Borderline personality disorder: current drug treatments and future prospects

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***Abstract*:** Individuals with borderline personality disorder (BPD) suffer from marked affective disturbance, an unstable sense of self, difficulty in interpersonal relationships and heightened impulsivity, leading to high rates of self-harm and suicide. Patients are often refractory to treatment and are at high risk for acute or dangerous presentations, with a serious impact on mental health services. There has been much debate on the effectiveness of pharmacotherapy in treating different facets of the psychopathology of the disorder. Several guidelines recommend the use of antidepressant agents, mood stabilizers for affective dysregulation and impulsive-behavioural dyscontrol, and antipsychotics for cognitive-perceptual symptoms. However, concerns have recently been raised regarding the strength of evidence for these treatment recommendations in BPD. Here, we review the evidence for efficacy of the main psychotropic medications used in BPD, drawing, in particular, on evidence from randomized controlled trials and meta-analyses. Overall, meta-analysis provides little evidence to support the use of antidepressant medication in BPD outside episodes of major depression. However, there is evidence for the use of both mood stabilizers and antipsychotic medications for the treatment of specific aspects of the disorder. Most existing studies have been conducted on small numbers of patients, and there is a requirement for further large-scale trials to substantiate these findings. In addition, given the limitations of current pharmacological treatment of BPD, there is a pressing need to investigate potential new therapeutic targets, including neuropeptides, such as the opioids and vasopressin, and drugs targeted at ameliorating the biological effects of early life stress.

***Keywords*:** antidepressants, antipsychotic medications, borderline personality disorder, mood stabilizers, epigenetics

Introduction

Borderline personality disorder (BPD) is a common and disabling psychiatric condition. Epidemiological studies suggest that 2% of the general population have BPD, and the condition is diagnosed in up to 15% of psychiatric inpatients and 50% of inpatients with a diagnosis of personality disorder [Torgersen *et al.* 2001; Widiger and Weismann, 1991]. BPD is a clinically heterogeneous condition, encompassing disturbances of affective regulation and impulsivity [Links *et al.* 1999], with symptom clusters of impulse-behavioural dyscontrol, cognitive perceptual symptoms and disturbed interpersonal interrelatedness [Skodol *et al.* 2002; American Psychiatric Association, 2001], as well as associated affective states including depression, anxiety, anger and tension [Coid, 1993]. Research on the management of BPD has been challenging; the multifaceted nature of the disorder [Clarkin *et al.* 1983] and comorbid diagnoses [Zanarini *et al.* 1998a, 1998b], mitigate against homogeneity in patient cohorts. In addition, heterogeneity in outcome measures and methodology across clinical trials mean that treatment efficacy is often difficult to assess [Mercer *et al.* 2009; Binks *et al.* 2006].

There is evidence that long-term psychotherapy can be a useful form of treatment in those with BPD [Zanarini, 2009; Davidson *et al.* 2006], and it is often preferred to pharmacological treatment due to reports of the limited efficacy of drug therapy [Zanarini, 2004]. Despite this, pharmacotherapy has been recommended as an adjunctive, symptom-targeted component of treatment

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[Oldham *et al.* 2004; American Psychiatric Association, 2001]. Previous meta-analyses have concluded that pharmacotherapy could exert a beneficial effect on certain core traits of BPD [Lieb *et al.* 2010; Mercer *et al.* 2009; Binks *et al.* 2006; Nose *et al.* 2006] and there is a growing body of evidence that different classes of agents, such as antidepressants, mood stabilizers, antipsychotics and neuroleptics, can be used in the treatment of specific symptoms [Abraham and Calabrese, 2008; Binks *et al.* 2006; Nose *et al.* 2006]. Polypharmacy is common [Lieb *et al.* 2004; Zanarini *et al.* 2001] but the use of multiple drugs is not evidence based, and is likely to reflect the failure of any one agent to provide adequate symptom amelioration.

A number of studies have been conducted to assess the efficacy of various medications in the management of patients with BPD. Here, we present a summary of randomized clinical trials (RCTs) of antidepressants, antipsychotics and mood stabilizers for the treatment of BPD.

Pharmacotherapy for BPD

Antidepressants

There is strong evidence that depressive symptoms are common in individuals meeting criteria for BPD. Previous studies have reported comorbidity rates between BPD and major depressive disorder of up to 61% [Comtois *et al.* 1999], with this figure rising to as high as 98% in hospitalized inpatients prior to treatment [Zanarini *et al.* 2003]. The suggestion that BPD is an atypical form of affective disorder led researchers to investigate the use of therapies aimed at treating the mood disorder in BPD [Kroll and Ogata, 1987]. The use of antidepressants in the management of BPD has been investigated for decades, and evidence supporting their effectiveness in treating BPD has ranged from case reviews [Pinto and Akiskal, 1998] to double-blind, randomized and controlled trials [Simpson *et al.* 2004; Rinne *et al.* 2002; Coccaro and Kavoussi, 1997; Soloff *et al.* 1993; Parsons *et al.* 1989; Cowdry and Gardner, 1988].

Selective serotonin reuptake inhibitors (SSRIs) have been widely appraised as being amongst the first-line therapies in the pharmacological management of BPD [American Psychiatric Association, 2001]. However, trials of these agents have demonstrated only modest differences compared with control groups [Simpson *et al.* 2004; Zanarini *et al.* 2004; Rinne *et al.* 2002; Coccaro and Kavoussi, 1997; Salzman *et al.* 1995]. Indeed, in one study, a negative effect for depression was observed in patients who received concurrent treatment with dialectical behavioural therapy and fluoxetine [Simpson *et al.* 2004], and another study was confounded by substantial dropout rates of up to 60% in SSRI recipients [Coccaro and Kavoussi, 1997].

The evidence for antidepressant treatment in BPD has recently been investigated in a Cochrane systematic review and meta-analysis of randomized trials [Lieb *et al.* 2010]. In this study, little evidence was found for the value of several commonly prescribed antidepressants in BPD, including SSRIs, mianserin and the monoamine oxidase inhibitor, phenelzine. The only antidepressant medication shown to have a positive effect on BPD symptoms outside episodes of major depression was amitriptyline, a tricyclic antidepressant [Lieb *et al.* 2010]. However the use of amitriptyline in BPD, a condition associated with a substantial risk of impulsive self-harm, is limited by its severe toxicity in overdose.

Mood stabilizers and anticonvulsants

BPD is associated with marked affective instability and high rates of self-harm. In general psychiatric practice, mood stabilizers have been used effectively to treat affective disorders, such as bipolar illness, and to decrease suicidal behaviours [Saunders and Hawton, 2009]. This has led to the investigation of the utility of mood stabilizers to treat core symptoms of BPD, such as affective instability and impulsivity.

Initial placebo-controlled trials of lithium in patients with emotionally unstable character disorder provided evidence of improvement in global functioning and mood [Rifkin *et al.* 1972], although subsequent studies in BPD failed to demonstrate the therapeutic efficacy of lithium use [Links *et al.* 1990]. The pharmacological profile of lithium also prevents it being used in first-line management, with a high risk of toxicity on overdose.

Trials that have investigated the efficacy of carbamazepine have yielded mixed results. Although a relatively early placebo-controlled trial in 16 BPD patients reported a significant decrease of impulsivity measures [Cowdry and Gardner, 1988], no significant positive effects of carbamazepine was reported in a more recent, similarly

designed trial of 20 patients [De la Fuente and Lotstra, 1994]. Overall, therefore, the present findings do not support the use of carbamazepine in BPD [Lieb *et al.* 2010].

Stronger evidence exists for the use of the mood stabilizers topiramate, lamotrigine and valproate semisodium in BPD. Topiramate and lamotrigine have both been shown in small RCTs to be effective in the treatment of symptoms of aggression in BPD [Nickel *et al.* 2005, 2004; Tritt *et al.* 2005]. In addition, there is evidence from one placebo-controlled trial of a broader effect of topiramate in treating other symptoms of BPD, including interpersonal problems and anxiety [Loew *et al.* 2006]. Two small RCTs have demonstrated efficacy for divalproex sodium in the treatment of BPD [Hollander *et al.* 2001], or BPD with comorbid bipolar II disorder [Frankenberg and Zanarini, 2002]. Improvements were seen in these studies on global function [Hollander *et al.* 2001], and measures of interpersonal sensitivity and hostility and aggression [Frankenberg and Zanarini, 2002].

Antipsychotic medications

Antipsychotics are widely used in BPD, as they are believed to be effective in improving impulsivity, aggression, anxiety and psychotic symptoms [Nose *et al.* 2006; American Psychiatric Association, 2001]. Evidence supports their use in the treatment of cognitive-perceptual symptoms [Herpertz *et al.* 2007]. However, the common occurrence of adverse side effects in this class of medications means that they are often preferred for the treatment of acute relapses only [Díaz-Marsá *et al.* 2008; Newton-Howes and Tyrer, 2003; Benedetti *et al.* 1998; Teicher *et al.* 1989]. The most commonly studied antipsychotic, olanzapine, has been found to reduce impulsivity, hostility, affective instability and psychotic symptoms in BPD [Lieb *et al.* 2010; Soler *et al.* 2005; Zanarini *et al.* 2004; Bogenschutz and Nurnberg, 2004; Hallmayer, 2003], although it is associated with metabolic side effects, which may limit its tolerability [Reynolds and Kirk, 2010; Kantrowitz and Citrome, 2008]. A more limited literature supports the use of aripiprazole and haloperidol in BPD, the latter especially for symptoms of anger [Lieb *et al.* 2010].

Future perspectives and therapeutic opportunities

In current clinical practice, there is a broad spectrum of pharmacotherapeutic interventions used for the symptomatic treatment of BPD, as demonstrated above. However, the evidence base for the usage of these treatments remains generally limited [Lieb *et al.* 2010], and further progress will require: (a) larger trials of existing agents; (b) the development of novel, specific drugs to use in BPD. The latter will involve a critical appraisal of possible underlying biological contributions to the development of the disorder. A number of theoretical models have been proposed, each emphasizing a different aspect of the disorder [Crowell *et al.* 2009; Siever, 2008; Zanarini and Frankenburgh, 2007; Siever and Davis, 1991]. Models of altered biological function merit further investigation for their role in BPD, particularly if considered as candidates for possible therapeutic targets. Exploring these new avenues for treatment is particularly important for BPD, as current approaches are far from satisfactory [Kendall *et al.* 2009], and do not lead to remission of the disorder. On this background, there has been recent interest in the role of neuropeptide systems, such as the opioids and vasopressin, and in the role epigenetic modifications following early life stressors; the relevance of each is reviewed below.

Opioid dysfunction in BPD

Brain opioids play an important role in behaviour, mediating social effect in the context of isolation and exclusion [Bodnar, 2009]. Dysregulation of the endogenous opioid system has been implicated in nonsuicidal self-harm [Tiefenbacher *et al.* 2005; Schmahl *et al.* 2002], interpersonal vulnerabilities and social attachments [Panksepp *et al.* 1978], all of which are implicated to some degree in the clinical spectrum of BPD. Evidence for this has been demonstrated in human studies, revealing altered opioid neurotransmission associated with negative affect [Zubieta *et al.* 2003, 2002], altered opioid levels in patients with a history of self-harm [Stanley *et al.* 2009; Sandman *et al.* 1997; Coid *et al.* 1983], and genetic single nucleotide polymorphisms in the μ-opioid receptor gene associated with identity disturbance [Stanley and Siever, 2010].

These studies have important research and treatment implications. The use of opioid antagonists to ameliorate self-harming behaviours has had some success [Casner *et al.* 1996; Kars *et al.* 1990], although the strength of evidence for their use in BPD is limited by the fact that patients included in both studies did not have BPD, and by the retrospective study design [Casner *et al.* 1996].

Future investigations into the potential efficacy of medications that act on the opioid system will be valuable in advancing the treatment of BPD.

Vasopressin activity in BPD

Vasopressin is also implicated in social behaviour and aggression as demonstrated by animal studies using vasopressin antagonists and receptor knockouts [Caldwell *et al.* 2008; Bielsky *et al.* 2004]. In human studies, its has been observed that vasopressin concentration in the cerebrospinal fluid is positively correlated with disinhibited aggression, including patients with BPD [Coccaro *et al.* 1998], and that administration of intranasal vasopressin increases the perception to threat in response to neutral stimuli [Thompson *et al.* 2004], which is consistent with the tendency of patients with BPD to interpret neutral faces as potentially threatening [Putnam and Silk, 2005].

It has been suggested that, in the context of close interpersonal relationships, the predisposition towards enhanced irritability and aggression in BPD patients is partially explained by increased vasopressin concentrations [Stanley and Siever, 2010]. As such, vasopressin antagonists may be helpful in the management of BPD, as has been proposed previously for major depressive disorder [Schüle *et al.* 2009].

Epigenetic reprogramming and valproate

Evidence supports the causal relationship between early life stressors, such as childhood maltreatment, and the development of BPD, with up to 70% of patients reporting major childhood trauma [Ball and Links, 2009]. The outcome of early life stress is the modification of limbic brain structure [Hall *et al.* 2010; Nunes *et al.* 2009], sensitization of stress hormone responses [Carrasco *et al.* 2007] and changes in neurotransmitter levels [Leyton *et al.* 2001; Soloff *et al.* 2000]. There has been recent interest in the role of epigenetic modifications to explain the persisting effects of early life stress many years after the environmental challenge has passed.

Environmental stressors, such as early life adversity, can lead to sustained changes in gene expression through epigenetic modification of DNA sequences. Such epigenetic processes include DNA methylation and posttranslational modification of histone proteins [Handel *et al.* 2010; Szyf *et al.* 2008]. There is increasing evidence that developmental adversity can affect epigenetic patterns, with important implications for mental health in adulthood [McGowan and Szyf, 2010; Rutten and Mill, 2009; Szyf *et al.* 2007]. For example, there has been interest in developmental influences on vasopressin and its receptor and it appears that early social experience [Cushing and Kramer, 2005], manipulations of oxytocin [Yamamoto *et al.* 2004], and early maternal separation [Veenema *et al.* 2006] can modulate vasopressin through epigenetic mechanisms and gene expression [Stanley and Siever, 2010]. There has also been interest in the correlation between early social experience and changes in the methylation status of the promoter of the glucocorticoid receptor gene [Weaver *et al.* 2004].

A number of studies have shown that epigenetic modifications can be altered, and even reversed, in adult life [Weaver, 2007; Weaver *et al.* 2005]. Remarkably, recent studies have identified therapeutic benefits of histone deacetylase inhibitors, which alter the epigenetic modification of histones, for a diverse range of central nervous system disorders [Kazantsev and Thompson, 2008]. The recent discovery of the histone deacetylase inhibitory properties of sodium valproate [Göttlicher, 2004; Göttlicher *et al.* 2001] has been a significant, exciting advancement in the field [Nalivaeva *et al.* 2009; Santini *et al.* 2007]. Sodium valproate is currently the drug of choice in various neurological and psychiatric disorders [Haddad *et al.* 2009; Bowden, 2007], and its efficacy in BPD may be partly attributable to its ability to reverse epigenetic modifications and gene expression. This has potential implications for reversing the biological substrates of early childhood stress in the pathophysiology of BPD, and merits further exploration and investigation.

Overview

Although most qualitative, narrative reviews suggest that there is a promising role for medications in the treatment of BPD [Saunders and Silk, 2009; Abraham and Calabrese, 2008; Bellino *et al.* 2008; Díaz-Marsá *et al.* 2008; Grootens and Verkes, 2005; Lieb *et al.* 2004; Markovitz, 2004; Raj, 2004; Zanarini, 2004; Newton-Howes and Tyrer, 2003; Links *et al.* 2001; Soloff, 2000; Dimeff *et al.* 1999; Coccaro, 1998], several recent large-scale meta-analyses of these psychotropic agents in BPD have highlighted a number of limitations in the currently available evidence regarding the pharmacological treatment of BPD [Lieb *et al.* 2010; Mercer *et al.* 2009; Binks *et al.* 2006; Nose *et al.* 2006].

Evidence-based pharmacological treatment guidelines for BPD are still in their infancy and larger scale trials of promising treatments, such as divalproex sodium, are urgently needed. In addition, there is ground for future advances in the field through the study of novel potential therapeutic agents, such as drugs targeting neuropeptide systems and therapies aimed at specifically ameliorating the biological consequences of early life adversity. It is to be hoped that by conducting well-designed preclinical studies and clinical trials, we can achieve a greater understanding of the biological basis of the disorder and advance the treatment of its core symptoms.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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