Prescribing in borderline personality disorder – the clinical guidelines

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Drug prescription and polypharmacy are commonly seen in the management of borderline personality disorder (BPD) in clinical practice, and the 'placebo effect of medications' in BPD patients is significant. However, it is to be noted that 'no drug' has a UK market authorisation or Food & Drug Administration approval in the USA for BPD. Here Dr Yadav reviews the guidelines.

Borderline personality disorder (BPD), tends to demonstrate a number of deeply ingrained, enduring, maladaptive and dysfunctional patterns of behaviour, manifesting themselves as inflexible responses to a broad range of personal and social situations. In BPD, women present to clinical services more than men, and this condition affects about 1–2% of individuals in the general population, approximately 6% in primary care settings, while the reported prevalence of BPD in psychiatric settings approaches 20%.[1]

BPD presents with varied symptoms and signs, including affective or emotional instability, a tendency to act impulsively without consideration of the consequences; intense anger is often present, which may often lead to violence, and there can be a marked tendency to quarrelsome behaviour manifesting as ubiquitous irritability and conflict with others, for example (see Box 1 for definition). There is also evidence of emotional instability, problems with self-image, aims and internal preferences – including sexual – which are often unclear or disturbed, there are chronic feelings of emptiness along with intense and unstable relationships, emotional crisis, excessive efforts to avoid abandonment, and repeated suicidal threats or acts of self-harm.[2]

In BPD, comorbid diagnoses occur more frequently and the lifetime risk of having at least one comorbid mental disorder approaches 100%. Comorbid diagnoses commonly associated with BPD are anxiety disorder, depressive disorder, bipolar disorder, substance misuse and post-traumatic stress disorder (PTSD).[3]

BPD has a variable course, with a higher rate of remission than previously thought. Social and interpersonal difficulties may sometimes persist even after treatment. The suicide rate in BPD is similar to that seen in affective disorder and schizophrenia.[4]

Box 1: Definitions of BPD

According to DSM-V (Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association)), the key features of borderline personality disorder are instability of interpersonal relationships, self-image and affect, combined with marked impulsivity beginning in early adulthood. It specifies 5 out of the following 9 symptoms must be present for the diagnosis to be made.[2]

A stand-alone category of borderline personality disorder does not exist within the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) published by the World Health Organization.[22] ICD-10 includes a description of emotional unstable personality disorder (F60.3) and divides it into two categories:

- The impulsive variant – 'emotionally unstable personality disorder, impulsive type' (F60.30) – is characterised by a tendency to conflict and outbursts of anger or violence, difficulty in maintaining any course of action that offers no immediate reward, and instability of mood.
- The borderline variant – 'emotionally unstable personality disorder, borderline type' (F60.31) – is characterised by disturbances of self-image, a tendency to unstable relationships, efforts to avoid abandonment, and threats or acts of self-harm (including suicide).

The ICD-10 category does not include brief quasi-psychotic features (criterion 9 of the DSM-V category). DSM-V also defines all personality disorders as Axis II disorders.[23]

Many leading experts in the field of borderline personality disorder endorse a symptom-targeted approach to treatment – targeting cognitive perceptual symptoms, impulsive behavioural dyscontrol and affective dysregulation.

Clinical guideline recommendations for pharmacological treatment of BPD currently lack consensus. This article summarises the recommendations from various guidelines across the UK, America and Australia.

Methods

In this article, the summary of prescribing guidelines in BPD was obtained by searching the World Wide Web for prescribing guidelines and borderline personality disorder (BPD); and a subsequent search for these guidelines across UK, America, and Australia.

Guidelines

The following is an attempt to summarise the prescribing guidelines in BPD in a narrative form highlighting the important recommendations conveyed by their authors, across continents.

To start with, there are no randomised controlled trials (RCTs) in BPD comparing psychotherapy and pharmacotherapy – so, we do not really know which is

best; single modality treatment, combination treatment or no treatment.

The evidence base for psychotherapy in BPD is increasing, covering modalities such as: DBT – dialectical behavioural therapy, MBT – mentalisation-based therapy, SFT – schema-focussed therapy, and TFP – transference-focussed therapy.

In some clinical settings, psychological therapies are not always available due to non-availability of a qualified psychotherapist, and in some cases some patients do not engage in psychological therapy in spite of psychotherapists trying different modes of therapy. Also, if antisocial traits predominate or threat of violence is imminent, psychotherapy may prove ineffective. If violence is threatened or imminent, hospitalisation may be indicated and potential victims may need to be warned.[5]

The American Psychiatric Association guidelines for BPD endorse a symptom-targeted approach and provide pharmacological algorithms targeting cognitive perceptual symptoms, impulsive behavioural dyscontrol and affective dysregulation.[5]

In the cognitive perceptual symptoms domain, suspiciousness, referential thinking, transient paranoid thoughts, illusion, derealisation, depersonalisation or feelings of dissociation in stressful situations are mostly present along with identity disturbance in terms of self-perception.

Impulsive behavioural dyscontrol manifests as impulsive, self-destructive and aggressive behaviours, and a failure to exhibit well balanced problem-solving behaviour as well as future-oriented perspectives on life. Self-injurious behaviour, the clinically most troubling manifestation of behavioural dyscontrol, is associated with diminished affective pain processing and dissociation. Promiscuous sex, substance misuse and reckless spending is also present.

Affective dysregulation comprises experiences of more intense aversive emotions, higher tension and more rapidly rising mood swings between dysphoria and euthymia in patients with BPD compared with healthy individuals. Mood lability, inappropriate intense anger or outbursts of anger, rejection sensitivity and depressive 'mood crashes'.

Besides the American Psychiatric Association guidelines for BPD, many eminent experts in the field of personality disorder also endorse a symptom-targeted approach to treating BPD. In the book, edited by Bert Van Luyn, Salman Akhtar and W. John Livesley (*Severe Personality Disorders – Everyday Issues in Clinical Practice*) pharmacotherapeutic strategies in severe personality disorders are discussed and recommended by Rinne and Ingenhoven.[6] This book is a very useful read. It summarises the evidence base and the authors make their own recommendations as noted in Table 1. A summary of the guidelines from APA 2001 is also included in Table 1.

Summaries of other guideline recommendations

World Federation of Societies of Biological Psychiatry

In 2007, in the guidelines for biological treatment of personality disorder,[7] the recommendations made by authors representing the World Federation of Societies of Biological Psychiatry included:

- Mood stabilisers as a second-line treatment for impulsive or aggressive behaviour.
- SSRIs for emotional dysregulation (mood swings, anxiety and depressive mood).
- Typical and atypical antipsychotics for impulsive behavioural dyscontrol, cognitive-perceptual symptoms and anger.

NICE guidelines for BPD were developed in January 2009;[8] and since then two further independent systematic reviews have been published in 2010 by Cochrane[9] and by Ingenhoven T *et al.*[10]

NICE guideline

- There is little evidence of the effectiveness of pharmacological treatments for people with personality disorders.
- Drug treatment should not be used routinely for borderline personality disorder or for the individual symptoms or behaviour intrinsically associated with the disorder; for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms.
- No drug has UK marketing authorisation for BPD.
- Drug treatment may be considered in the overall treatment of comorbid conditions.
- Short-term use of sedative medication may be considered as part of the overall treatment plan for people with borderline personality disorder in a crisis.

NICE is aware of changes to the classification of personality disorder in the latest version of the International Classification of Diseases (ICD-11).[11] NICE will perform an exceptional surveillance review in 2021, in order to gauge the reaction of the community to ICD-11 and consider any potential impact on the guideline.

Table 1. Summary of treatment guidelines

Domains	Algorithms: Practice guideline for the treatment of patients with BPD (Appendix 1–3; APA guideline watch 2005)[5]	Recommendations: Rinne and Ingenhoven (January 2007)[6]
Affective dysregulation symptoms in patients with BPD	Initial treatment: SSRI or related antidepressants In partial efficacy or in cases of no efficacy, try a second SSRI or related antidepressant Add clonazepam, for symptoms of anxiety Add low-dose antipsychotic, for symptoms of anger If the above are ineffective, switch to MAOI The next step in partial efficacy is to add lithium, carbamazepine or valproate In cases of no efficacy, switch to lithium, carbamazepine or valproate	Affective lability SSRI (fluvoxamine) Valproate 'Depressed mood' (without major depression or affective lability) Atypical antipsychotic (olanzapine) MAOI (tranylcypromine) (avoid tricyclic antidepressants or carbamazepine) Anger, hostility, irritability (without behavioural dyscontrol) Topiramate or valproate Classical or atypical antipsychotics, low dose[a] Anxiety Classical or atypical antipsychotic, low dose[a] No medication; low-dose benzodiazepine? MAOI (tranylcypromine)
Impulsive-behavioural dyscontrol symptoms in patients with BPD	Initial treatment: SSRIs In partial efficacy or no efficacy, optimise SSRI dose; switch to another SSRI or other antidepressant. Also consider a low-dose antipsychotic In partial efficacy, add lithium; and if this is ineffective, switch to carbamazepine or valproate. In cases of no efficacy, switch to MAOI The next step in cases of no efficacy is to add an antipsychotic if not previously used or to try a different antipsychotic	Topiramate SSRI (fluoxetine) (male patient) or valproate (female and male patient) Add classical or atypical antipsychotics, low dose[a] or switch to lithium (avoid benzodiazepines, tricyclic antidepressants and polypharmacy)
Cognitive-perceptual symptoms in patients with BPD	Initial treatment: low-dose antipsychotics (eg perphenazine 4–12/day; olanzapine 2.5–10mg/day; risperidone —4mg/day) Increase the dose of antipsychotics in partial or no efficacy Add SSRIs (or MAOI) in partial efficacy and when there are prominent affective symptoms. Switch to other antipsychotic, including clozapine in cases of no efficacy with few affective symptoms	Psychotic-like symptoms Classical or atypical antipsychotics, low dose[a] Classical or atypical antipsychotics, increase dose[b] Dissociation 1. No recommendation (avoid benzodiazepines, tricyclic antidepressants and polypharmacy)

[a] Classical antipsychotic, low dose = equivalent haloperidol 1–4mg [b] Classical antipsychotic, increase dose = up to equivalent haloperidol 4–6mg

Cochrane review

- Twenty-eight trials involving a total of 1742 trial participants were included.
- The Cochrane review concluded that 'total BPD severity' was not influenced by any drug and that there were no drugs available for BPD treatment specifically.
- The Cochrane findings tended to suggest some benefit from using second-generation antipsychotics, mood stabilisers, and omega-3 fatty acids, but most effect estimates were based on single study effects, so repeat studies would be useful.
- The small amount of available information for individual comparisons indicated marginal effects for first-generation antipsychotics and antidepressants.
- No medications show promise for 'the core BPD symptoms of chronic feelings of emptiness, identity disturbance, and abandonment'.
- The data also indicated that there may be an increase in self-harming behaviour in patients treated with olanzapine; and the long-term use of these drugs has not been assessed.
- In general, attention must be paid to adverse effects. Most trials did not provide detailed data on adverse effects and thus could not be considered within this review. All drugs were well tolerated in terms of attrition.
- Very few beneficial effects were identified for first-generation antipsychotics and antidepressants. However, they may be helpful in the presence of comorbid problems that are not part of BPD core pathology, but can often be found in BPD patients.
- The only trial testing single versus combined drug

treatment (olanzapine versus olanzapine plus fluoxetine; fluoxetine versus fluoxetine plus olanzapine) yielded no significant differences in outcomes.

Ingenhoven et al.

- Antipsychotics have a moderate effect on cognitive-perceptual symptoms, with a standardised mean difference [SMD]=0.56 and a moderate-to-large effect on anger, with a SMD=0.69.
- Antidepressants have no significant effect on impulsive-behavioral dyscontrol and depressed mood. They have a small but significant effect on anxiety, SMD=0.30 and anger, SMD=0.34.
- Mood stabilisers have a very large effect on impulsive-behavioral dyscontrol, SMD=1.51 and anger, SMD=1.33; a large effect on anxiety, SMD=0.80; but a moderate effect on depressed mood, SMD=0.55. Mood lability as an outcome measure was seldom assessed.
- Mood stabilisers have a more pronounced effect on global functioning with a SMD=0.79, than have antipsychotics, which has a SMD=0.37. The effect of antidepressants on global functioning is negligible.
- The authors conclude that drug therapy tailored to well defined symptom domains can have a beneficial effect on patients with severe personality disorder. The findings from this study raise questions about currently available pharmacological algorithms.

Australian guidelines

- The guidelines recommend that medications are to be used as an adjunct to psychological therapy rather than as primary therapy; and when medications are considered, these are prescribed for a time-limited period for specific symptoms.[12]
- The guidelines also note that mood stabilisers (topiramate, sodium valproate, lamotrigine) have shown some effect in reducing affective dysregulation and impulsive aggression. Also antipsychotics such as aripiprazole, olanzapine and quetiapine have shown some effect in reducing cognitive–perceptual symptoms and affective dysregulation. Omega-3 polyunsaturated fatty acids might reduce the overall severity of borderline personality disorder.

Limitations of trials

In the reviews by NICE, Cochrane and Ingenhovan *et al.* the same studies were considered and, where applicable, numerical data were combined in meta-analyses. These studies noted that drug treatment in BPD was hampered by small trials (fewer than 50 patients) of numerous drugs, short treatment periods (mean duration of 12 weeks), diverse outcome measures, infrequent replication of findings, and lack of independence from the pharmaceutical industry. There are only few study results per drug comparison, with small numbers of included participants. Cochrane concluded that current findings of trials were not robust and could easily be changed by future research endeavours.

Pharmacological prescription studies and surveys in BPD

In a naturalistic study of changes in pharmacological prescription for borderline personality disorder in clinical practice,[3] changes in prescription patterns over time were also evaluated. Patients received an average of 2.7 drugs; only 6% were drug-free; 56% were taking ≥3 drugs, and 30% ≥4 drugs. From 2002 to 2010, prescription of antidepressants has remained stable; there has been a significant reduction in prescription of benzodiazepines, and an increase in the use of mood stabilisers and atypical antipsychotics. Comorbidity with Axis I disorders was the main factor associated with drug prescription. Drug prescription and polypharmacy are common in the management of BPD in clinical practice.

The Prescribing Observatory for Mental Health (POMH-UK) in 2012 found that 82% of personality disorder patients with no comorbid mental illness were prescribed at least one psychotropic medication.[13]

Although the evidence for drug therapy is less conclusive than for the psychosocial interventions, US data indicate that prescribing rates for borderline personality disorder are paradoxically high. Drugs are prescribed for 78% of patients for more than 75% of the time over a six–year period and polypharmacy occurs in 37% of patients, perhaps reflecting clinical needs and pressures. To date, there has been no study of Australian prescribing practices, but the authors of a paper in *Australian Prescriber* report that clinical experience suggests the situation might be similar.[14]

Guideline recommendations for pharmacological treatment currently lack consensus (see Box 2 for a summary).

In a UK survey published in 2015, 92% of patients who had a diagnosis of BPD were prescribed psychotropic medication – most commonly an antidepressant or an antipsychotic – principally for symptoms and behaviours that characterise BPD, particularly affective dysregulation.[15]

Management of crisis in BPD

In BPD, by their very nature, symptoms experienced by patients can be expected to wax and wane[4] and medications may then be required, intermittently, during periods of crisis, when 'symptoms' can be severe, distressing and potentially life threatening.

NICE in 2009 recommended a sedative antihistamine – promethazine – rather than benzodiazepines or antipsychotics.

The duration of treatment should be agreed with patients, but should not be more than a week – a time-limited prescription. NICE recommends not to use benzodiazepines, antipsychotics or tricyclic antidepressants. NICE notes that benzodiazepines can cause disinhibition in this group of patients, potentially compounding problems; antipsychotics can cause extrapyramidal side-effects and metabolic syndrome, and tricyclic antidepressants can be toxic in overdose.

A Cochrane review in 2012 noted that to date in BPD little was known about what might help people with BPD when they were experiencing an acute crisis. A comprehensive search of the literature showed that there was no RCT-based evidence for the management of acute crises in people with BPD. Therefore, the authors could not reach any conclusions about the effectiveness of any single crisis intervention. High-quality, large-scale, adequately powered RCTs in this area are urgently needed. Given that crises in this population may be associated with an increased risk of suicide, further research is needed. These Cochrane review authors reported that two trials are ongoing and the results were therefore not included in the review, although they will be incorporated into future updates.[19]

Conclusion

Drug prescription and polypharmacy are commonly seen in the management of BPD in clinical practice and the 'placebo effect of medications' in BPD patients is considerable. However, it is to be noted that no drug has a UK marketing authorisation or Food & Drug Administration approval in the USA for BPD. Medications prescribed in BPD are mostly 'off-label use', targeting symptom clusters. Reviews and prescribing observations note that comorbidity with Axis I disorders was the main factor associated with drug prescription.

In clinical practice, prescribers should be mindful of prescribing psychotropic medications to patients with BPD. The first step is to have an open conversation with patients around their diagnosis and about how they would like to effectively manage their distress.

To achieve the best outcome, if the treating clinician and the patient jointly discuss the proposed benefit and also harm from psychotropic medications, then this would hopefully lead to ethical prescribing in BPD. Training for all prescribing clinicians on judicious use of psychotropic medication in this population group will surely help. This article aims to support improvement in one of the four core ethical principles, namely, nonmaleficence – non-harming or inflicting the least harm possible to reach a beneficial outcome.

It is important to highlight to patients with BPD that most eminent authors on BPD recommend psychological therapies as the first-line treatment, in line with the ethical principle of nonmaleficence. NICE guidelines recommend that from the currently available data available at the time of the review, which were not robust enough, psychotropic medications should not be recommended to patients with BPD in the NHS. This approach also applies well across continents, if a patient presents with mild symptoms and makes no request for medications.

If a patient is showing some engagement in psychological therapy, and they request medication, cite the Australian guidelines published in 2012 – that medications are used as an adjunct to psychological therapy, rather than as primary therapy; and the fact that when medications are considered, these are prescribed for a time-limited period, for specific symptoms.

Box 2: Brief summary of guideline recommendations for psychotropic medications

Antipsychotics: In BPD, all the three symptom clusters – affect dysregulation, impulsive behavioural dyscontrol and cognitive-perceptual symptoms – respond to antipsychotics, which are most effective in cognitive-perceptual symptoms and anger. Placebo-controlled RCTs generally show more modest benefits for active drug over placebo over a wide range of symptoms and open studies have found benefit for a number of first- and second-generation antipsychotics over a wide range of symptoms. Open studies report reductions in aggression and self-harming behaviour with clozapine.[16–18]

Clozapine is an atypical antipsychotic medicine that can cause significant side-effects, including neutropenia and agranulocytosis, necessitating strict full blood count monitoring and close supervision. Clozapine is only licensed to treat patients diagnosed with treatment-resistant schizophrenia and psychotic disorder in Parkinson's disease.

In clinical practice clozapine is often prescribed 'off-licence' in severe cases of borderline personality disorder, hence, clozapine prescribing is often contentious. Clozapine appears to be efficacious in the management of self-injurious behaviours, chronic suicidality and aggression in patients with severe BPD.

Clozapine may offer an advantage over other antipsychotics, in BPD 'treatment resistance' cases or in 'complex BPD cases' with comorbidity (for example: in forensic inpatient units when conventional approaches have failed to decrease the risk of aggression and when the risk of not treating is detrimental to the wellbeing of patients). The APA also includes clozapine in its guidelines, for cognitive-perceptual symptoms.

Antidepressants: RCTs have not found any evidence that SSRIs reduce impulsivity and aggression; however, several open studies have found that SSRIs reduce impulsivity and aggression in BPD. SSRIs are the first and second choice in the treatment algorithms for impulsive behavioural dyscontrol and affective dysregulation

Mood stabilisers: Comorbid bipolar spectrum disorder is seen in up to 50% of BPD patients and mood stabilisers are commonly prescribed. There is some evidence that mood stabilisers and lamotrigine reduce impulsivity, anger and affect dysregulation in people with BPD. Lithium is licensed for the control of aggressive behaviour or intentional self-harm. Mood stabilisers outperform SSRIs on impulsive behavioural dyscontrol and affective dysregulation and are most effective in these two domains.

However, this approach may not be applicable in situations where patients present in crisis or when a patient is reluctant to engage in the recommended therapies, or if they have severe symptoms or complex comorbid diagnoses, which is sometimes more often the case in a hospital setting, where more than 25% or so of patients with BPD have a traumatic history. And if a patient makes a request for medication to help alleviate their distress, then the recommendations from the Cochrane and Ingenhovan *et al.* reviews are relevant. The authors concluded that prescribing in BPD showed promising results and recommended that the findings from clinical trials were sufficiently cogent to inform clinical practice.

The American Psychiatric Association guidelines for BPD endorse a symptom-targeted approach and provide pharmacological algorithms targeting cognitive perceptual symptoms, impulsive-behavioural dyscontrol and affective dysregulation.

This approach was criticised by NICE who reflected that the above domains were a *post hoc* conclusion drawn by authors and that there are currently no robust data to draw the above conclusions. However, in clinical practice, as summarised in Table 1, and as recommended by many eminent researchers, these domain-based approaches to treatment have some clinical utility.

Unfortunately, specific neurobiological effects of the domains in BPD remain ill defined. Drugs for psychiatric problems are prescribed on the assumption that they mostly act against neurochemical substrates of disorders or symptoms. Joanna Moncrieff and David Cohen argue against this assumption, based on their views of the available evidence. They hold the view that the drugs' actions should be seen as producing an altered, drug-induced state, a view the authors call 'the drug-centred model of action'. The authors recommend that patients choose a drug through collaborative discussion and argue that if a patient exercises more control about the decisions surrounding their treatment, then the value of prescribing is enhanced.[20]

If patients are jointly involved in decision making, taking into account their preferences and values, then prescribing of medications might achieve better outcomes.[21] Also, most guidelines, agree that high-quality, large-scale, adequately powered RCTs in this diverse and complex population group with BPD are urgently needed.

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Declaration of interests

No conflicts of interest were declared.

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