Psychopharmacologic treatment of borderline personality disorder

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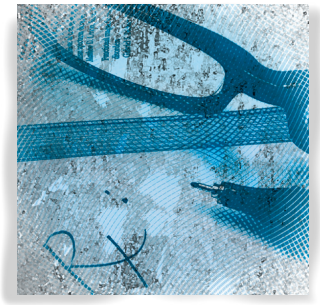

The best available evidence for psychopharmacologic treatment of borderline personality disorder (BPD) is outlined here. BPD is defined by disturbances in identity and interpersonal functioning, and patients report potential medication treatment targets such as impulsivity, aggression, transient psychotic and dissociative symptoms, and refractory affective instability. Few randomized controlled trials of psychopharmacological treatments for BPD have been published recently, although multiple reviews have converged on the effectiveness of specific anticonvulsants, atypical antipsychotic agents, and omega-3 fatty acid supplementation. Stronger evidence exists for medication providing significant improvements in impulsive aggression than in affective or other interpersonal symptoms. Future research strategies will focus on the potential role of neuropeptide agents and medications with greater specificity for 2A serotonin receptors, as well as optimizing concomitant implementation of evidence-based psychotherapy and psychopharmacology, in order to improve BPD patients' overall functioning.

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Introduction

Various theoretical orientations have converged upon the conceptualization of borderline personality disorder (BPD) as a disturbance in mental representations of self and other, contributing to core difficulties in identity, intimacy, empathy, and self-directed motivation.[1-3] In BPD, this core psychopathology contributes to the characteristic syndrome of impulsivity, aggression, suicidality, transient dissociation or psychosis, affective instability, chronic emptiness, identity diffusion, and tumultuous interpersonal dysfunction oscillating between idealization and devaluation.[4] BPD symptoms are most severe in the context of interpersonal stressors such as perceived rejection or abandonment. Affective dysregulation and impulsive aggression often contribute to self-destructive behavior,[5] with worsening symptoms, frank dissociation, and worsening suicidality occurring in the context of interpersonal stressors.[6-8] The prevalence of BPD may be as high as 5% to 6%, with high comorbidity with mood, anxiety, and substance abuse disorders.[9-10] Patients with BPD have suicide rates 50 times that of the general population[11] and utilize more mental health resources than individuals with other psychiatric disorders.[12,13]

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BPD arises in the context of variable interactions between specific genetic risk factors and developmental factors related to early care-giving, eliciting a pattern of psychopathological personality traits and potential differences in neurobiological functioning.[14-17] With the increasing recognition over the past several decades of the underlying neurobiology associated with BPD, treatment has shifted from the exclusive use of psychotherapy to the development of strategic approaches for evidence-based psychopharmacology. Although developmental heterogeneity and individual differences within BPD complicate general psychopharmacologic management strategies, BPD patients manifest persistent, intrapsychic pain and interpersonal hypersensitivity, subjectively experienced as aversive and/or aggressive reactions to what might otherwise be mild interpersonal stressors.

Not surprisingly, some BPD symptoms are more amenable to treatment than others. When patients are followed prospectively, *interpersonal affective* symptoms, such as intolerance of aloneness and conflicted feelings about dependency, are slowest to remit, while symptoms reflecting impulsive behavior, self-injury, and aggression tend to resolve more quickly.[18-21] Although impulsive aggression and suicidality are often acute presenting symptoms motivating concern and psychopharmacologic consultation, paradoxically, these symptoms may be most apt to resolve. Meanwhile, interpersonal affective symptoms reflective of core psychopathology persistently contribute to chronic functional impairment, intrapsychic pain, and difficulty maintaining social support.

Methods

The following review discusses the results of a search of the PubMed database, utilizing the MeSH terms "borderline personality disorder" or "borderline personality disorder: drug therapy" (with limits restricted to articles in English, on humans, clinical trials, and reviews). The focus is primarily on highest-level original research (ie, randomized controlled trials, either with placebo control or comparing multiple active medications). Moreover, this review adds studies published since the author's last comprehensive review of pharmacotherapy for personality disorders.[22] Additional, recently published systematic reviews add consensus data in the psychopharmacologic treatment of BPD.[23-29] The primary aim of this review is to present the most up-to-date, evidence-based clinical approach to psychopharmacologic management of BPD. Secondary aims include detailing current difficulties and future directions in research on BPD psychopharmacology.

General considerations

The evidence base for psychopharmacological treatment of BPD is limited by relatively small sample sizes, high rates of placebo response, and brief trial durations. Most trials in the past have lasted 3 months or less, or else suffered from high dropout rates.[30-31] Because of high comorbidity of BPD with Axis I disorders, subjects often report other disorders whose presence may complicate response to the study medication. Without this comorbidity, however, results would not be generalizable to clinical practice. BPD trials are also prone to high placebo response rates,[12,22,32] meaning that open-label trial data should be interpreted with caution. Nevertheless, clinicians can provide optimal evidence-based treatment by implementing the specific medications studied in randomized placebo-controlled trials, along with evidence-based psychotherapy.

An older literature characterized BPD subjects with a distinct diagnostic nosology,[33] or included subjects with highly comorbid or other personality disorder diagnoses.[34-40] Findings may therefore be difficult to apply to current practice. Clinicians should exercise caution in attempting to apply research findings to severely ill BPD patients, as many medication trials recruited only outpatients, who further were excluded if they expressed acute suicidality[30,41-43] or had made a recent suicide attempt.[44] Impulsive aggression has been targeted more effectively with medications relative to other symptoms, as evident in the conclusions of recent systematic reviews.[22-29] This suggests that these symptoms, though acutely dangerous, may be more amenable to treatment than identity and interpersonal dysfunction, whose functional neurobiology is less well understood. As noted above, impulsive aggression is more apt to resolve spontaneously, compared with interpersonal affective symptoms.[18-21]

There are no medications approved by the US Food and Drug Administration (FDA) for the treatment of BPD, and very limited data exist for any single medication improving overall BPD severity. This has led to symptom-based approaches to psychopharmacologic man-

agement, often resulting in unnecessary polypharmacy, despite little benefit from this in the main trial studying such a practice.[43] Instead, practicality dictates targeting patients' most distressing symptoms with the most efficacious and tolerable medications, and repeated evaluation of risks versus benefits of continued pharmacotherapy. Others interpret limitations in the evidence base to advocate use of medication only during crises.[45] Coordination between psychopharmacologist, psychotherapist, and others involved in patients' treatment is often necessary for targeted, timely intervention and ongoing re-evaluation of attendant risks versus benefits of treatment.

Several recent articles are considered only briefly here. An open-label comparison of sertraline and olanzapine in patients with BPD who were also receiving methadone maintenance treatment for opioid dependence[46] showed that both agents were effective, but comorbidity limited the findings' generalizability. Another study was a randomized, double-blind comparison of olanzapine and haloperidol, with both agents demonstrating similar efficacy but distinct side-effect profiles.[47] There have also been recent positive, open-label trials with duloxetine,[48] quetiapine,[49-52] oxcarbazepine,[53] the traditional herb *yi gan san*,[54] and other medications, but lack of randomized, double-blind methodology significantly limits applicability of these results. One could speculate about potential benefits of these medications on noradrenergic, serotonergic, γ-aminobutyric acid (GABA)-ergic, and glutamatergic neurotransmission. The lack of placebo control methodology and the propensity of BPD trials for high placebo response rates makes open-label trials difficult to interpret.

Antidepressants

Four attachment classifications have been identified in developmental research on the enduring impact of early attachment relationships on representations of self and others in relationships.[55] BPD is associated with a higher prevalence of the *disorganized* attachment classification,[56] characterized by dissociative lapses in reason with respect to significant past and present attachment relationships. Serotonergic genetic polymorphisms, mainly related to the serotonin transporter, are associated with disorganized attachment classification in the context of trauma and adverse care-giving environments.[17] Despite neurobiological evidence of a disturbance in serotonin signaling associated with BPD and associated phenomena such as impulsivity, aggression, and suicidality,[57-69] the clinical significance of these findings in terms of psychopharmacologic enhancement of serotonergic neurotransmission has recently been called into question. In contrast to the 2001 American Psychiatric Association (APA) guidelines for treatment of BPD,[70] recent systematic reviews have highlighted a limited role for antidepressants in the treatment of BPD, due to more modest therapeutic effects on these symptom domains relative to other medication classes.[23-26,29] Nevertheless, antidepressants are often used to treat commonly comorbid anxiety and mood disorders.

Selective serotonin reuptake inhibitors (SSRIs) have minimal effect on impulsive aggression in BPD, but may have modest effects in decreasing anxiety, depression, and possibly affective lability (the latter, particularly with fluvoxamine[71]). Older BPD trials showed lack of effectiveness of tricyclic antidepressants, likely because anticholinergic sequelae may worsen effortful control of

Medication	Dosing	Effects
MAOIs		
Phenelzine	15-90 mg/d	Improvements primarily in depression, impulsive aggression. Some patients experience uncomfortable activation.
Tranylcypromine	Mean dose 40 mg/d	Improvements primarily in affective symptoms, interpersonal sensitivity, but limited data.
SSRIs		
Fluoxetine	20-80 mg/d	Mild improvements in affective symptoms, anger, impulsive aggression. Effects may be pronounced in males, patients with high levels of impulsive aggression.
Fluvoxamine	150-250 mg/d	Mild improvement in affective instability, not impulsivity.
Paroxetine	20-40 mg/d	Possible decrease in suicidality without significant effect on depression, though limited data.

Table I. Antidepressants demonstrating efficacy in borderline personality disorder. MAOI, monoamine oxidase inhibitor; SSRIs, selective serotonin reuptake inhibitors

impulsivity, aggression, and suicidality.[22,72-74] Historically, monoamine oxidase inhibitors (MAOIs) have been considered the treatment of choice for patients with atypical depression characterized by rejection sensitivity and affective reactivity. Consistent with the high rates of rejection sensitivity associated with BPD,[75,76] MAOIs demonstrated robust improvements (particularly in aggression and anxiety) in older trials.[77-80] However, lower tolerability profiles of MAOIs and potential adverse reactions (eg, hypertensive crises during dietary indiscretion) have limited their utility for BPD patients with severe impulsivity or suicidality. Refer to *Table I* for a summary of pertinent positive findings within the antidepressant class.

Because antidepressants have not demonstrated significant high-level evidence of therapeutic benefit, these medications currently lack strong recommendations in treating BPD. Serotonin regulates amygdala hyperreactivity in BPD, thought to be a central neurobiological correlate of affective instability.[61] Interpersonal hypersensitivity in BPD may be associated with the combination of lack of amygdalar and psychophysiologic habituation to social affective stimuli on the one hand, and blunted empathic understanding of these stimuli on the other.[81] Nevertheless, current antidepressants may not efficiently target the receptors or mesocorticolimbic brain regions associated with clinically significant amygdala hyper-reactivity. Limited therapeutic effectiveness of antidepressants in BPD may be related to lack of serotonin receptor specificity, since 5-HT_{2A} but not 5-HT_{2C} antagonism is associated with decreasing impulsivity.[82,83] Complex, coordinated agonism and antagonism of 5-HT_{2A}, $_{-2C}$, and $_{-6}$ receptors is needed for adaptive, deliberate decision-making.[84] Similarly, pharmacologic alteration of 5-HT_{1A} signaling yields distinct effects on animal models of impulsive aggression, depending on brain regions targeted, whether signaling is tonic or phasic, and concomitant modulation by GABAergic, glutamatergic, or neuropeptide signaling.[85]

Antipsychotics

BPD patients demonstrate higher plasma and cerebrospinal fluid levels of the dopamine metabolite homovallinic acid.[22] Dopamine receptor genetic polymorphisms interact with traumatic attachment stressors to yield attachment insecurity and disorganization, thought to be central to development and intergenerational transmission of interpersonal dysfunction in BPD.[17] The functional neurobiology of attachment insecurity and disorganization remain unclear, but impulsivity and transient psychotic symptoms associated with BPD provide further evidence for targeting dopamine neurotransmission.

Dopaminergic signaling has distinct effects on cognition, reward processing, and impulsivity, depending on whether it affects D_1 or D_2 receptors, brain region, and tonic versus phasic patterns of synaptic release.[86] Older trials demonstrated significant improvements in anger for haloperidol, and suicidality for flupenthixol decanoate, as well as inconsistent effects on psychosis,[36,72] irritability, and affective symptoms.[22,72,77,78] Despite improvement with some classical neuroleptics on individual symptoms, the antipsychotic class as a whole was associated with worsening overall severity of BPD in a recent meta-analysis.[29] Classical neuroleptics may improve anger and impulsive aggression, but patients must be closely monitored for notable risks of extrapyramidal symptoms, tardive dyskinesia, and worsening overall functioning.

Atypical antipsychotics are prescribed more often, due to greater tolerability and broader therapeutic benefits associated with serotonergic and noradrenergic activity beyond classical neuroleptics' stronger D_2 receptor antagonism. Atypical antipsychotics are efficacious in the treatment of impulsive aggression.[23-27] Across trials, this therapeutic effect is driven primarily by olanzapine and aripiprazole.[31,43,44,87-93] These antipsychotics significantly improved affective instability, impulsivity, psychosis, and interpersonal dysfunction, leading to clinical consensus of breadth of efficacy in BPD.[22,28]

Despite one trial failing to establish statistically significant improvement with low-dose olanzapine,[91] a larger, multisite sample recently showed significant but modest decreases in *overall* BPD severity,[92] with further improvements seen in open-label continuation.[93] Similarly broad benefits are seen in trials of aripiprazole improving impulsivity, aggression, affective instability, self-injury, and interpersonal symptoms.[87-88] Aripiprazole has a long half-life and favorable metabolic profile, which may contribute to ease in administration and effectiveness. The coordinated serotonergic and dopaminergic activity of aripiprazole as a partial agonist at D_2 and 5-HT_{1A} receptors, and antagonist at 5-HT_{2A} receptors, may be more efficacious in treating impulsivity and aggression in BPD. Despite similar noradrener-

gic and serotonergic effects and favorable metabolic profile, ziprasidone has not proven efficacious in BPD.[94]
No studies have examined long-term risk versus benefit ratios associated with atypical antipsychotics in BPD. Dose ranges are typically lower than for primary psychotic disorders. Well-documented metabolic risks are associated particularly with olanzapine.[22,29,43,47,89-93] The only benefit of polypharmacy elicited in one randomized controlled trial with BPD patients is lower risk of metabolic side effects when patients were administered the combination olanzapine-fluoxetine, relative to olanzapine alone.[43] However, this effect has not been replicated sufficiently to recommend polypharmacy for this reason. High comorbidity of BPD with eating disorders[32,95] and obesity[96] indicates that treatment with atypical antipsychotics in this population should remain circumscribed to avoid long-term health risks. Refer to *Table II* for pertinent positive results within the class of antipsychotic medications.

Anticonvulsants

Affective symptoms associated with BPD, particularly those related to intolerance of aloneness and dependency, are refractory relative to impulsive aggression and self-injurious behavior.[18-21] Despite phenomenological similarity between BPD and the bipolar spectrum, characteristic, associated interpersonal and identity disturbances distinguish affective instability in BPD.[97-101] Although older studies indicated lithium as efficacious for BPD,[33,102] risks associated with toxicity or noncompliance and the need for frequent monitoring have limited its clinical utility.

Temporal aspects of affective instability in BPD appear to be similar to rapid-cycling variants of bipolar disorder, motivating more frequent use of other mood stabilizers. Despite early documentation of clinical benefit from carbamazepine, its efficacy in trials was inconsistent and possibly associated with worsening depressive symptoms.[103-105] Valproate, lamotrigine, and topiramate offer greater therapeutic benefits in treating affective instability and impulsivity in BPD.[22,29] As a class, anticonvulsant medications offer moderate-to-large effects on impulsive aggression, affective instability, and overall functioning, with potentially greater effect size than associated with atypical antipsychotic treatment.[25,27] Trials with topiramate suggest a broad spectrum of therapeutic benefit, particularly in anger and interpersonal functioning.[106-110] However, adverse cognitive sequelae may interfere with psychotherapy for some BPD patients, and potential weight loss may become troubling for patients with comorbid eating disorders. Lamotrigine treatment improves impulsivity, affective symptoms,[111] and aggression,[41,112] but it requires lengthy titration to avoid life-threatening rash and toxicity. Valproate appears to be particularly efficacious in BPD patients with prominent impulsive aggression, rather than affective instability.[113]
Table III shows pertinent positive results within the class of mood stabilizer/anticonvulsant medications. These medications stabilize excitatory neurotransmission, but they differ greatly in mechanism of action and effects on glutamatergic and GABAergic signaling, so specific mechanisms of therapeutic response in BPD remain unclear. The long-term risk versus benefit analysis for

Medication	Dosing	Effects
Classical neuroleptics		
Fluphenazine decanoate; flupenthixol depot	Variable	Improvements in suicidality, self-injurious behavior. Requires regular injections, limited data on effectiveness.
Haloperidol	Mean doses 3-7.8 mg/d	Improvements in paranoia, anger, possibly anxiety/affective symptoms. Superior to tricyclic antidepressant but not MAOI. Possibly worsening overall status due to worsening sedation, depression, side-effects.
Loxapine	Mean dose 14.5 mg/d	Improvements in depression and anger (relative to chlorpromazine), but limited data.
Thiothixene	Variable	Improvements primarily in cognitive-perceptual symptoms, psychoticism, but limited data.
Atypical antipsychotics		
Aripiprazole	15 mg/d	Improvements in affective symptoms, aggression, paranoia, overall functioning
Olanzapine	2.5-10 mg/d	Improvements in affective instability, impulsivity, aggression, interpersonal sensitivity, and overall borderline personality disorder severity. High risk of weight gain, metabolic effects.

Table II. Antipsychotics demonstrating efficacy in borderline personality disorder. MAOI, monoamine oxidase inhibitor

these medications in BPD needs to be determined case by case, particularly with respect to recognized risks of teratogenicity for women of child-bearing age.

Other medications

Alprazolam and other benzodiazepines are strongly discouraged in treating BPD, due to risks of worsening impulsivity and suicidality.[78] BPD patients may be at increased risk for benzodiazepine dependence, in an effort to self-medicate chronic, refractory affective symptoms by fostering dissociative symptomatology. Targeting noradrenergic signaling has been less frequently studied in psychopharmacological treatment of BPD. The α-adrenergic agonist clonidine proved effective in treating comorbid post-traumatic stress disorder (PTSD) and BPD, but this effect seemed specific to PTSD symptoms.[114] Consistent with increasing recognition of omega-3 fatty acids in mood stabilization, one trial demonstrated tolerability and efficacy of omega-three ethyl-eicosapentaenoic acid (EPA) supplementation, decreasing aggression and affective symptoms in patients with moderate to severe BPD.[43]

Neuropeptides

Recent psychopharmacological research in BPD has involved neuropeptides such as opioids and oxytocin, which modulate broadly-distributed neural networks associated with coordinating complex behavior. Other relevant neuropeptides include vasopressin and neuropeptide Y. Recent neurobiological research has suggested endogenous opioid modulation as a potential avenue for treatment of BPD.[115-116] Endogenous opioid signaling is involved in consummatory reward processing, pain modulation, social affiliation,[117] rejection sensitivity, and maternal-infant attachment,[118-119] which may have implications for impulsivity, self-injurious behavior, and interpersonal dysfunction in BPD. Dysregulated opioid signaling is also associated with affective instability in BPD.[120] Despite promise in terms of potential implications in the developmental psychopathology of BPD, opioid medications have not demonstrated consistent therapeutic benefit.

An early open-label study of the opioid antagonist naltrexone showed early promise in treating dissociative symptoms in BPD.[121] Stabilization of opioid signaling may improve self-injury, dissociation, impulsivity, and interpersonal functioning.[115-116] Moreover, opioid antagonism may prevent adverse effects of dissociation on behavioral conditioning,[122] suggesting a potential synergistic role with psychotherapy to improve interpersonal hypersensitivity. Nevertheless, both opioid agonists[123,124] and antagonists[125] have shown limited efficacy in preliminary research with BPD patients. A more recent, placebo-controlled trial of naltrexone also failed to demonstrate statistically significant improvement in dissociative symptoms.[126] Therefore, opioid medications lack clear role in treating BPD, and they are associated with substantial risks of dependence (primarily for agonists) and other potential adverse effects.

Oxytocin is associated with empathic processing, self-similarity evaluation, attuned parental care-giving, and affiliative bonding.[127-129] This has led to similar considerations for treating interpersonal dysfunction in BPD. Nevertheless, placebo-controlled administration of intranasal oxytocin led BPD patients to cooperate less than healthy controls, an adverse effect mediated by higher levels of attachment anxiety.[130] A separate small, placebo-controlled study indicated subtle effects of oxy-

Medication	Dosing	Effects
Carbamazepine	Therapeutic blood levels	Potential improvement in impulsivity, but also possible worsening in melancholic depression.
Divalproex sodium over 80 µg/mL	Highest tolerated dose	Improvements (primarily in patients with high impulsive aggression), in interpersonal sensitivity, irritability, and aggression.
Lamotrigine target 200 mg/d	Highest tolerated dose,	Improvements in anger, affective instability, impulsivity. Risk of potentially life-threatening rash.
Lithium carbonate	Therapeutic blood levels	Improvement in affective instability, possibly overall functioning, but limited data.
Topiramate	Target dose 200-250 mg/d	Improvements in anger, anxiety, interpersonal dysfunction, self-reported quality of life. Associated with weight loss.

Table III. Mood stabilizers demonstrating efficacy in borderline personality disorder.

tocin in decreasing social stress reactivity, particularly for patients with history of childhood trauma and attachment insecurity.[131] Seemingly divergent effects of oxytocin on social stress on the one hand, and cooperative behavior on the other, suggest that it may have opposing roles in different social cognitive processing networks in BPD. Further research is needed before advising clinical use of oxytocin in psychopharmacological management of BPD.

Future directions

Olanzapine[89-90] and fluoxetine[132] have been studied in conjunction with evidence-based psychotherapy for BPD, but respective treatment effects of psychotherapy versus medication remained unclear in these trials. Whether different medications differ in their capacity to synergize with psychotherapy in treating specific BPD symptoms or overall functioning has never been rigorously studied. Many BPD patients are treated with a combined approach, and yet there is limited information for rational clinical decision-making. Further understanding of the *neurobiological* effects of psychotherapy, relative to mechanisms of action of specific medications may eventually predict which BPD patients will respond to which approach and how to combine different treatments.

BPD patients show lack of psychophysiological and amygdala indicators of habituation to repeated interpersonal affective stimuli of positive or negative valence.[81] Working through interpersonal experiences in psychotherapy may be difficult for BPD patients, and adjunctive medication treatment targeting this capacity for habituation may optimize overall treatment efficacy. Dependent on neuroplasticity and changes in receptor density, habituation is fundamentally affected by glutamatergic N-methyl-D-aspartate (NMDA) signaling, suggesting a role for glutamatergic medications in improving impulsivity, interpersonal symptoms, and cognition in BPD.[133] Enhancing learning and psychophysiological habituation modulated by NMDA signaling could synergize psychopharmacology and psychotherapy, analogous to strategies proposed for PTSD with respect to enhancement of fear extinction and interference of traumatic memory consolidation.[134,135] This type of combination strategy has not been studied in randomized controlled trials.

Endocannabinoid neurotransmission has also been implicated in impulsivity,[136] suicidality,[137] affective instability, and psychosis,[138] perhaps partly via its role in modulating dopaminergic signaling.[139] Medications active on CB receptors have also been hypothesized to facilitate extinction and interfere with consolidation of traumatic memories, if used in conjunction with psychotherapy.[140] Psychopharmacological applications of cannabinoid medications remain theoretical at best, and associated risks remain too uncertain.

Opioid dysregulation may be associated with affective instability, impulsive self-injury, dissociation, and intolerance of aloneness in BPD, while abnormalities in oxytocin signaling may be associated with empathic dysfunction, pervasive shame, and attachment insecurity.[116] Nevertheless, individual differences in genetics, developmental history, and immediate interpersonal context may contribute to inconsistent effects of neuropeptides on interpersonal functioning. Thus, in addition to genetic differences, compensatory postsynaptic receptor changes in response to prior cumulative opioid exposure and developmental environment may change the manifestations associated with neuropeptide signaling at any given moment.

Interactions between monoamine and neuropeptide signaling modulate impulsive aggression,[84-85] but these interactions have not been studied sufficiently to suggest a psychopharmacological strategy for BPD that combines both neurotransmitter systems. Although full opioid agonists and antagonists have not yielded promising clinical results, the effect of partial agonists (eg, buprenorphine) on BPD symptoms has never been studied. Despite specific affinity of many opioid medications on mu receptor binding, kappa opioid receptor signaling may mediate immediate and cumulative effects of repeated trauma on worsening depression and anxiety.[141] Kappa antagonists have recently been considered as novel antidepressants or anxiolytics in animal models,[141-144] which may more accurately reflect affective instability in response to interpersonal stressors and attachment insecurity associated with BPD. Limited psychopharmacological research exists with respect to effects of neuropeptides other than opioids and oxytocin in BPD. Further research may provide novel psychopharmacologic options.

Conclusions

Symptoms of BPD include impulsivity, aggression, affective instability, transient psychotic symptoms, and interpersonal dysfunction, occurring as manifestations of core disturbances in representations of self and other.[1-3] This

core is associated with complex interactions between genetic risk factors and developmental attachment stressors.[14-17] Specific neurobiological effects of these risk factors in BPD remain ill-defined. The most up-to-date evidence suggests that anticonvulsant agents such as topiramate, valproate, or lamotrigine, and atypical antipsychotics such as aripiprazole and olanzapine, are most effective in treating BPD. Consistent with their benefits on impulsivity, a recent review recommended anticonvulsants and atypical antipsychotics for decreasing alcohol craving and consumption in BPD patients with comorbid alcoholism. Of the antidepressants, MAOIs and fluvoxamine may offer greater therapeutic benefit, but effects of antidepressants on BPD symptoms are more modest. Antidepressant medications may nevertheless be helpful to treat comorbid mood and anxiety disorders, and they may be more efficacious in treating male BPD patients with prominent impulsive aggression.[24] There are no medications approved for treatment of BPD as a whole, and targeted, transient use of medication for specific symptom domains is advised. Identity disturbance and interpersonal affective symptoms are less apt to improve with medication alone. Most available medications target impulsivity and aggression, symptoms that are most likely to resolve.

Experimental use of glutamatergic medications or alteration of endocannabinoid signaling may enhance affective habituation during processing of interpersonal stressors in psychotherapy. Neuropeptide research may inform understanding of interpersonal dysfunction and identity disturbance characteristic of BPD. There exists potentially great variability in oxytocin and opioid signaling across individuals with BPD, or within a single patient over time. Opioid partial agonists or kappa antagonists may be an efficacious psychopharmacological intervention in BPD, but no direct evidence exists for such a practice clinically. At best, these psychopharmacological strategies remain theoretical and require further research on safety and efficacy prior to drawing any conclusions.

Although antidepressants have shown limited efficacy in treating BPD, they are well-tolerated and greater receptor specificity may be needed for effective serotonergic treatment of impulsive aggression. Atypical antipsychotics and anticonvulsants provide broader and more prominent benefit on some BPD symptoms, but are also associated with potential risks. Thus far, basic research has been difficult to translate into novel psychopharmacologic treatments for BPD. Further research on the functional neurobiology of BPD may improve understanding of chronic, refractory symptoms and assist in predicting treatment response. By relying on the best available evidence, clinicians can assist BPD patients in alleviating debilitating symptoms. ❑

REFERENCES

1. Bender DS, Skodol AE. Borderline personality as a self-other representational disturbance. *J Personal Disord*. 2007;21:500-517.
2. Choi-Kain LW, Gunderson JG. Mentalization: ontogeny, assessment, and application in the treatment of borderline personality disorder. *Am J Psychiatry*. 2008;165:1127-1135.
3. Fonagy P, Luyten P. A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. *Dev Psychopathol*. 2009;21:1355-1381.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
5. Black DW, Blum N, Pfohl B, Hale N. Suicidal behavior in borderline personality disorder: prevalence, risk factors, prediction, and prevention. *J Personal Disord*. 2004;18:226-239.
6. Brodsky BS, Groves SA, Oquendo MA, Mann JJ, Stanley B. Interpersonal precipitants and suicide attempts in borderline personality disorder. *Suicide Life Threat Behav*. 2006;36:313-322.
7. Jovev M, Jackson HJ. The relationship between borderline personality disorder, life events, and functioning in an Australian psychiatric sample. *J Personal Disord*. 2006;20:205-217.
8. Stiglmayr CE, Ebner-Priemer UW, Bretz J, et al. Dissociative symptoms are positively related to stress in borderline personality disorder. *Acta Psychiatr Scand*. 2008;117:139-147.
9. Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder:results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69:533-545.
10. Gross R, Olfson M, Gameroff M, et al. Borderline personality disorder in primary care. *Arch Intern Med*. 2002;162:53-60.
11. Skodol A, Gunderson J, McGlashan T, et al. Functional Impairment in patients with schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. *Am J Psychiatry*. 2002;159:276-283.
12. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet*. 2004;364:453-461.
13. Zanarini MC, Frankenburg FR, Khera GS, Bleichmar J. Treatment histories of borderline inpatients. *Compr Psychiatry*. 2001;42:144-150.
14. Gunderson JG, Lyons-Ruth K. BPD's interpersonal hypersensitivity phenotype:a gene-environment-developmental model. *J Personal Disord*. 2008;22:22-41.
15. Judd PH. Neurocognitive impairment as a moderator in the development of borderline personality disorder. *Dev Psychopathol*. 2005;17:1173-1196.
16. Luyten P, Blatt SJ. Integrating theory-driven and empirically-derived models of personality development and psychopathology: a proposal for DSM-V. *Clin Psychol Rev*. 2011;31:52-68.
17. Steele H, Siever LJ. An attachment perspective on borderline personality disorder:advances in gene-environment considerations. *Curr Psychiatry Rep*. 2010;12:61-67.

Tratamiento psicofarmacológico del trastorno de personalidad borderline

En este artículo se describe la mejor evidencia disponible acerca del tratamiento psicofarmacológico del trastorno de personalidad borderline *(TPB). El TPB está definido por alteraciones en la identidad y en el funcionamiento interpersonal, y los pacientes refieren potenciales tratamientos medicamentosos orientados al manejo de la impulsividad, la agresividad, los síntomas psicóticos y disociativos transitorios, y la inestabilidad afectiva refractaria. Aunque recientemente se han publicado unos pocos ensayos terapéuticos controlados y randomizados para el TPB, hay múltiples revisiones que han coincidido en la eficacia de anticonvulsivantes específicos, antipsicóticos atípicos y suplementos de ácido graso omega-3. Hay una mayor evidencia para los fármacos que ofrecen un control significativo de la agresividad impulsiva respecto a los síntomas afectivos u otros síntomas interpersonales. Las estrategias de futuras investigaciones se centrarán en el papel potencial de los neuropéptidos y los medicamentos con mayor especificidad sobre los receptores serotoninérgicos 2A, como también en la optimización de la implementación concomitante de la psicoterapia y la psicofarmacología basadas en la evidencia, con el objetivo de mejorar el funcionamiento global de los pacientes con TPB.*

Traitement psychopharmacologique de la personnalité borderline

Les meilleures données disponibles pour le traitement psychopharmacologique de la personnalité borderline *(PB) sont exposées ici. La PB est définie par des perturbations de l'identité et du fonctionnement interpersonnel ; l'impulsivité, l'agressivité, les symptômes transitoires dissociatifs et psychotiques et l'instabilité affective réfractaire présentés par les patients sont autant de cibles potentielles médicamenteuses. Peu d'études randomisées contrôlées sur les traitements pharmacologiques de la PB ont été publiées récemment alors que de nombreuses analyses s'accordent sur l'efficacité d'anticonvulsivants spécifiques, de molécules antipsychotiques atypiques et d'une supplémentation en acide gras oméga 3. Les médicaments capables d'améliorer significativement l'impulsivité agressive sont plus documentés que ceux dédiés aux symptômes affectifs ou interpersonnels. Les stratégies de recherche à venir s'intéresseront au rôle potentiel des neuropeptides et des médicaments plus spécifiques des récepteurs 2A à la sérotonine, comme à l'optimisation de l'apport concomitant d'une psychothérapie et d'une psychopharmacologie basées sur les preuves, afin d'améliorer le fonctionnement global des patients PB.*

18. Choi-Kain LW, Zanarini MC, Frankenburg FR, Fitzmaurice GM, Reich DB. A longitudinal study of the 10-year course of interpersonal features in borderline personality disorder. *J Personal Disord*. 2010;24:365-376.

19. Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder:a 10-year follow-up study. *Am J Psychiatry*. 2007;164:929-935.

20. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. The 10-year course of psychosocial functioning among patients with borderline personality disorder and axis II comparison subjects. *Acta Psychiatr Scand*. 2010;122:103-109.

21. Gunderson JG, Stout RL, McGlashan TH, et al. Ten-year course of borderline personality disorder: psychopathology and function from the collaborative longitudinal personality disorders study. *Arch Gen Psychiatry*. 2011;68:827-837.

22. Ripoll LH, Triebwasser J, Siever LJ. Evidence-based pharmacotherapy for personality disorders. *Int J Neuropsychopharmacol*. 2011;15:1-32.

23. Abraham PF, Calabrese JR. Evidence-based pharmacologic treatment of borderline personality disorder: a shift from SSRIs to anticonvulsants and atypical antipsychotics? *J Affect Disord*. 2008;111:21-30.

24. Bellino S, Rinaldi C, Bozzatello C, Bogetto F. Pharmacotherapy of borderline personality disorder:a systematic review for publication purpose. *Curr Med Chem*. 2011;18:3322-3229.

25. Ingenhoven T, Lafay P, Rinne T, Passchier J, Duivenvoorden H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. *J Clin Psychiatry*. 2010;71:14-25.

26. Lieb K, Vollm B, Rucker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *Br J Psychiatry*. 2010;196:4-12.

27. Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. *J Personal Disord*. 2009;23:156-174.

28. Saunders EF, Silk KR. Personality trait dimensions and the pharmacological treatment of borderline personality disorder. *J Clin Psychopharmacol*. 2009;29:461-467.

29. Stoffers J, Vollm BA, Rucker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. *Cochrane Database Syst Rev*. 2010;6:CD005653.

30. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry*. 2002;63:442-446.

31. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. 2001;62:849-854.

32. Salzman C, Wolfson AN, Schatzberg A, et al. Effects of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmacol*. 1995;15:23-29.
33. Rifkin A, Quitkin F, Carrillo C, Blumberg AG, Klein DF. Lithium carbonate in emotionally unstable character disorder. *Arch Gen Psychiatry*. 1972;27:519-523.
34. Battaglia J, Wolff TK, Wagner-Johnson DS, Rush AJ, Carmody TJ, Basco MR. Structured diagnostic assessment and depot fluphenazine treatment of multiple suicide attempters in the emergency department. *Int Clin Psychopharmacol*. 1999;14:361-372.
35. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry*. 1997;54:1081-1088.
36. Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs. placebo. *Arch Gen Psychiatry*. 1986;43:680-686.
37. Montgomery SA, Roy D, Montgomery DB. The prevention of recurrent suicidal acts. *Br J Clin Pharmacol*. 1983;15:183S-188S.
38. Serban G, Siegel S. Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. *Am J Psychiatry*. 1984;141:1455-1458.
39. Soloff PH, George A, Nathan RS, et al. Progress in pharmacotherapy of borderline disorders. *Arch Gen Psychiatry*. 1986;43:691-697.
40. Verkes RJ, van der Mast RC, Hengeveld MW, Tuyl JP, Zwinderman AH, Van Kempen GM. Reduction by paroxetine of suicidal behavior in patients with repeated suicide attempts but not major depression. *Am J Psychiatry*. 1998;155:543-547.
41. Tritt K, Nickel C, Lahmann C, et al. Lamotrigine treatment of aggression in female borderline patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol*. 2005;19:287-291.
42. Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry*. 2003;160:167-169.
43. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry*. 2004;7:903-907.
44. Bogenschutz MP, Nurnberg PH. Olanzapine versus placebo in the treatment of borderline personality disorder. *J Clin Psychiatry*. 2004;65:104-109.
45. Tyrer P, Silk KR. A comparison of UK and US guidelines for drug treatment in borderline personality disorder. *Int Rev Psychiatry*. 2011;23:388-394.
46. Jariani M, Saaki M, Nazari H, Birjandi M. The effect of olanzapine and sertraline on personality disorder in patients with methadone maintenance therapy. *Psychiatr Danub*. 2010;22:544-547.
47. Shafti SS, Shahveisi B. Olanzapine versus haloperidol in the management of borderline personality disorder:a randomized double-blind trial. *J Clin Psychopharmacol*. 2010;30:44-47.
48. Bellino S, Paradiso E, Bozzatello P, Bogetto F. Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder:a pilot study. *J Psychopharmacol*. 2010;24:333-339.
49. Adityanjee, Romine A, Brown E, Thuras P, Lee S, Schulz SC. Quetiapine in patients with borderline personality disorder: an open-label trial. *Ann Clin Psychiatry*. 2008;20:219-226.
50. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of quetiapine in the treatment of borderline personality disorder: a pilot study. *J Clin Psychiatry*. 2006;67:1042-1046.
51. Van den Eynde F, Senturk V, Naudts K, et al. Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. *J Clin Psychopharmacol*. 2008;28:147-155.
52. Villeneuve E, Lemelin S. Open-label study of atypical neuroleptic quetiapine for treatment of borderline personality disorder: impulsivity as main target. *J Clin Psychiatry*. 2005;66:1298-1303.
53. Bellino S, Paradiso E, Bogetto F. Oxcarbazepine in the treatment of borderline personality disorder: a pilot study. *J Clin Psychiatry*. 2005;66:1111-1115.
54. Miyaoka T, Furuya M, Yasuda H, Hayashia M, Inagaki T, Horiguchi J. Yigan san for the treatment of borderline personality disorder: an open-label study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:150-154.
55. Hesse E. The Adult Attachment Interview:Protocol, method of analysis, and empirical studies. In: Hesse E, ed. *Handbook of Attachment, Second Edition: Theory, Research, and Clinical Applications*. New York, NY:Guilford Press; 2008:552-598.
56. Agrawal HR, Gunderson J, Holmes BM, Lyons-Ruth K. Attachment studies with borderline patients: a review. *Harv Rev Psychiatry*. 2004;12:94-104.
57. Coccaro EF, Kavoussi RJ, Hauger RL. Physiological responses to d-fenfluramine and ipsapirone challenge correlate with indices of aggression in males with personality disorder. *Int Clin Psychopharmacol*. 1995;10:177-179.
58. Coccaro EF, Siever LJ, Klar HM, Maurer G, et al. Serotonergic studies in patients with affective and personality disorders:correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry*. 1989;46:587-599.
59. Evenden J. Impulsivity: a discussion of clinical and experimental findings. *J Psychopharmacol*. 1999;13:180-192.
60. Malone KM, Corbitt EM, Li S, Mann JJ. Prolactin response to fenfluramine and suicide attempt lethality in major depression. *Br J Psychiatry*. 1996;168:324-329.
61. New AS, Goodman M, Triebwasser J, Siever LJ. Recent advances in the biological study of personality disorders. *Psychiatr Clin North Am*. 2008;31:441-461.
62. New AS, Hazlett EA, Buchsbaum MS, et al. Blunted prefrontal cortical 18fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. *Arch Gen Psychiatry*. 2002;59:621-629.
63. New AS, Trestman R, Mitropoulou V, et al. Low prolactin response to fenfluramine in impulsive aggression. *J Psychiatr Res*. 2004;38:223-230.
64. New AS, Trestman R, Mitropoulou V, et al. Serotonergic function and self-injurious behavior in personality disorder patients. *Psychiatry Res*. 1997;69:17-26.
65. Oquendo MA, Krunic A, Parsey RV, et al. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge in major depressive disorder with and without borderline personality disorder. *Neuropsychopharmacology*. 2005;30:1163-1172.
66. Pitchot W, Hansenne M, Pinto E, Reggers J, Fuchs S, Ansseau M. 5-Hydroxytryptamine 1A receptors, major depression, and suicidal behavior. *Biol Psychiatry*. 2005;58:854-58.
67. Samuelsson M, Jokinen J, Nordstrom AL, Nordstrom P. CSF 5-HIAA, suicide intent and hopelessness in the prediction of early suicide in male high-risk suicide attempters. *Acta Psychiatr Scand*. 2006;113:44-47.
68. Siever LJ, Buchsbaum MS, New AS, et al. D,L-fenfluramine response in impulsive personality disorder assessed with [18F]fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology*. 1999;20:413-423.
69. Silva H, Iturra P, Solari A, et al. Serotonin transporter polymorphism and fluoxetine effect on impulsiveness and aggression in borderline personality disorder. *Actas Esp Psiquiatr*. 2007;35:387-392.
70. American Psychiatric Association Practice guideline. Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association. *Am J Psychiatry*. 2001;158(10 suppl):1-52.
71. Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am J Psychiatry*. 2002;159:2048-2054.
72. Soloff PH, George A, Nathan RS, Schulz PM, Ulrich RF, Perel JM. Amitryptiline and haloperidol in unstable and schizotypal borderline disorders. *Psychopharmacol Bull*. 1986;22:177-182.
73. Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Behavioral dyscontrol in borderline patients treated with amitryptiline. *Psychopharmacol Bull*. 1987;23:177-181.
74. Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Paradoxical effects of amitryptiline on borderline patients. *Am J Psychiatry*. 1986;143:1603-1605.
75. Ayduk O, Zayas V, Downey G, Cole AB, Shoda Y, Mischel W. Rejection sensitivity and executive control:joint predictors of borderline personality features. *J Res Pers*. 2008;42:151-168.
76. Staebler K, Helbing E, Rosenbach C, Renneberg B. Rejection sensitivity and borderline personality disorder. *Clin Psychol Psychother*. 2011;18:275-283.
77. Cornelius JR, Soloff PH, Perel JM, Ulrich RF. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. *Am J Psychiatry*. 1993;150:1843-1848.

78. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder:alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry*. 1988;45:111-119.
79. Parsons B, Quitkin FM, McGrath PJ, et al. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. *Psychopharmacol Bull*. 1989;25:524-534.
80. Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch Gen Psychiatry*. 1993;50:377-385.
81. Hazlett EA, Zhang J, New AS, et al. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol Psychiatry*. 2012;72:448-56.
82. Higgins GA, Enderlin M, Haman M, Fletcher PJ. The 5-HT2A receptor antagonist M100,907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism. *Psychopharmacology (Berl)*. 2003;170:309-319.
83. Winstanley CA, Theobald DE, Dalley JW, Glennon JC, Robbins TW. 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. *Psychopharmacology (Berl)*. 2004;176:376-385.
84. Homberg JR. Serotonin and decision-making processes. *Neurosci Biobehav Rev*. 2012;36:218-236.
85. Takahashi A, Quadros IM, de Almeida RM, Miczek KA. Behavioral and pharmacogenetics of aggressive behavior. *Curr Top Behav Neurosci*. 2012;12:73-138.
86. Assadi SM, Yucel M, Pantelis C. Dopamine modulates neural networks involved in effort-based decision-making. *Neurosci Biobehav Rev*. 2009;33:383-393.
87. Nickel MK, Loew TH, Pedrosa Gil F. Aripiprazole in treatment of borderline patients, part II:an 18-month follow-up. *Psychopharmacology*. 2007;191:1023-1026.
88. Nickel MK, Muehlbacher M, Nickel C, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2006;163:833-838.
89. Linehan MM, McDavid JD, Brown MZ, Sayrs JH, Gallop RJ. Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder:a double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. 2008;69:999-1005.
90. Soler J, Pascual JC, Campins J, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am J Psychiatry*. 2005;162:1221-1224.
91. Schulz SC, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder:variable dose 12 week randomised double-blind placebo-controlled study. *Br J Psychiatry*. 2008;193:485-492.
92. Zanarini MC, Schulz SC, Detke HC, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12 week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2011;72:1353-1362.
93. Zanarini MC, Schulz SC, Detke HC, et al. Open-label treatment with olanzapine for patients with borderline personality disorder. *J Clin Psychopharmacol*. 2012;32:398-402.
94. Pascual JC, Soler J, Puigdemont D, et al. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J Clin Psychiatry*. 2008;69:603-608.
95. Zanarini MC, Reichman CA, Frankenburg FR, Reich DB, Fitzmaurice G. The course of eating disorders in patients with borderline personality disorder: a 10-year follow-up study. *Int J Eat Disord*. 2010;43:226-232.
96. Frankenburg FR, Zanarini MC. Obesity and obesity-related illnesses in borderline patients. *J Personal Disord*. 2006;20:71-80.
97. Bolton S, Gunderson JG. Distinguishing borderline personality disorder from bipolar disorder: differential diagnosis and implications. *Am J Psychiatry*. 1996;153:1202-1207.
98. Critchfield KL, Levy KN, Clarkin JF, Kernberg OF. The relational context of aggression in borderline personality disorder:using adult attachment style to predict forms of hostility. *J Clin Psychol*. 2008;64:67-82.
99. Gunderson, JG. Disturbed relationships as a phenotype for borderline personality disorder. *Am J Psychiatry*. 2007;164:1637-1640.
100. Henry C, Mitropoulou V, New AS, Koenigsberg HW, Silverman J, Siever LJ. Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *J Psychiatr Res*. 2001;35:307-312.
101. Paris J. Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. *Harv Rev Psychiatry*. 2004;12:140-145.
102. Links PS, Steiner M, Boiago I, Irwin D. Lithium therapy for borderline patients:preliminary findings. *J Personal Disord*. 1990;4:173-181.
103. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol*. 1986;6:236-239.
104. Gardner DL, Cowdry RW. Positive effects of carbamazepine on behavioral dyscontrol in borderline personality disorder. *Am J Psychiatry*. 1986;143:519-522.
105. de la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. *Eur Neuropsychopharmacol*. 1994;4:479-486.
106. Loew TH, Nickel MK, Muehlbacher M, et al. Topiramate treatment of women with borderline personality disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2006;26:61-66.
107. Loew TH, Nickel MK. Topiramate treatment of women with borderline personality disorder, part II:an open 18-month follow-up. *J Clin Psychopharmacol*. 2008;28:355-357.
108. Nickel MK, Loew TH. Treatment of aggression with topiramate in male borderline patients, part II: 18-month follow-up. *Eur Psychiatry*. 2008;23:115-117.
109. Nickel MK, Nickel C, Kaplan P, et al. Treatment of aggression with topiramate in male borderline patients:a double-blind, placebo-controlled study. *Biol Psychiatry*. 2005;57:495-499.
110. Nickel MK, Nickel C, Mitterlehner FO, et al. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2004;65:1515-1519.
111. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int Clin Psychopharmacol*. 2009;24:270-275.
112. Leiberich F, Nickel MK, Tritt K, Pedrosa Gil F. Lamotrigine treatment of aggression in female borderline patients, part II: an 18-month follow-up. *J Psychopharmacol*. 2008;805-808.
113. Hollander E, Swann AC, Coccaro EF, et al. Impact of trait impulsivity and state aggression on divalproex vs. placebo response in borderline personality disorder. *Am J Psychiatry*. 2005;162:621-624.
114. Ziegenhorn AA, Roepke S, Schommer NC, et al. Clonidine improves hyperarousal in borderline personality disorder with or without comorbid post-traumatic stress disorder:a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2009;29:170-173.
115. Bandelow B, Schmahl C, Falkai P, Wedekind D. Borderline personality disorder:a dysregulation of the endogenous opioid system? *Psychol Rev*. 2010;117:623-636.
116. Stanley B, Siever LJ. The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. *Am J Psychiatry*. 2010;167:24-39.
117. Depue RA, Morrone-Strupinsky JV. A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. *Behav Brain Sci*. 2005;28:313-395.
118. Higham JP, Barr CS, Hoffman CL, Mandalaywala TM, Parker KJ, Maestripieri D. Mu opioid receptor variation, oxytocin levels, and maternal attachment in free-ranging rhesus macaques Macaca mulatta. *Behav Neurosci*. 2011;125:131-136.
119. Troisi A, Frazzetto G, Carola V, et al. Variation in the –opioid receptor gene (OPRM1) moderates the influence of early maternal care on fearful attachment. *Soc Cogn Affect Neurosci*. 2012;7:542-547.
120. Prossin AR, Love TM, Koeppe RA, Zubieta JK, Silk KR. Dysregulation of regional endogenous opioid function in borderline personality disorder. *Am J Psychiatry*. 2010;167:925-933.
121. Bohus MJ, Landwehrmeyer GB, Stiglmayr CE, Limberger MF, Bohme R, Schmahl CG. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder:an open-label trial. *J Clin Psychiatry*. 1999;60:598-603.
122. Ebner-Priemer UW, Mauchnik J, Kleindienst N, et al. Emotional learning during dissociative states in borderline personality disorder. *J Psychiatry Neurosci*. 2009;34:214-22.

123. Saper JR. Borderline personality, opioids, and naltrexone. *Headache*. 2000;40:765-766.
124. Thurauf NJ, Washeim HA. The effects of exogenous analgesia in a patient with borderline personality disorder (BPD) and severe self-injurious behavior. *Eur J Pain*. 2000;4:107-109.
125. Philipsen A, Schmahl C, Lieb K. Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. *Pharmacopsychiatry*. 2004;37:196-199.
126. Schmahl C, Kleindienst N, Limberger M, et al. Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *Int Clin Psychopharmacol*. 2012;27:61-68.
127. Bartz JA, Zaki J, Bolger N, Ochsner KN. Social effects of oxytocin in humans: context and person matter. *Trends Cogn Sci*. 2011;15:301-309.
128. De Dreu CKW, Greer LL, Van Kleef GA, Shalvi S, Handgraaf MJ. Oxytocin promotes human ethnocentrism. *Proc Natl Acad Sci U S A*. 2011;108:1262-1266.
129. Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychol Sci*. 2007;18:965-970.
130. Bartz J, Simeon D, Hamilton H, et al. Oxytocin can hinder trust and cooperation in borderline personality disorder. *Soc Cogn Affect Neurosci*. 2011;6:556-563.
131. Simeon D, Bartz J, Hamilton H, et al. Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. *Psychoneuroendocrinology*. 2011;36:1418-1421.
132. Simpson EB, Yen S, Costello E, et al. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J Clin Psychiatry*. 2004;65:379-385.
133. Grosjean B, Tsai GE. NMDA neurotransmission as a critical mediator of borderline personality disorder. *J Psychiatry Neurosci*. 2007;32:103-115.
134. Diergaarde L, Schoffelmeer AN, De Vries TJ. Pharmacological manipulation of memory consolidation: towards a novel treatment of pathogenic memories. *Eur J Pharmacol*. 2008;585:453-457.
135. Steckler T, Risbrough V. Pharmacological treatment of PTSD—established and new approaches. *Neuropharmacology*. 2012;62:617-627.
136. Pattij T, Vanderschuren LJ. The neuropharmacology of impulsive behaviour. *Trends Pharmacol Sci*. 2008;29:192-199.
137. Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci*. 2006;27:539-545.
138. Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. *Exp Neurol*. 2010;224:3-14.
139. Fitzgerald ML, Shobin E, Pickel VM. Cannabinoid modulation of the dopaminergic circuitry:implications for limbic and striatal output. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;38:21-29.
140. de Bitencourt RM, Pamplona FA, Takahashi RN. A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories:potential extinction enhancers. *Neuropharmacology*. 2013;64:389-395.
141. Knoll AT, Carlezon WA Jr. Dynorphin, stress, and depression. *Brain Res*. 2010;1314:56-73.
142. Carr GV, Bangasser DA, Bethea T, Young M, Valentino RJ, Lucki I. Antidepressant-like effects of kappa opioid receptor antagonists in Wistar Kyoto rats. *Neuropsychopharmacology*. 2010;35:752-763.
143. Chartoff E, Sawyer A, Rachlin A, Potter D, Pliakas A, Carlezon WA. Blockade of kappa opioid receptors attenuates the development of depressive-like behaviors induced by cocaine withdrawal in rats. *Neuropharmacology*. 2012;62:167-76.
144. Peters MF, Zacco A, Gordon J, et al. Identification of short-acting κ-opioid antagonists with anxiolytic-like activity. *Eur J Pharmacol*. 2011;661:27-34.