Antipsychotics in the Treatment of Impulsivity in Personality Disorders and Impulse Control Disorders

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Abstract: In the last years, second generation antipsychotics have shown to be useful in the treatment of disorders with predominant impulse dyscontrol symptoms, in particular borderline personality disorder (BPD) and impulse control disorders (ICDs).

The present review aims to provide a comprehensive examination of data from randomized controlled trials (RCTs), open label studies, and case reports concerning efficacy and safety of atypical antipsychotics in treating symptoms of impulsivity in BPD and ICDs.

Empirical evidences in favor of these pharmacological agents are generally promising, but still initial and heterogeneous among different drugs. Data concerning clozapine are limited in BPD as well as in ICDs, as they usually derive from samples with concomitant psychotic symptoms or disorders. Concerning risperidone and its metabolite paliperidone, only few studies considered the effects on impulsive-aggressive behaviors in BPD patients**.** Some RCTs found that risperidone was effective against disruptive behaviors in adolescents, suggesting it could be tried in treating ICDs, such as intermittent explosive disorder. Quetiapine was found efficacious to control impulsivity in several open label studies of BPD and in one case report of trichotillomania (TTM). Ziprasidone has been poorly investigated in the treatment of impulsive-behavioral dyscontrol and the only RCT performed in BPD patients produced no significant effects on borderline psychopathology.

At present, more solid and encouraging evidences of efficacy in treating impulsive disturbances of BPD have been provided from several RCTs of olanzapine and from fewer controlled studies of aripiprazole. Olanzapine was also found effective in a single RCT of TTM patient, while it has obtained controversial results in other ICDs. Aripiprazole also produced some benefit in the treatment of TTM, but findings are limited to case-reports.

Further large-scale well-designed investigations are required to replicate and complete these data.

Keywords: Antipsychotics, personality disorders, borderline personality disorder, impulse controlled disorders, trichotillomania, pathological gambling, skin picking, intermittent explosive disorder, efficacy, adverse effects.

INTRODUCTION

The concept of impulsivity can be defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli, without regard to the negative consequences to the impulsive individual or to others [1]. Impulsive behaviors are related to risk taking, lack of planning, and making up one's mind quickly and includes decreased inhibitory control and intolerance of delay to rewards [2, 3].

In the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision [4], several psychiatric disorders include impulsive dyscontrol symptoms in diagnostic criteria. According to Zanarini's concept of impulsive spectrum, spanning both Axis I and II, personality disorders (PDs) and impulse control disorders (ICDs) share a common impulsivity trait and PDs often co-occur in patients with ICDs [5-7]. Concerning PDs, impulsive behavioral dyscontrol is more strictly related to facets of Cluster B than cluster A and C personality disorders.

Although some differences must be considered, impulsivity is a shared dimension underlying traits of all Cluster B personality disorders, borderline personality disorder (BPD), antisocial personality disorder (ASPD), narcissistic personality disorder (NPD), and histrionic personality disorder (HPD) and represents the primary determinant of their natural history and outcome [8-10]. Impulsive behaviors are also the core feature of ICDs that are defined as "difficulty to resist urges and behaviors that are excessive and/or harmful to oneself or others" [4]. This group includes intermittent explosive disorder (IED), kleptomania (KM), trichotillomania (TTM), pyromania, and pathological gambling (PG). Other disorders have been proposed for inclusion: skin picking, compulsive buying, compulsive internet using, and non-paraphilic compulsive sexual behavior, which are now classified under the category of ICD not otherwise specified.

In the last years, the role of impulsivity in psychiatric disorders has received increasing attention for its relevance in terms of clinical presentation and therapeutic implications. In fact, impulsive behavioral dyscontrol has been identified

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as a target dimension of pharmacotherapy. Studies concerning efficacy and indications of second-generation antipsychotics are rapidly growing and there is some evidence that these drugs are effective for treating impulsivity in several psychiatric disorders [11, 12]. Given the ability of new generation antipsychotics to modulate dopamine and serotonin neuronal systems (dual mechanism of action) and the role of these neurotransmitters in modulating and controlling impulsivity, it is reasonable to investigate their effects in treating impulsive dyscontrol symptoms.

Despite the high prevalence rates of both PDs and ICDs in the general population [13] and in psychiatric patients [14], pharmacotherapy of these disorders has been relatively understudied and data concerning the use of atypical antipsychotics in impulse control disorders and personality disorders other than borderline personality disorder (BPD) are still sparse.

The aim of this review is to provide a complete account of the empirical evidences of efficacy and safety that are currently available for atypical antipsychotics in the treatment of impulsivity in personality disorders and impulse control disorders. Randomized controlled trials (RCTs), open label studies, and case reports have been systematically searched for in the Medline database provided by the U.S. National Library of Medicine. Data from these trials and reports will be presented and discussed for each antipsychotic agent. Drugs are ordered according the date of their introduction in Italy.

CLOZAPINE

Personality Disorders

A few open-label studies designed to investigate the use of clozapine in BPD patients have been performed [15-18], but only two trials [16, 17] and two case reports [19, 20] examined the efficacy of this drug on impulsivity and aggression.

In the first prospective study, Benedetti and colleagues [16] administered a low dose of clozapine (ranged from 25 to 100 mg/day; average: 43.8 mg/day) to 12 BPD patients for 16 weeks. This therapy led to the improvement of main psychopathological dimensions: impulsivity, affective instability, and cognitive-perceptual symptoms. In the second trial, Chengappa and colleagues [17] treated with clozapine (300-550 mg/day) up to 1 year 7 BPD women with psychotic symptoms, severe self-mutilating behaviors and aggression, resistant to previous treatment with other antipsychotics. According to literature data, self-mutilating behaviors are commonly related to high levels of impulsivity [21-23]. After clozapine treatment patients showed significant reduction of self-mutilating acts, seclusion and hetero-aggressive behaviors. The two case-reports confirm these findings. Ferrerri and colleagues [19] reported that clozapine up to 300 mg/day stopped self-injuries in a case of woman with severe BPD. More recently, Vohra [20] described a significant improvement in impulsive, aggressive, and self-mutilating behaviors in one BPD patient treated with clozapine at the dose of 175 mg/day (Table **1**).

Impulsive Control Disorders

The therapeutic use of clozapine in impulse control disorders has been scarcely studied.

Neither RCTs, nor open trials are available. Three case reports collected by Rotondo and colleagues [24] have tested the use of this drug in patients with Parkinson's disease who developed pathological gambling after treatment with dopamine agonists. In these cases PG persisted despite the discontinuation of dopamine agonists and SSRIs, but remitted in two of the three patients after adjunctive treatment with clozapine. The first case described a marked improvement of PG symptoms after 4 weeks of treatment with clozapine at the dose of 37.5 mg/day. The second patient was treated with clozapine at the dose of 50 mg/day and maintained the remission of PG during 6 months of follow-up. In the third patient, a slightly higher dose of clozapine (75 mg/day) did not succeed in treating PG (Table **1**).

RISPERIDONE

Personality Disorders

Among cluster B PDs, risperidone has been reported to be effective in the treatment of impulsivity of both BPD and ASPD patients. In particular, one double blind, placebo-controlled trial [25], three open-label trials [26-28] and one case-report [29] evaluated the efficacy of this drug in patients with a diagnosis of BPD. In one case-report risperidone was tested in ASPD [30].

Results of the controlled study conducted by Schulz *et al.* [25] were partly effective. In fact, the 8-week trial performed in 27 BPD patients receiving risperidone (mean dosage: 2.5 mg/day) or placebo indicated that the active drug was not more effective in improving global functioning and impulsive-behavioral symptoms (measured with Barratt Impulsivity Scale; BIS-11), while it significantly decreased psychoticism, paranoid ideas, phobic anxiety, and interpersonal sensitivity (measured with HSCL-90). Rocca and colleagues [26] obtained more favorable findings in an 8-week open-label study of risperidone (mean dose of 3.27 mg/day) in 15 BPD patients. BPD symptoms, including impulsive and aggressive behaviors, depressive symptoms and global functioning improved after treatment in the 13 patients who completed the study. Concordant results were found in the open trial performed by Friedel and colleagues [27]. Risperidone was administered at the mean final dose of 1.8 mg/day in 18 BPD patients, who reported a significant improvement in the behavioral dimensions of the Borderline Disorder Rating Scale (BDRS): impulsivity, affective dysregulation, cognitive-perceptual impairment and disturbed relationships. In the same year, Díaz-Marsá and colleagues [28] investigated the efficacy of long-acting injectable risperidone in 20 BPD patients refractory to previous therapies, who were treated for a 6 months period. Findings showed a significant improvement in global symptomatology and functioning, impulsive aggressiveness, and anxiety.

Two case reports, the first in a patient with BPD [29], the second in a case of ASPD [30], specifically investigated the efficacy of risperidone on symptoms of impulsivity and aggressiveness. The first [29] reported decrease of impulsive

Table 1. Case reports, open-label studies, and double blind controlled trials of clozapine in the treatment of cluster B personality disorders and impulse control disorders.

Drug and Study	Dose	Method	Treatment Duration	Sample	Findings
CLOZAPINE					
Frankenburg and Zanarini, 1993 [15]	253.3 mg/day	open trial	9 months	15 BPD patients with psychotic symptoms	↓ psychotic symptoms, ↓ global symptoms, ↑ social functioning
Benedetti *et al.*, 1998 [16]	25-100 mg/day	open trial	16 weeks	12 BPD patients with psychotic symptoms	↓ psychotic symptoms
Chengappa *et al.*, 1999 [17]	300-550 mg/day	open trial	12 months	7 BPD patients with resistant psychosis	↓ auto/hetero aggression, ↓ abuse behaviors
Parker *et al.*, 2002 [18]	175-550 mg/day	open trial	3 years	8 BPD patients with psychotic symptoms	↓ psychotic symptoms, ↑ social functioning
Ferrerri *et al*., 2004 [19]	300 mg/day	case report	4 weeks	1 BPD female	↓ self-mutilating behaviors
Vohra, 2010 [20]	175 mg/day	case report	8 weeks	1 BPD female	↓ self-harming behaviors, ↓ depressive symptoms
Rotondo *et al.*, 2010 [24]	37.5-75 mg/day	case report	4 weeks (case 1), 6 months (case 2)	3 PG in Parkinson's disease	improvement of PG (case1), remission of PG (case 2), no effects on PG (case 3)

Abbreviations: BPD: borderline personality disorder; PG: pathological gambling; ↓ decrease of; ↑ increase of.

symptoms associated with self-mutilating behaviors in a patient with BPD treated with up to 4 mg/day of risperidone. The second [30] found that this antipsychotic (at the dose of 3 mg/day) produced remission of severe aggression and impulsivity in a man with diagnosis of ASPD throughout 6 months of follow up (Table **2**).

Impulse Control Disorders

In the last decade, multiple studies [31-37] have supported the efficacy of risperidone in the treatment of intermittent explosive disorder (IED). We have to notice that these studies have been conducted in patients with impulsive-aggressive behaviors, rather than with a specific diagnosis of IED. Nevertheless, the presence of impulsive aggression within the core facets of IED allows us to include these trials in our review.

The first double-blind study conducted by Findling and colleagues [31] showed that risperidone (0.25-1.5 mg/day) was superior to placebo in ameliorating impulsive aggression in 20 youths with conduct disorder during a period of 10 weeks. Similar findings were reported in another RCT [33] performed in 13 adolescents with behavioral disturbances treated with risperidone (mean dose of 1.2 mg/day) for 4 weeks. Buitelaar and colleagues [34] administered risperidone (mean dose of 2.9 mg/day) to control impulsivity and aggression in hospitalized adolescents with disruptive behaviors and low IQ in a 6 week RCT. The Authors found a significant improvement of global symptoms and decrease of impulsive aggression measured with the Overt Aggression Scale-Modified (OAS-M).

The efficacy of risperidone on impulsive behavioral dyscontrol in patients with conduct disorder was later confirmed by other Authors [32, 35-37]. All these studies have been performed in similar samples of young patients with disruptive behavior disorder. The conduct problem subscale of the Nisonger Child Behavior Rating Form (NCBRF) was used to measure the improvement of disruptive behaviors. The results showed that risperidone (mean dose of 1.16-1.5 mg/day) was more effective than placebo in the acute phase therapy [35, 36], as well as in relapse prevention [32, 36, 37].

Concerning other ICDs, risperidone has been tested only in four patients with trichotillomania (TTM) [38, 39] and in two cases of pathological gambling with Parkinson's disease. Epperson and colleagues [38] treated three patients successfully by adding risperidone (0.5 to 3 mg/day) to treatment of TTM refractory to SSRIs, while Sentürk & Tanriverdi [39] showed the efficacy of this drug (2 to 4 mg/day) alone in a woman with TTM previously unsuccessfully treated with pharmacotherapy and psychotherapy.

With the same approach as clozapine, risperidone has been tested in patients with Parkinson's disease who have developed pathological gambling during dopaminergic drugs administration. Gschwandtner and colleagues [40] showed that two male patients with Parkinson's disease and PG had a noticeable decrease in impulse behavioral dyscontrol in a few months of treatment with risperidone [41] (Table **2**).

OLANZAPINE

Personality Disorders

Several investigations on olanzapine in the treatment of impulsive aggression dimension in BPD are available, while studies are strikingly absent from other personality disorders. Three RCTs investigated the effects of olanzapine compared with placebo.

Zanarini and Frankenburg [42] performed a 6-month trial of olanzapine (mean dose of 5.33 mg/day) in 28 females with BPD. Patients were recruited if they did not meet current criteria for major depression or lifetime criteria for schizophrenia, schizoaffective disorder, or bipolar disorder and if they did not consume any psychotropic medications. Authors found that

Table 2. Case reports, open-label studies, and double blind controlled trials of risperidone in the treatment of cluster B personality disorders and impulse control disorders.

Drug and Study	Dose	Method	Treatment Duration	Sample	Findings
RISPERIDONE					
Khouzam and Donnelly, 1997 [29]	4 mg/day	case report	11 months	1 BPD female	↓ impulsivity, ↓ self-mutilating behaviors
Schulz *et al.*, 1998 [25]	2.5 mg/day	double blind versus placebo	8 weeks	27 BPD patients	↓ psychotic symptoms, ↓ paranoid ideation, ↓ phobias, ↓ interpersonal sensitivity
Hirose, 2001 [30]	3 mg/day	case report	6 months	1 ASPD male	↓severe aggression, ↓ impulsivity
Rocca *et al.*, 2002 [26]	3.27 mg/day	open trial	8 weeks	15 BPD patients, 2 drop-outs	↓ aggressive behaviors, ↓ affective instability
Friedel *et al.*, 2008 [27]	1.8 mg/day	open trial	8 weeks	18 BPD patients	↓ affective instability, ↓ impulsivity, ↓ cognitive impairment
Díaz-Marsá *et al.*, 2008 [28]	long-acting risperidone	open trial	6 months	12 BPD patients refractory to previous therapies	↓ anxiety, ↓ aggressiveness, ↓global symptomatology, ↑ social functioning
Findling *et al.*, 2000 [31]	0.25-1.5 mg/day	double blind versus placebo	10 weeks	20 youths with conduct disorder	↓ aggressiveness
Van Bellinghen and De Troch, 2001 [33]	1.2 mg/day	double blind versus placebo	4 weeks	13 adolescents with behavioral disturbances and low IQ	↓ aggressiveness
Buitelaar *et al.*, 2001 [34]	2.9 mg/day	double blind versus placebo	6 weeks	hospitalized adolescents with disruptive behaviors	↓global symptomatology, ↓ impulsive aggression
Aman *et al.*, 2002 [35]	1.16 mg/day	double blind versus placebo	6 weeks	118 children with disruptive behaviors and low IQ	↓ aggressiveness
Findling *et al.*, 2004 [32]	1.51 mg/day	open trial	48 weeks	107 children with disruptive behaviors	↓ aggressiveness
Croonenberghs *et al.*, 2005 [36]	1.5 mg/day	open trial	52 weeks	504 children with disruptive behaviors and low IQ	↓ aggressiveness
Reyes *et al.*, 2006 [37]	0.02 mg/kg per day	double blind versus placebo	6 months	335 children and adolescents with disruptive behaviors	↓global symptomatology, ↓ impulsive aggression
Epperson *et al.*, 1999 [38]	0.5-3 mg/day	open trial, risperidone in addition to SSRI		3 patients with SSRI-refractory TTM	↓ hair pulling
Sentürk and Tanriverdi, 2002 [39]	2-4 mg/day	case report	8 months	1 TTM female	↓ hair pulling
Gschwandtner *et al.*, 2001 [40]		case report		2 patients with PG in Parkinson's disease	improvement of PG symptomatology

Abbreviations: BPD: borderline personality disorder; ASPD: antisocial personality disorder; PG: pathological gambling; trichotillomania: TTM; ↓ decrease of; ↑ increase of.

olanzapine was a safe and effective agent in the treatment of all four core-areas of borderline psychopathology (assessed with the Symptom Checklist-90-Revised; SCL-90-R): impulsivity, affect, cognition, and interpersonal relationships. Concerning impulsivity, less encouraging findings were presented by Bogenschutz and Nurnberg [43] who designed a 12-week study to evaluate the efficacy of olanzapine (5-10 mg/day) versus placebo in 40 BPD outpatients free of psychotropic drugs for at least two weeks. Exclusion criteria were the same as the study by Zanarini and Frankenburg [42]. The results indicated that patients treated with olanzapine improved more than placebo-treated subjects in global borderline psychopathology measured with the Clinical Global Impression (CGI) scale modified for BPD, from the fourth week and continuing to 12 weeks, while impulsive aggression measured with OAS-M did not improve significantly. The more recent multicenter RCT performed by Schulz and colleagues [44] on 314 outpatients with BPD compared olanzapine (2.5-20 mg/day) with placebo during a period of 12 weeks. This study demonstrated no effect of this drug on BPD symptoms assessed by Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD), OAS-M, and SCL-90-R. However, they found that the time to response was shorter for olanzapine (effect size: 0.03) and suggested that possible causes for a lack of advantage of this antipsychotic compared with placebo may have been secondary to underdosing in this participant sample.

On the contrary, Zanarini and colleagues [45] outlined favorable results of olanzapine on impulsive behavioral dyscontrol. A 12-week randomized, double blind, placebo-controlled trial in 451 outpatients with BPD and with no co-diagnosis was conducted. Actually, this investigation included two RCTs that compared olanzapine with placebo: in one study

[45] patients received a fixed dose (low dose: 2.5 mg/day, or moderate dose: 5-10 mg/day) of olanzapine, while in the other [46] olanzapine was administered at a variable dose (2.5 to 20 mg/day). Findings from the variable-dose study have already been discussed [44]. In the fixed-dose study [45], both low and moderate doses groups improved more than controls in terms of symptoms of irritability (OAS-M) and suicidality/self-mutilating behaviors (ZAN-BPD), while only moderate dose (5-10 mg/day) of olanzapine showed significantly greater mean reductions on anger, affective instability, and paranoid ideation or dissociation (ZAN-BPD, effect size = 0.29). Also in this study the time to response was significantly shorter for subjects consuming olanzapine 5-10 mg/day than for patients treated with placebo.

In recent years, other investigations considering combinations of olanzapine with another active drug or with psychotherapy have been published. Zanarini and colleagues [46] performed an 8-week, randomized, double blind study to compare the efficacy of fluoxetine (10 mg/day), olanzapine (2.5 mg/day), or the olanzapine-fluoxetine combination (2.5 mg + 10 mg) with respect to impulsive-aggression behavior and mood symptoms in 45 female BPD patients with no current major depressive disorder. In this trial there was no placebo control group. The results showed a significant improvement in impulsive aggression measured with OAS-M and in affective symptom of chronic dysphoria assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) with all three compounds. However, olanzapine monotherapy and olanzapine-fluoxetine combination were found superior to fluoxetine monotherapy to ameliorate both symptom areas of BPD.

Successively, two RCTs [47, 48] compared olanzapine to placebo in a combined treatment with dialectical behavioral therapy (DBT) obtaining similar findings. In the first 12-week study [47], 60 BPD outpatients with no comorbid Axis I disorders were treated with olanzapine or placebo and received a concomitant psychotherapy with DBT. Soler and colleagues found that DBT combined with olanzapine (mean dosage of 8.83 mg/day) resulted in significantly larger improvements in impulsivity, aggression, depressive symptoms, and anxiety, as well as a nonsignificant trend toward less self-injuring/suicidal behavior. In the following trial with a similar design, Linehan and colleagues [48] included 24 women outpatients with BPD, who were randomly assigned to receive olanzapine (mean dose: 5 mg/day) plus DBT or placebo plus DBT for 21 weeks. Authors found that both groups presented a considerable improvement of irritability (effect size: 0.8), aggression (effect size: 0.5), self-injury (effect size: 1.5), and depressive symptoms (effect size: 0.2). Irritability and aggression scores (measured with OAS-M) decreased more quickly in the olanzapine group (Table **3**).

Impulse Control Disorders

Olanzapine is the most extensively studied antipsychotic in the treatment of ICDs. To data three RCTs were performed: two studies [49, 50] have tested the use of olanzapine in PG subjects, and one trial [51] investigated the efficacy of this drug in treating TTM. Concerning PG both studies suggested that olanzapine provide no more benefit than placebo, while the data for TTM were more persuasive. Fong and colleagues [49] performed a 7-week double blind, placebo-controlled trial in 23 pathological gamblers, whose primary gambling activity was video-poker. Findings reported consistently reduced gambling urges, gambling behavior (measured with the Breksville Gambling Craving Scale; BGCS and the Desire to Gamble; DES), impulsive behavior (measured with BIS-11) and improved mood state; however olanzapine (2.5-10 mg/day) was not associated to significantly ameliorated outcomes over placebo. In the same year, McElroy and colleagues [50], conducted a 12-week, flexible-dose trial to investigate the efficacy of olanzapine (2.5-15 mg/day) in the treatment of 42 outpatients with PG. In order to avoid the possibility that this drug was treating pathological gambling secondary to mania, subjects with bipolar I disorder were excluded. According to previously mentioned study olanzapine was not found superior to placebo in reducing PG behaviors measured with the Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS).

On the other hand, a 12-week RCT [51] outlined a significant improvement on measure of TTM severity (Yale-Brown Obsessive Compulsive Scale for Trichotillomania; TTM-YBOCS) in 25 patients with TTM, who received olanzapine at the mean dose of 10.8 mg/day. These findings confirmed the results of a previous 3-month open-label study performed by Stewart & Nejtek [52] in 18 patients with TTM treated with olanzapine (ranged from 2.5 mg to 10 mg/day). In this investigation, Authors showed a significant improvement in hair pulling measured by the Massachusetts General Hospital Hair Pulling Scale.

In addition to the above studies, some case reports on olanzapine augmentation of fluoxetine in subjects with TTM or pathological skin picking (PSP) have been published [53-55]. Three patients with TTM [53, 55] and one patient with pathological skin picking [54] who had not any improvement in their symptoms with fluoxetine alone were treated with olanzapine (2.5-10 mg/day) in addition to fluoxetine (40-80 mg/day) and showed an important decrease of repetitive TTM behaviors or psychogenic excoriation during and after the treatment (Table **3**).

QUETIAPINE

Personality disorders

Several open label studies and case reports on the efficacy of quetiapine in BPD patients are available, but no RCTs have been published, yet.

Adityanjee and Schulz [56] tested the efficacy of quetiapine (25-300 mg/day for 8 weeks) in 10 patients with diagnosis of BPD. Authors reported a significant improvement of impulsivity evaluated with the BIS-11 and other parameters including hostility, global symptomatology, and social functioning. The same Authors performed a second trial [57], administering an average dose of 286.1 mg/day of quetiapine to 16 BPD subjects. Only nine patients completed the entire 8-week trial. Impulsive behaviors and global symptomatology obtained a significant degree of amelioration, confirming the data of the first study.

Table 3. Case reports, open-label studies, and double blind controlled trials of olanzapine in the treatment of borderline personality disorders and impulse control disorders.

Drug and Study	Dose	Method	Treatment Duration	Sample	Findings
OLANZAPINE					
Zanarini and Frankenburg, 2001 [42]	5.33 mg/day	double blind versus placebo	24 weeks	28 BPD females	↓anger, ↓interpersonal sensitivity, ↓anxiety, ↓ paranoid ideation, ↑ global functioning, effect size: 0.03
Zanarini *et al.*, 2004 [46]	fluoxetine (Fl) 10 mg/day, olanzapine (Ol) 2.5 mg/day	double blind, Fl versus Ol versus Ol + Fl	8 weeks	45 BPD females with no affective disorders	both Ol and Ol +Fl > Fl on impulsive aggression and depression
Bogenschutz and Nurnberg, 2004 [43]	5-10 mg/day	double blind versus placebo	12 weeks	40 BPD patients	↓anger, ↓global symptoms
Soler *et al.*, 2005 [47]	5-20 mg/day	double blind versus placebo	12 weeks	60 BPD patients treated with DBT	↓anxiety, ↓depression, ↓impulsive-aggression
Schulz *et al.*, 2008 [44]	2.5-20 mg/day	double blind versus placebo	12 weeks	314 BPD patients	no significant differences for generic symptoms, ↓ BPD severity faster in the olanzapine group
Linehan *et al.*, 2008 [48]	5 mg/day	double blind versus placebo	21 weeks	24 BPD females treated with DBT	no significant differences for generic symptoms, ↓ irritability and aggression, faster in the olanzapine group, effect sizes: 0.5-0.8
Zanarini *et al.*, 2011 [45]	2 dose groups: low dose: 2.5 mg/day; moderate dose: 5-10 mg/day	double blind versus placebo	12 weeks	451 BPD	↓ anger, affective instability, paranoid ideation and dissociation (only moderate dose) ↓ irritability and suicidality symptoms (low and moderate doses)
Fong *et al.*, 2008 [49]	2.5-10 mg/day	double blind versus placebo	7 weeks	23 patients with PG	↓gambling urges, ↓ gambling behaviors, ↓ impulsive behaviors, improvement of mood state. However, no statistical differences with placebo
McElroy *et al.*, 2008 [50]	2.5-15 mg/day	double blind versus placebo	12 weeks	42 outpatients with PG	no statistical differences with placebo
Potenza *et al.*, 1998 [53]	fluoxetine 40 mg/day olanzapine 5-10 mg/day	case report	39 weeks	1 patient with TTM resistant to SSRI monotherapy	↓ hair pulling
Stewart and Nejtek, 2003 [52]	2.5-10 mg/day	open trial	3 months	12 patients with TTM	↓ hair pulling, ↓ anxiety
Christensen, 2004 [54]	fluoxetine 40 mg/day olanzapine 5 mg/day	case report	6 months	1 PSP patient resistant to SSRI monotherapy	↓ hair pulling
Srivastava *et al.*, 2005 [55]	fluoxetine 60-80 mg/day olanzapine 2.5-5 mg/day	case report	8 weeks (case 2)	2 young patients with TTM resistant to SSRI monotherapy	↓ hair pulling
Van Amerigen *et al.*, 2010 [51]	10.8 mg/day	double blind versus placebo	12 weeks	25 patients with TTM	↓ hair pulling

Abbreviations: BPD: borderline personality disorder; TTM: trichotillomania; PG: pathological gambling; PSP: pathological skin picking; DBT: dialectical-behavior therapy; ↓ decrease of; ↑ increase of.

A further replication of these results was provided by, Villeneuve and Lemelin [58] in a 12 week open-label study. They administered quetiapine (mean daily dose 251 ± 50 mg; range 175-400 mg) to 23 outpatients who met criteria for BPD, obtaining a considerable reduction of impulsivity, hostility, anxious and depressive symptoms, and a significant improvement of social functioning.

A positive effect of quetiapine on impulsivity was found also by the Authors of this review [59] in a 12-week pilot study. Fourteen BPD patients were treated with a mean dose of 309 ± 83.12 mg/day of this antipsychotic. The 11 patients who completed the trial showed not only a significant change of global symptoms, anxiety and social functioning, but also a considerable improvement of the items "impulsive behaviors" and "outbursts of anger" of the BPDSI.

More recent indications on the effects of quetiapine in BPD patients were published by Perrella and colleagues [60] and Van den Eynde and colleagues [61]. In the first 12-week open-label trial [60], 29 patients with diagnosis of BPD were treated with quetiapine at an average dose of 540 mg/day (400-800 mg/day). Authors found a favorable clinical impact of quetiapine on hostility and suspiciousness (assessed with the BPRS), aggressive symptoms (measured with the Aggression Questionnaire, AQ), and depression. The second 12 week study [61] found that quetiapine (100-800 mg/day) produced effects on different domains of impulsivity in a sample of 41 BPD out- and in-patients. In fact, the results indicated a significant change of attention, motor, and cognitive domains of impulsivity measured with the BIS-11.

However, not all the studies are concordant on the anti-impulsive effects of quetiapine. Roepke and colleagues [62] did not find any significant improvement of impulsivity measured with the BIS-10 (German version) in a 8 week open-label trial testing the efficacy of quetiapine at a fixed daily dose of 400 mg in 15 patients with diagnosis of borderline, histrionic, or narcissistic PDs.

In two case reports of severe BPD patients quetiapine was found effective on the dimension of impulsive dyscontrol symptoms [63]. In the first case, the Authors observed a gradual reduction of self-harm behaviors in a

Table 4. Case reports and open-label studies of quetiapine in the treatment of cluster B personality disorders and impulse control disorders.

Drug and Study	Dose	Method	Treatment Duration	Sample	Findings
QUETIAPINE					
Adityanjee and Schulz, 2002 [56]	25-300 mg/day	open trial	8 weeks	10 BPD patients, 4 drop-outs	↓ impulsivity and hostility, ↑ global functioning
Hilger *et al.*, 2003 [63]	400-800 mg/day	case report	6 months	2 BPD patients	↓ impulsivity and auto-aggression, ↑ level of functioning
Villeneuve and Lemelin, 2005 [58]	175-400 mg/day	open trial	12 weeks	34 BPD patients, 11 drop-outs	↓ impulsivity / hostility, ↓ anxiety / depression, ↑ social functioning
Bellino *et al.*, 2006 [59]	200-400 mg/day	open trial	12 weeks	14 BPD patients, 3 drop-outs	↓ impulsivity / outbursts of anger, ↓ anxiety, ↑ global symptoms, ↑ social functioning
Perrella *et al.*, 2007 [60]	400-800 mg/day	open trial	12 weeks	29 BPD patients, 3 drop-outs	↓ hostility and aggressiveness, ↓ depressive symptoms and suspiciousness, ↑ level of functioning
Adityanjee *et al.*, 2008 [57]	286.1 mg/day	open trial	8 weeks	16 BPD patients, 5 drop-outs	↓ impulsivity, ↑ social functioning
Roepke *et al.*, 2008 [62]	400 mg/day	open trial	8 weeks	15 patients with a diagnosis of cluster B personality disorders (borderline, histrionic, or narcissistic)	no efficacy for the treatment of impulsivity, but positive effects on depressive symptoms
Van den Eynde *et al.*, 2008 [61]	100-800 mg/day	open trial	12 weeks	41 BPD patients, 9 drop-outs	↓ impulsivity / anger, ↓ affective instability, ↓ anxiety / depression
Walker *et al.*, 2003 [64]	600-800 mg/day (case 3: gabapentin 300 mg/day and paroxetine 20 mg/day in addition); (case 4: nefazodone 200 mg/day and trazodone 75 mg/day)	case report		4 ASPD patients	↓ impulsive behaviors, ↓ impulsive suicide attempts, ↓ hostility and aggression
Khouzam *et al.*, 2002 [65]	200 mg/day	case report	3 months	1 patient with TTM	↓ urge frequency, ↓ urge intensity, ↑ self-control over hair pulling

Abbreviations: BPD: borderline personality disorder, ASPD: antisocial personality disorder; TTM: trichotillomania; ↓ decrease of; ↑ increase of.

BPD woman treated with 400 mg/day of quetiapine for 6 months. In the second report, they found that a high dose of quetiapine (800 mg/day) produced a significant improvement of both impulsive and psychotic symptoms.

In a recent study, Walker and colleagues [64] tested the efficacy of quetiapine (600-800 mg/day) in 4 patients with ASPD. They obtained a relevant goal: to relieve or reduce the most harmful and destructive manifestations of ASPD, such as impulsive behaviors, impulsive suicide attempts, hostility and aggression. Quetiapine was associated with a mood stabilizer (gabapentin) in patients with prominent affective instability and with antidepressants in patients with depressive symptoms (Table **4**).

Impulse Control Disorders

The literature about the treatment of ICDs with quetiapine is really poor: our review found only one case report concerning the therapeutic management of trichotillomania [65].

A woman with hair pulling, after failures of different medications, was treated with quetiapine at the daily dose of 200 mg for 3 months. Her hair pulling behavior was assessed on a weekly basis using the Massachusetts General Hospital Hair Pulling scale. After 21 days of treatment the urge frequency, urge intensity and self-control over urges considerably decreased, and on day 45 the patients scored zero in all subscales (Table **4**).

ARIPIPRAZOLE

Personality Disorders

A single RCT evaluated the efficacy of aripiprazole for patients with BPD [66]. To our knowledge, no data on this drug in the treatment of other personality disorders have been published. In the 8-week RCT, 57 patients with BPD randomly received aripiprazole (15 mg/day) or placebo. Authors found that the active drug therapy led to significant improvements in impulsive behavioral dyscontrol, affective symptoms and cognitive perceptual symptoms, measured with the SCL-90. Aripiprazole-treated patients were also found less likely to engage in self-mutilating acts. The same Authors [67] published the results of an 18 months follow-up observation and confirmed the results of the first trial in the continuation phase.

Similar findings were also reported in a 12-week open-label study [68], in which we tested the efficacy of aripiprazole (10-15 mg/day) augmentation of ongoing sertraline therapy (100-200 mg/day) in 21 refractory BPD patients. Aripiprazole augmentation improved overall borderline psychopathology and was found selectively effective on impulsivity, measured with the BIS-11, and on cognitive-perceptual symptoms (dissociation and paranoid ideation) (Table **5**).

Impulse Control Disorders

Concerning ICDs, only two case reports of TTM patients treated with aripiprazole are available. Both reports showed the efficacy of this drug in reducing hair plucking. In the first case [69], a patient with treatment resistant TTM received aripiprazole (15 mg/day) with cessation of TTM behavior. This result was maintained for a period of 2 years. In the second case [70], aripiprazole (5 mg/day) was added to clonazepam (2 mg/day) in a woman with restless legs syndrome and TTM and produced the complete remission of symptoms (Table **5**).

ZIPRASIDONE

Personality Disorders

Only one RCT [71] was performed to investigate the efficacy of ziprasidone in treating BPD, which found no favourable effect. Authors administered ziprasidone at the mean dose of 84 mg/day during 12 weeks in 60 BPD patients selected from clinical services (outpatients and psychiatric emergency services). Impulsivity, cognitive perceptual symptoms, and affective symptoms were assessed with the BIS-11, the BPRS, and the SCL-90, but the trial failed to show a significant change of any scale. In particular, no differences were found with regard to the frequency of impulsive or aggressive behaviors and self-injuring/suicidal conducts (Table **5**).

Impulse Control Disorders

To date no studies regarding the use of ziprasidone in the treatment of ICDs have been performed.

PALIPERIDONE

Personality Disorders

In the last years, several clinical trials investigated the efficacy of paliperidone ER in treating positive and negative symptoms, depression and anxiety and uncontrolled hostility in patients with schizophrenia [72-75]. Only sparse data are available regarding the use of this antipsychotic in the treatment of personality disorders. We have recently published the results of a 12-week pilot study evaluating 18 BPD outpatients who received 3-6 mg/day of paliperidone ER [76]. In addition to the improvement of global psychopathology and cognitive distortion, our findings outlined that paliperidone ER produced significant effects on dyscontrol of impulsivity and anger measured with the BIS-11 and the BPDSI items (Table **5**).

Impulse Control Disorder

One case report concerning the use of paliperidone in treating pathological skin picking has been published [77]. A PSP patient who had obtained only limited improvement with fluoxetine titrated to 80 mg/day achieved the complete remission of skin picking behavior (measured with the Skin Picking Scale) after the addition of paliperidone 3-6 mg/day for eight weeks (Table **5**).

Adverse Effects

Second generation antipsychotics have been associated to the onset of several adverse effects, with noticeable differences among different drugs. The most of available data derive from studies on schizophrenia, while data on

Table 5. Case reports, open-label studies, and double blind controlled trials of ziprasidone, aripiprazole, and paliperidone in the treatment of borderline personality disorders and impulse control disorders.

Drug and Study	Dose	Method	Treatment Duration	Sample	Findings
ZIPRASIDONE					
Pascual *et al.*, 2008 [71]	84 mg/day	double blind versus placebo	12 weeks	16 BPD	no significant effects
ARIPIPRAZOLE					
Nickel *et al.*, 2006 [66]	15 mg/day	double blind versus placebo	8 weeks	57 BPD patients, 4 drop-outs	↓depression / anxiety ↓anger, ↓aggressiveness, ↓paranoia, ↑ global functioning
Nickel *et al.*, 2007 [67]	15 mg/day	follow up study	18 months	26 BPD patients	long-term efficacy
Bellino *et al.*, 2008 [68]	10-15 mg/day augmentation of ongoing sertraline therapy (100-200 mg/day)	open trial	12 weeks	21 drug-refractory BPD patients	↓ impulsivity, ↓ cognitive-perceptual symptoms, ↓ overall psychopathology
Jefferys and Burrows, 2008 [69]	15 mg/day	case report	24 months	1 patient with resistant TTM	cessation of hair-plucking
Virit *et al.*, 2009 [70]	aripiprazole 5 mg/day clonazepam 2 mg/day	case report	3 months	1 patient with TTM and restless legs syndrome	complete remission of symptoms
PALIPERIDONE					
Bellino *et al.*, in press [76]	3-6 mg/day	open trial	12 weeks	18 BPD patients, 4 drop-outs	↓ impulsivity / anger, ↓ cognitive-perceptual symptoms, ↓ overall psychopathology
Spiegel and Finklea, 2009 [77]	paliperidone 3-6 mg/day fluoxetine 80 mg/day	case report	8 weeks	1 PSP patient	complete remission of skin picking behavior

Abbreviations: borderline personality disorder: BPD; TTM: trichotillomania; PSP: pathological skin picking; ↓ decrease of; ↑ increase of.

personality disorders and impulse control disorders are sparse.

The use of clozapine in clinical practice has been limited because of infrequent but serious side effects, including eosinophilia, seizures, myocarditis, diabetes, metabolic syndrome, fever, constipation, ileus, urinary incontinence. The risk of severe granulocytopenia and agranulocytosis in about 1% of treated patients determines the need for repeated count of white cells and neutrophil granulocytes during treatment period. Also sedation, excessive salivation, orthostatic dizziness, and weight gain are common and sometimes impairing adverse effects during clozapine treatment [16-19]. The only way to deal with the current underuse of clozapine is full awareness of its side effects and competence to minimize their severity and consequences [78].

Risperidone has been associated with a higher incidence of extrapyramidal symptoms than other second generation antipsychotics, due to the high affinity for D2 post-synaptic receptors. In particular, the comparisons of risperidone with olanzapine and ziprasidone confirmed the dose effect of risperidone on extrapyramidal symptoms [79]. Other common adverse reactions of risperidone are weight gain and hyperprolactinemia. Sleepiness, fatigue, headache, and dizziness are also reported, but are usually mild and well tolerated [26-28].

Patients treated with olanzapine showed an increased risk of developing hyperglycemia and diabetes. This risk may be related to the effects of olanzapine on appetite and weight gain, although there are some of metabolic changes in the absence of weight gain. Olanzapine may also cause significant increases of triglycerides and total and LDL cholesterol. In general, this drug is related to a rise in incidence of metabolic syndrome. Metabolic effects and increased weight seem to be dose related events [47]. Other effects, such as somnolence, sedation, and fatigue are commonly reported.

Quetiapine exhibits a rather favourable adverse event profile and does not usually induce appreciable modifications of physical and laboratory parameters. However, quetiapine blockade of the histaminic and adrenergic receptors can produce sedation and dizziness. Histaminic blockade is also linked to weight gain. This may be one reason of the increased cardiovascular risk reported in some patients treated with quetiapine [80]. The rate of

extrapyramidal symptoms is much lower with quetiapine than other antipsychotics [79].

The most common side effects of aripirazole are headache, nausea, numbness, insomnia, and anxiety. Aripiprazole appears to provoke less weight gain than other second generation antipsychotics. A few studies reported that weight, waist circumference, low-density lipoprotein, fasting glucose, and triglycerides decreased significantly in patients switched from olanzapine to aripiprazole [81, 82]. Substantial decreases in several metabolic risk factors were also found in patients switched from quetiapine. Trials of BPD patients confirmed that aripiprazole was not responsible for significant changes of weight or other metabolic factors [66-68].

Among adverse effects observed with ziprasidone, dizziness, uneasy feeling, and gastrointestinal symptoms were rather common [71]. A lengthening of the QTc interval may occur in some patients and increases the risk of a potentially lethal type of arrhythmia known as torsades de pointes.

Paliperidone ER has similar side effects than risperidone and is associated with increases in serum prolactin levels and extrapyramidal symptoms [87, 88]. Incidence of Parkinsonism and akathisia and use of anticholinergic medications increase in a dose-related manner. Other common adverse events associated with paliperidone ER were insomnia, gastrointestinal disturbances, and tachycardia.

In conclusion, second generation antipsychotics are related to a variable incidence of metabolic adverse effects, including severe weight gain, type II diabetes mellitus, hyperglycemia, dyslipidemia, insulin resistance, cardiovascular disease, hyperprolactinemia, and hypertension [83-85]. The risk of weight gain is high with clozapine and olanzapine, moderate with quetiapine, low with risperidone, and minimal with aripiprazole and ziprasidone [83]. Therefore, treatment with atypical antipsychotics can result in side effects that produce an increase in morbidity. This risk should suggest clinicians carefully considering their off-label use [86]. Thus, drugs with a lower incidence of metabolic effects can be considered a better option to treat patients with personality disorders and impulse control disorders.

New generation antipsychotics can also be responsible for cases of tardive dyskinesia and rare, but life-threatening, neuroleptic malignant syndrome.

CONCLUSIONS AND FUTURE PERSPECTIVES

In last years classical neuroleptics have largely been superseded by second generation antipsychotics, which have broader therapeutic indications. In addition to a strictly defined antipsychotic and antimanic effect, newer antipsychotics are indicated as mood stabilizers in the long-term treatment of bipolar disorders.

Although there is not a general consensus on the choice of specific pharmacological agents, some second-generation antipsychotics have shown to be useful in treating mental disorders with prominent impulsive behavioral dyscontrol, particularly borderline personality disorder and impulse control disorders. Information regarding the use of these drugs is increasing, but data from RCTs are still limited and the most of findings derive from open trials or case reports.

Forthcoming research on antipsychotics in treatment of impulsive behavioral dyscontrol should focus on a series of core topics: controlled trials of drugs tested in open-label case series; large-scale multi-center RCTs in order to replicate initial findings in small samples; drug-to-drug comparisons to explore differential effects on symptom dimensions; fixed-dosage and long term studies to determine appropriate doses and duration of treatments; careful examination of proper modalities to combine pharmacotherapy and psychotherapy.

Another noticeable and debated issue is that BPD and ICDs present a frequent comorbidity with other personality disorders and/or with Axis I disorders, including mood disorders, anxiety and somatoform disorders, substance-related disorder, eating disorders and sometimes transient psychotic symptoms. At the moment, investigators do not have a shared approach to the problem of comorbidity when they decide inclusion criteria for clinical trials. Some authors retain that is preferable to include patients with Axis I or II comorbidity, in order to collect data of efficacy and tolerability that can be reliably applied to everyday practice. Other investigators prefer to define stricter exclusion criteria, as they consider comorbidity as a relevant bias that limits validity of findings.

In summary, available evidences in favor of the efficacy of new antipsychotics to treat impulsive disturbances in PDs and ICDs are generally encouraging, but very heterogeneous among different drugs and sometimes controversial. For instance, data concerning the effects of clozapine in BPD were mainly collected in samples of patients with co-occurring psychotic symptoms and do not allow to assess specific effects on core BPD pathology. Studies about risperidone and its metabolite paliperidone in BPD were mainly focused on cognitive-perceptual symptoms and only in few cases considered the effects on impulsive-aggressive behaviors**.** Some data from RCTs indicated that risperidone is useful in treating adolescents with disruptive behavior disorders. These indications can be cautiously extended to ICDs, such as intermittent explosive disorder. Quetiapine was found efficacious to control impulsivity in open label studies of BPD and in one case report of TTM, but reliability of findings is reduced by lack of controlled trials. Ziprasidone has been poorly investigated in impulsive-behavioral dyscontrol. Although this drug is indicated in disorders with high degree of impulsivity, as bipolar disorders, it was evaluated only in one RCT of BPD patients and produced no significant effects.

At the present state of knowledge, more solid and promising data of efficacy in the treatment of BPD derive from RCTs of olanzapine and aripiprazole. These investigations indicated that olanzapine and aripiprazole may be effective in reducing impulsive-behavioral dyscontrol symptoms. Olanzapine was also found effective in a controlled trial of patients with trichotillomania, while it obtained controversial results in other ICDs. Aripiprazole also showed to produce some benefit in trichotillomania, but data are limited to case-reports.

Clinical meta-analyses and practice guidelines are available only for treatment of BPD, but not for ICDs. The American Psychiatric Association (APA) treatment guidelines [89, 90] provided three separate algorithms targeted at the main symptom dimensions of BPD, affective dysregulation, impulsive-behavioral dyscontrol, and cognitive-perceptual symptoms, but substantially recommended the choice of serotonergic antidepressants as first line therapy and limited the use of low-dose antipsychotics to refractory patients or to cases with prominent cognitive-perceptual symptoms. More recently, the British National Institute for Health and Clinical Excellence [91] has achieved less favorable conclusions on pharmacotherapy of BPD and do not recommend the use of drugs other than for mental disorders in comorbidity, especially mood disorders. The Cochrane Systematic Review [92] concluded that second generation antipsychotics, together with mood stabilizers and omega-3 fatty acids, have obtained some evidence of efficacy for treating specific BPD symptoms. Among second-generation antipsychotics, these authors considered aripiprazole the most promising drug having as robust effects as do the mood stabilizers. On the contrary, they outlined an increase in self-harming and suicidal behaviors in BPD patients receiving olanzapine. The reasons of this finding are not clear and an explanation is not provided in the Review. In our opinion, data on increase of suicidal conducts with the use of olanzapine could be explained by a selection bias in studies treating more severe patients or patients with peculiar clinical features. However, this risk cannot be ignored in clinical practice.

In conclusion, the role of second-generation antipsychotics in the treatment of disorders with impulse dyscontrol symptoms registered a growing interest in the last years. The empirical evidence is not robust yet, because studies suffer from considerable limitations and must be viewed as the first phase of a new research pathway. So, well-designed investigations are needed to replicate data and provide reliable recommendations for clinical practice.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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