012; di Giacomo *et al.*, 2017). It is also true that although distinguishing BD type I from BPD is generally less problematic, reflecting the severity and frequent psychotic nature of manic symptoms, the differential diagnosis of BD type 2 from BPD can be particularly difficult, especially in the event of few hypomanic symptoms, prevalence of mixed features, and ultra-rapid or ultradian cycling (Zimmerman and Morgan, 2013).

In the present study, patients with BD type I/BPD showed significantly higher mean scores for the total scale of AQ and on PA and H subscales in comparison with pure BD patients; levels of impulsivity between the two groups were instead found to be similar. These findings are partially in line with previous studies (Henry *et al.*, 2001; Wilson *et al.*, 2007). In particular, a recent study by Carpiniello *et al.* (2011) reported that patients with a primary diagnosis of BD (type 1 or type 2) and additional BPD obtained significantly higher scores on both the AQ and the BIS-11 scales compared with those with bipolar alone or with any other concomitant personality disorder. Furthermore, bipolar patients with a borderline component reported a higher rate of suicide attempts in their history compared with the other two groups. Thus, a particular prominence of impulsivity and aggressiveness in the clinical picture of a patient with BD should lead to the suspicion, often overlooked in the common medical practice (Zimmerman and Mattia, 1999), of a comorbid borderline personality disorder. Undoubtedly, detection of this specific subgroup of patients appears to be of considerable importance even to address the increased risk for self-injuries and harmful behaviors, already related to the single disorder.

In treating patients with both BD and BPD, clinicians have to rely on scarce literature evidence on the preferable pharmacotherapy option.

To our knowledge, very few studies have been carried out so far to evaluate the efficacy of some drugs in treating this comorbidity. In a 6-month controlled study of Frankenburg and Zanarini (2002), which included 30 BPD patients with comorbid BD type II, prominent effects of valproate (plasma levels were in 50–100 g/ml) were detected on interpersonal sensitivity, anger, hostility, and aggressiveness. Preston *et al.* (2004), instead showed that lamotrigine was effective in reducing borderline dimensions in bipolar patients who qualified for a concomitant diagnosis of BPD after a retrospective evaluation. In terms of antipsychotic use in this particular clinical context, there is only a very recent case-report of a patient with a BD/BPD comorbidity, complicated by substance abuse, who experienced a significant improvement after off-label prescription of aripiprazole long acting injection therapy, although changes in specific symptom dimensions were not evaluated (Martinez and Caballero, 2017).

Different from the above-mentioned studies, our open-label trial evaluated exclusively the efficacy of asenapine as an adjunctive drug in improving the control of impulsive–aggressive behaviors in BD type I patients – with or without a comorbid BPD – who were already taking psychotropic medications (in particular mood stabilizers) as a therapeutic strategy.

After 12 weeks of administration, asenapine was proven to be effective in reducing impulsivity and aggressiveness levels in both subgroups of patients.

We recorded a significant decrease for each subdimension of aggressiveness (PA, VA, A, H) and for impulsivity, irrespective of concomitant BPD. However, after controlling for confounding baseline factors, the magnitude of variations was influenced by BPD co-diagnosis. Borderline component was associated negatively with total aggressiveness and H score decrease, but correlated positively to PA score reduction.

Indeed, among patients presenting a significant response (considered as a 50% score reduction in the proper subscale) in reduction of the physical aggressiveness component, we found a higher percentage of patients with comorbid personality disorder. Instead, percentages of responders in all remaining subscale did not differ significantly between the two groups.

This finding may be related to the ability of asenapine to target typical features of borderline personality involved in triggering physical aggressive behaviors. We may assume that asenapine – probably because of its antipsychotic properties – may exert a modulating effect on specific BPD features involved in physical impulsive–aggressive acts, such as reality distortion, affect instability, and feelings of emptiness as shown in a recent study by Martín-Blanco *et al.* (2014). Among these borderline traits, the feeling of emptiness appears to be involved in eliciting self-mutilations and para-suicidal ideation, and it has been reported as mostly unresponsive to treatment (Stoffers *et al.*, 2010).

However, the opposite finding of a lesser magnitude of variation in total aggressiveness score in BD type I/BPD sample may be interpreted considering the BPD component as an additional obstacle to drug efficacy in modulating these dimensions. Furthermore, it probably implies a different selectivity of asenapine in targeting physical aggressiveness-related neural mechanisms (Blake and Grafman, 2004; Siever, 2008), compared with nonphysical ones, although further investigations are needed to clarify this aspect. A resistance of BPD patients in achieving a satisfying improvement in aggressiveness control was also reported in a study carried out to evaluate the efficacy and tolerability of asenapine in comparison with olanzapine, the most broadly studied antipsychotic in BPD. Although asenapine and olanzapine were shown to have a similar efficacy, with a superiority of asenapine in treating affective instability, neither drug significantly improved aggressive symptoms, but an analysis accounting for each single subcomponent of the aggressiveness dimension was not carried out.

A beneficial use of asenapine in reducing physical aggressiveness was also recently shown in a prospective naturalist pilot study carried out on a sample of hospitalized psychiatric patients with different diagnoses and a current history of aggressive behavior (Amon *et al.*, 2017). Among the patients

included in the study, those receiving asenapine, irrespective of diagnosis, experienced a greater reduction in the level of aggressive or disruptive behavior than patients receiving treatment as usual, but this reached statistical significance only for PA. However, no patient with comorbid or pure BPD was included in that study.

In our study, asenapine showed a good tolerability and safety profile, with no patient experiencing EPS or weight gain.

These findings represent further confirmations of the quite benign safety profile of asenapine, with limited effects on body weight and metabolism (Shahid *et al.*, 2009; Tarazi and Stahl, 2012). This does not constitute a simple secondary advantage considering the impact of fattening and body image changes on discontinuation of therapy by BD and BPD patients (Zittel and Westen, 2005; Torrent *et al.*, 2008; Shrivastava and Johnston, 2010).

Limitations

There are many limitations that must be taken into consideration when interpreting our results.

First of all, this is an open-label study and it cannot be compared with a randomized-controlled trial where randomization and allocation concealment protect from various biases. Indeed, our baseline scores differ significantly between groups. Lack of sufficient numbers of patients made it impossible to match patients with and without borderline traits. Moreover, our small sample might be not sufficient to highlight differences in scale score variations between the two groups, even if they may be present.

Second, a systematic administration of clinical evaluation is missing. Finally, the role of concomitant medication was not analyzed and might affect asenapine response.

The strength of this study is the sample homogeneity, by recruiting only patients clinically judged to be in the euthymic phase and considered to be in stable remission, whereas different polarity of the current episode is a factor that can influence the expression of aggressiveness and impulsivity. The same remark can be made on the exclusion of patients affected by comorbid alcohol and/or drug abuse/dependence, considering the high prevalence of those in patients similar to ours.

Conclusion

An accurate clinical definition of comorbidity between BD and BPD is extremely important as the two conditions require different therapeutic modalities, respectively, a mood stabilizer and a cognitive-behavioral psychotherapy being prioritized. Misdiagnosis can deprive the patient of potentially effective treatment or conversely lead to unnecessary and improper pharmacological prescription. A qualitative and quantitative evaluation of impulsive and aggressive behaviors in BD patients may help clinicians when there is a reasonable suspicion of a comorbid BPD, especially during the euthymic phases of disease. At the same time, the presence of comorbidity might be an opportunity to differentiate psychopathological assets that belong to each condition. Furthermore, given the burden of impulsivity and aggressiveness in the morbidity and mortality associated with these disorders, in the pharmacotherapy approach, clinicians should consider drugs able to specifically target these dimensions without jeopardizing other treatment outcomes. Our results suggest a promising role of asenapine in managing.

Aggressive–impulsive behaviors in bipolar patients, with or without comorbid BPD, posing itself as suitable alternative to other SGA commonly used in these conditions, especially because of its safety and tolerability profile.

Further studies are still needed to increase the level of evidence and to assess the efficacy of asenapine during the active phases of BD. Finally, as described in the limitations of the study, it is necessary to conduct methodologically superior trials to moderate the effect of cofounding variables.

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Conflicts of interest

There are no conflicts of interest.

Disclosure

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