BORDERLINE PERSONALITY DISORDER

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ABSTRACT| Caretakers are often intimidated or alienated by patients with borderline personality disorder (BPD), compounding the clinical challenges posed by the disorder's severe morbidity, high social costs, and substantial prevalence in many health care settings. BPD is found in ~1.7% of the general population, but in 15-28% of patients in psychiatric clinics or hospitals, and in a large proportion of individuals seeking help for psychological problems in general health facilities. BPD is characterized by extreme

sensitivity to perceived interpersonal slights, an unstable sense of self, intense and volatile emotionality, and impulsive behaviors that are often self-destructive. Most patients gradually enter symptomatic remission and their rate of remission can be accelerated by evidence-based psychosocial treatments. Although self-harming behaviors and proneness to crisis can decrease over time, the natural course and otherwise effective treatments of BPD usually leave many patients with persistent and severe social disabilities, relating to depression or self-harming behaviors. Thus, clinicians need to actively inquire about the more central issues of interpersonal relations and unstable identity. Failure to correctly diagnose patients with BPD begets misleading pharmacological interventions that rarely succeed. Whether the definition of BPD should change is under debate, linked to not fully knowing the nature of this disorder.

[H1] INTRODUCTION

Borderline personality disorder (BPD) has a suspect origin within psychoanalysis, an uncertain fit within classification systems and a reputation for being untreatable, which collectively, have all made the ownership of this disorder by psychiatry and by medicine insecure. Aggravating this insecurity are the insistent complaints by the many patients with this disorder of being ignored or mistreated. Indeed, patients with BPD face severe stigma not only from the public but also from clinicians, owing to their reputation for being hostile and intractable.[1]

BPD was initially defined in 1978, following which, this disorder was indexed in the Diagnosis and Statistical Manual of Mental Disorders (DSM), Third Edition (DSM-III) in 1980 and in the International Classification of Diseases 10 years later (as emotionally

unstable personality disorder; Figure 1). The clinical and research literature subsequently has logarithmically risen.

BPD is characterized by extreme sensitivity to perceived interpersonal slights, an unstable sense of self, intense and volatile emotions, and impulsive behaviors (Figure 2). As efforts to treat patients with BPD are often thwarted by patient anger, recurrent suicidality, and non-compliance, the diagnosis has a reputation for intractability and untreatability. However, three independent scientific developments have challenged this reputation. Studies have demonstrated that BPD is treatable[2–4], that most patients recover symptomatically[5,6] and that the disorder has a biological and genetic basis[7]. Given these developments, the BPD diagnosis has met most of the standards for diagnostic validity. However, persistent questions about the definition, core pathology, and treatments of BPD remain, and patients are often avoided, misunderstood, and mistreated.

This Primer identifies the significant advances that have been made in understanding, treating, and validating BPD. In addition, this Primer describes the epidemiology of BPD, pathophysiology, diagnostic methods and challenges, and quality of life issues faced by patients.

[H1] EPIDEMIOLOGY

An overview of 13 epidemiological studies from different countries composed of face-to-face interviews of the general population reporting about all types of personality disorders demonstrated a two-year to five-year prevalence of between 0% and 4.5%,

with a median of 1.7% and a mean of 1.6 % for BPD, the fourth most prevalent of the ten DSM III and DSM IV personality disorders.[8–10] However, a two-year to five-year prevalence has limited value for understanding the importance of the disorder throughout life and from an individual's point of view, the lifetime prevalence is more relevant. The NESARC study in the United States showed a lifetime prevalence for BPD of 5.9%[11] close to four times as high as the average two-year to five-year prevalence found in epidemiological studies of the general population.. A four times as high lifetime prevalence as short time prevalence was also similar to what the NESARC study found for the seven personality disorders they investigated both for short-time and life-time prevalence (BPD was not studied short-time). More-accurate estimates are obtained by repeated assessment and not relying on retrospective memory. In one other study in the United States that evaluated individuals four times from 14 to 32 years of age [9], the average short-term prevalence of BPD was 1.5% and the cumulative prevalence was 5.5 %. Importantly, the short-term prevalence did not increase from year to year; some individuals lost the diagnosis, other individuals without the diagnosis previously received it later for the first time in the study. Relatively few patients had a stable diagnosis from one wave to the next. Generally, patients undergo remission, and few relapse (see Quality of life)[5,6]. BPD can also be diagnosed in childhood with reliability, validity, and stability similar to the diagnosis of BPD in adulthood[12] (Box 1). A notable finding from community based samples is that the prevalence of BPD is relatively similar in males and females, in contrast to the 3:1 female to male gender ratio of the diagnosis in clinical settings cited in the DSM-5[11,13].

Although the prevalence of BPD in the general population is not much higher than the average prevalence of personality disorders, the prevalence of BPD is dramatically higher among patients in psychiatric clinical populations. Indeed, BPD has a high prevalence in all treatment settings [14,15]; patients with BPD constitute ~15-28% of all patients in psychiatric outpatient clinics or hospitals[16–18] , 6% of primary care visits[19] and 10-15% of all emergency room visits[13,20]. In one study from Oslo, Norway, individuals receiving psychiatric treatment (by all institutions, even general practitioner) had a 14 times higher rate of BPD than individuals not receiving treatment[21]. No other personality disorder displayed by far the same tendency with regards to treatment, even if other personality disorders showed similar or higher reductions in quality of life[8,22,23].

[H2] Socio-demographics

As the number of short-time BPD cases even in large studies of the general population is rather low, not many statistically significant results are obtained, even if some non-significant differences between those with BPD and those without are observed. In one study, individuals with BPD were more often single , and had lower education and income than those without BPD[24]. To increase statistical power of epidemiological studies, the number of BPD diagnostic criteria met by individuals can be studied as a dimensional measure of BPD psychopathology and multivariate statistical analysis carried out to avoid results that are due to correlations between the predictors. This was carried out in a study in Oslo, Norway, that demonstrated an association between the number of BPD criteria present, and younger age, less education, and

being single in the center of the city; when controlled for covariance between the variables[8].

[H1] MECHANISMS/PATHOPHYSIOLOGY

A neurobiological model of BPD proposes phenotypes that are the product of interactions of genetic and environmental influences affecting brain development via hormones and neuropeptides. In addition, early childhood maltreatment and the quality of early life parenting care can affect gene expression and brain structure and functions, resulting in behavioral traits that are stable throughout life[25]. However, prefronto-limbic dysfunction (the brain mechanism most frequently associated with BPD) seems to be a transdiagnostic phenomenon that is related to negative affectivity in the context of social stress and is found in patients with other psychiatric disorders[26] and even in healthy individuals who have faced early life maltreatment[27]. Prefronto-limbic dysfunction seems sensitive to change over time, and research is needed to understand this process, as well as other processes that might be (or act) in the pathogenesis and progression of BPD. In general, a dysfunction of single brain circuits is not specific for BPD but rather is the co-occurrence of all or at least several of the dysfunctions described in this section.

[H2] Environmental risk factors

The risk of BPD results from the interaction of genetic factors and life experiences. Inherited temperamental factors sensitize and might predispose individuals to adverse life experiences[28] (see Genetic factors and Gene–Environment interactions, below).

Adverse childhood experiences are strongly associated with BPD in clinical and community samples[29,30]. Indeed, childhood trauma is the most significant environmental risk factor of a BPD diagnosis although it is not a necessary precondition for developing BPD.[31] Although not specific for BPD, childhood maltreatment including physical abuse, sexual abuse, and neglect significantly increased the risk of BPD in prospective community studies in children[32]. Inconsistent parenting, maternal over-involvement, aversive parental behaviors, and low parental affection are also associated with the development of BPD, but are also not specific[33]. In addition, separating children from mothers before 5 years of age predisposes to BPD in adulthood[34]. The personality profiles of children who have been mistreated are characterized by high neuroticism, low agreeableness, low conscientiousness, and low openness to experience, and tend to persist and are similar to the personality traits of adults with BPD[35].

Certain critical developmental periods are implicated in the genesis of personality pathology. Abnormal attachment to a primary caregiver, due to either separation or poor parenting, has been observed, and disrupted attachment early in life likely leads to impairments in emotional regulation and self-control[36]. High stress-reactivity in a child might contribute to problematic attachment. Disorganized attachment between mothers and children predicted borderline symptoms in young adults in a prospective community study[37]. In adolescence, the development of a stable identity or sense of self is a major task, and might lead to personality pathology if delayed or impeded.

Other types of childhood and adolescent psychopathology, such as depressive, anxiety, substance use, and disruptive behavior disorders (e.g., conduct disorder, oppositional defiant disorder, ADHD) predispose to the development of personality

163 pathology, including BPD, in adolescents and young adults[38,39]. Deliberate self-harm,
164 suicide attempts, and other BPD features, such as insecure identity, low goal-
165 directedness, negative affectivity, impulsivity, risk taking behaviors, anger and
166 interpersonal aggression, predict the development and persistence of BPD in children
167 and early adolescents[12,40]. Adolescents with BPD are more likely to present for clinical
168 care with the more acute manifestations (such as self-harm, suicidal behaviour,
169 impulsivity) of BPD than with the temperamental manifestations (such as identity
170 disturbance, unstable relationships and fears of abandonment)[12].

171 **[H2] Genetic factors**

172 The heritability of BPD is high although studies are rare and different values have been
173 reported; notably, data from twin studies suggest that a common family environment
174 has little contribution to the aggregation of BPD within families[41] . When twins are
175 studied using the same person to interview both twins (hence avoiding interviewer
176 variance), the heritability was found to be ~0.70[7]. Similar values have been reported in
177 studies that used both interview and self-report questionnaires[42] and in studies that
178 measured BPD twice, namely 10 years apart[43]. Accordingly, a heritability of ~0.70 is
179 probably the most correct estimate.

180 BPD and the four symptom phenotypes (Figure 2) aggregate in families[44,45–47]. A
181 meta-analysis did not detect a significant association of BPD with typical candidate
182 genes for vulnerability to psychiatric disorders, e.g. *SLC6A4* (encoding the serotonin
183 transporter gene)[48]. The first genome-wide association study in ~1,000 patients with
184 BPD indicates a genetic overlap with bipolar disorder, schizophrenia and major
185 depression; the implicated genes have effects on very basic properties of neural

processing such as cell adhesion or myelination and include *DPYD* (encoding dihydropyrimidine dehydrogenase), *PKP4* (encoding plakophilin-4), and *SERINC5* (encoding serine incorporator 5) [49]. Accordingly, gene variants in individuals with BPD are likely not specific for BPD, but raise the question whether genetic overlap is linked to transdiagnostic clinical symptoms or reflects an increased risk for psychiatric disorders in general. Although genetic factors and neurobiological factors have been pursued as risk factors for BPD; they do not have sufficient specificity for early identification or intervention, which is also true for all psychiatric illnesses.

[H2] Gene–environment interactions

Given the significant role of early life maltreatment in the etiology of BPD, detecting epigenetic alterations that could explain BPD symptoms is of high interest. A genome-wide methylation analysis found increased methylation of some genes, for example, *MIR124-3*, the gene product of which is involved in the regulation of neural plasticity and amygdala functioning; this gene was associated with BPD and childhood maltreatment and might have a role in the pathway from maltreatment in early life to BPD in adulthood[50]. Alterations in methylation of other genes, e.g. increased methylation of *BDNF* (encoding brain-derived neurotrophic factor), are associated with early life maltreatment and susceptibility to BPD[51].

In addition, polymorphisms in genes involved in hypothalamic–pituitary–adrenal (HPA) axis activity, such as *FKBP5* and *CRHR*, may be involved in the etiology of BPD. These variants are more frequent in patients with BPD who had childhood maltreatment than those without childhood maltreatment[52]. However, associations between childhood

trauma and polymorphisms in HPA axis genes have also been found in other psychiatric disorders, such as depression, suicide, and post-traumatic stress disorder (PTSD)[53]. Abnormalities in HPA hormones might mediate the effect of early adversity on brain structure and function in BPD, and impairment of the affect regulation circuitry is a key biopsychological mechanism of this. Variants of *FKBP5* and *CRHR* that are associated with BPD result in enhanced cortisol secretion[25], which leads to structural and functional alterations in the brain, for example, the hippocampus [54]. In addition, studies in healthy individuals suggest that polygenic variation linked to HPA axis function moderates the effect of early life stress on threat-related amygdala activity[55] and that cortisol influences functional connectivity between the amygdala and the dorsal anterior cingulate cortex[56]. Moreover, parent and child HPA-activity shows higher biological synchrony while contacting with one another, that is they show higher correlations in the context of at-risk conditions such as poor quality of parent-child interaction[57]. Furthermore, peripheral oxytocin levels seems to be closely linked to parent-child interaction; oxytocin levels rise in parents and offspring as a function of fine-tuned behavioral synchrony [58]. Behavioural synchrony is whereby in a synchronous relationship, when a child becomes distressed, the parent will succeed in regulating his/her own feelings of discomfort and adopt a soothing behavior, thereby helping the child to restore balance.

[H2] Neural circuitry

Alterations in several brain circuits have been demonstrated to underlie the phenotypes of BPD (Figure 3). Brain circuits related to the interpersonal instability phenotype include those involved in theory of mind (that is, inferring others' emotional,

cognitive and intentional states) and empathy (sharing others' emotions), and circuits related to the self-disturbance phenotype having a role in abnormalities of self-referential thinking and the sense of the self. Brain circuits related to the affective/emotional dysregulation phenotype consist of interacting bottom-up and top-down processes, whereas circuits involved in the behavioral dysregulation phenotype are involved in the prediction of negative outcomes and inhibitory control. The affective pain processing circuit is thought to mediate hypalgesia in non-suicidal self-injurious behavior in patients with BPD.

[H3] Interpersonal and the self phenotypes. Midline brain structures have a role in understanding the mental state of others and the understanding of the mental state of oneself, supporting Fonagy's generative model that the development of the self originates from the contingent resonance of others, particularly early care-givers[59] e.g. when the mother based on observing and rightly understanding the affect of her child reciprocates this. Consequently, the National Institute of Mental Health Research Domain Criteria (RDoC; criteria for the study of mental disorders based on dimensional, functional constructs with levels of information ranging from genomics and brain circuits to behavior and self-reports) have included the perception and understanding of the self and the other under the same construct of "Systems for Social Processes"(https://www.nimh.nih.gov/research-priorities/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml). Midline structures involved both, in understanding the mental state of others and the self, include the medial prefrontal cortex (including the anterior cingulate cortex and dorsomedial PFC), the precuneus and the posterior cingulate cortex, the

temporoparietal junction, and the temporal poles. These brain regions largely overlap with the default mode network (that is, regions that are active when no focus is on the outside world).

Individuals with BPD tend to hypermentalize (that is to overattribute intentions and emotions about the self and others) in a complex and abstract way[60]. Studies investigating the interference of task-irrelevant social information on performance of a cognitive exercise (whereby participants performed a working memory task while viewing emotional scenes for distraction) demonstrated stronger coupling of the amygdala and the medial prefrontal cortex and (para)-hippocampal areas in patients with BPD compared with healthy individuals[61]. This finding could be linked to problems in shifting attention away from self-relevant information to the external task in patients[61]. Another study examined the processing of self-representation or other-representation by instructing participants to evaluate personality traits of oneself (self-representation) and of a close friend (other-representation). Using a two-factorial design, participants had to answer four questions: Are you kind? (1st person on oneself); Is your friend nice? (1st person on the other); According to your friend, are you nice? (3rd person on oneself); According to your friend, is she/he nice? (3rd person on the other). Patients with BPD had higher activation of midline structures in both self-representation and other-representation tasks but no specific abnormalities for a single condition, compared with healthy controls, further supporting an overlap between the neural correlates of self-disturbance and other- disturbance. Interestingly, the hyperactivation of midline structures was associated with less stable social representations[62]. In addition, individuals with BPD show high levels of alexithymia [63], that is they have major

problems in identifying and describing their own emotions which may further deteriorate the understanding of others´ emotions[64] and has been shown to be related to behavioral dysregulation[65].

Other studies have assessed theory of mind and empathy in patients with BPD. Theory of mind and empathy are separate abilities and may not co-vary within an individual. Deficits in theory of mind might have a substantial role in interpersonal dysfunction in BPD. For example, in one study, patients with BPD were asked to evaluate the emotional state and – in a more complex task – the intention of another individual, showing decreased activity in the brain social cognition circuit (the temporoparietal junction and the superior temporal sulcus and gyrus, the latter of which is needed for decoding mimics and gestures of others, compared with healthy controls[66]. The difference between patients and healthy controls increased with task complexity. [66] In addition, reduced activity of the superior temporal sulcus was found in a study in which patients with BPD inferred the emotional state of a person from a situational context[67]**.**

Interestingly, poorly coordinated social exchange between patients with BPD and healthy individuals was recently demonstrated by reduced cross-brain neural coupling between temporoparietal junction networks compared with social exchange between two healthy individuals when performing a joint-attention task in a hyperscanning context [68]. Furthermore, patients with BPD showed reduced functional connectivity between the social cognition network and areas involved in emotional-regulation areas (such as the anterior cingulate cortex) compared with healthy individuals, which might

300 facilitate the distorted interpretation of others' mental states (that is, poor theory of mind,
301 hypermentalizing in particular) in conditions of emotional arousal and stress[69].

302 Although individuals with BPD have impairments in theory of mind, they exhibit a
303 comparable or higher degree of empathy than healthy controls[63]. For example, when
304 individuals were asked how much they feel for a person in distress (that is, were
305 encouraged to share others' emotions), patients with BPD outperformed controls in
306 terms of empathy and showed insular hyperactivity that was associated with enhanced
307 emotional arousal[67]. This finding is consistent with an affect-dominated, rather than
308 cognitive-dominated perception of others that makes patients with BPD vulnerable to
309 distressing contagion (although in "mature" empathy one does not confuse the other's
310 emotion with the self's emotion, this self-other distinction is missing in emotion
311 contagion) [70]. Although the specificity of brain mechanisms underlying abnormal social
312 cognition and empathy functions in BPD still has to be clarified, they differ from those
313 typical of antisocial personality disorder[70].

314 A further prominent characteristic of interpersonal dysfunction is rejection
315 hypersensitivity which is also influenced by emotional hypersensitivity (see below).
316 Across different paradigms of social rejection, the dorsal ACC has been found to be
317 activated and to represent a common neural alarm signal of physical and social pain[71].
318 In a virtual ball-tossing game where participants were either excluded, included or
319 participated in a control condition, patients with BPD showed higher activation of the
320 dorsal ACC in all conditions suggesting a higher sensitivity of the alarm signal even in
321 situations where exclusion was absent. In addition, higher activation in the dorsomedial

PFC and precuneus support the notion of hypermentalizing to be typical of BPD in social situations.[72]

[H3] Affect/emotion phenotype. Affective instability is a central feature of BPD psychopathology and describes frequently escalating negative affects which occur to more or less intense stressors and show a delayed regression to baseline. Neuroimaging studies have demonstrated abnormalities in so-called bottom-up and top-down processes in patients with BPD: bottom-up processes originate from perceptual stimulation of the external world and are important for detecting salience, whereas top-down processes involve cognitive control areas that have a role in pursuing goals and strategic decision-making. Bottom-up emotional processing involves the amygdala, hippocampus, insula and rostral anterior cingulate cortex, whereas top-down emotional processing involves prefrontal areas such as the dorsal anterior cingulate cortex and the orbitofrontal, ventrolateral and dorsolateral prefrontal cortices.

Emotional hypersensitivity (an attentional bias or hypervigilance towards negative environmental stimuli such as a perceived slight or a critical look by a friend or relative that makes patients vulnerable to rapid changes in affect), and the failure to recruit adaptive affect regulation strategies are apparent in patients with BPD[73]. In particular, hypervigilance to negative environmental stimuli occurs in response to social threat signals. For example, women with BPD had more frequent and faster fixations of the eyes to images of angry faces than healthy controls in an emotion classification task, and the abnormal eye fixation was associated with increased amygdala activation[74]. Event-related potentials, based on electroencephalography (EEG), showed increased early occipital P100 amplitudes (in the visual cortex) but decreased later

temporooccipital N170 and centroparietal P300 amplitudes in response to blends of happy and angry facial emotions, indicating a pre-attentive, rapid and coarse processing of social cues in BPD, instead of a more detailed, elaborate processing[75]. Interestingly, the P100 amplitudes normalized in individuals in remission from BPD, suggesting an enhanced perceptual bottom-up process reflects an acute feature rather than a trait [76]. However, prospective studies are needed.

A consistent feature in unmedicated patients with acute BPD is left amygdala hyper-reactivity in response to negative environmental stimuli[77]. Thus, amygdala hyperactivity is not restricted to stimulus onset, but also results from a deficit in habituation (that is, a form of learning whereby the response to a stimulus is reduced after repeated exposure)[78–80]. In addition, the central role of amygdala hyperactivity in BPD might also reflect maladaptive cognitive top-down processes that have a role in evaluating and prioritizing negative environmental stimuli[81]. Smaller volume and metabolic alterations such as reduced N-acetylaspartate concentration found using proton magnetic resonance spectroscopy of the left amygdala have been demonstrated in BPD[77,82], particularly in the centromedial amygdala[83], which projects to hormonal regulatory centers in the hypothalamus, and to autonomic and behavioral centers in the brainstem. The hypothalamus is enlarged[84] and the HPA stress axis is dysregulated in patients with BPD; volume reduction of the amygdala and hippocampus might be more pronounced in patients with early trauma and comorbid PTSD[85,86]. Notably, gray matter volume reductions in the amygdala are only found in older individuals with BPD, probably indicating a progressive pathology[77,87] which, nevertheless, appears to be reversible[88].

Intense and variable emotions are related to amygdala hyperactivity, whereas emotional regulation difficulties in general, and poor capacity of cognitive reappraisal (that is, recognizing the negative pattern of one's thoughts and changing that pattern to one that is more effective in regulating one's emotions), in particular, were negatively correlated with prefrontal cortical activity in BPD[89]. Studies instructing participants to use an adaptive affect regulation strategy (such as cognitive reappraisal), found lower activity in orbitofrontal, ventrolateral or dorsal anterior cingulate cortices in patients with BPD than healthy individuals[90,91]. However, studies using emotional paradigms (passively looking at emotional facial expressions or scenes) without instruction to regulate emotions demonstrated increased prefrontal cortical activity in patients with BPD, which might reflect patients' effort to cognitively down-regulate their emotions despite not being successful[92,93]. In addition, structural alterations of the prefrontal cortex have been demonstrated in patients with BPD, such as smaller grey matter volume[77,94], reduced cortical thickness[94] and microstructural abnormalities of white matter tracts[95]. Furthermore, preliminary data suggest low prefronto-limbic connectivity within the affect regulation circuit[93], which normalizes after successful psychotherapy[96] suggesting that this core mechanism of BPD is reversible.

Evaluative-regulatory feedback mechanisms of emotion regulation include interoceptive processes as the physiological dimension of emotional experience, and seem to be disrupted in patients with BPD. In one study, individuals with BPD had lower right dorsomedial prefrontal cortex activation than healthy controls when asked to attend to emotions and bodily feelings (for example, instructed to "feel yourself and be aware of your current emotions and bodily feelings", compared to cognitive self-reflection

(instructed to “Think about yourself, reflect who you are, about your goals”)[97]. As afferent signals from the periphery, such as heartbeat, are relayed via the spinal cord and brainstem to the midbrain and finally to structures of higher order, such as thalamus, insula and prefrontal cortex, decreased mental representation of bodily signals in patients with BPD was suggested by reduced heartbeat-evoked potentials in resting state EEG (a marker for the cortical representation of afferent bodily signals) compared with healthy volunteers[98]. Indeed, reduced heartbeat-evoked potentials were associated with the severity of emotion dysregulation and smaller volumes of some brain regions, e.g. the left insula which has a major role in the body-brain axis[98]. Remission from BPD was paralleled by an improvement in cortical representation of bodily signals[98].

Notably, similar abnormalities of brain function and structure - as described in this section up to now - have been reported in anxiety disorders, avoidant personality disorder and depression. Prefronto-amygdala dysfunction might manifest a transdiagnostic mechanism associated with negative affectivity or the related trait construct of neuroticism. Supporting the latter assumption, neuroticism was recently shown to modulate a wide network of brain regions, including the emotional regulatory network[99].

[H3] Behavioral dysregulation. Impulsivity is a multifaceted construct comprising various components. Impairments in delay discounting (that is, the ability to delay an immediate smaller reward for a larger, not immediate reward), high emotional interference in cognitive functioning, and a reduction in response inhibition (that is, the

ability to inhibit an already activated behavioral response) in the context of emotional stress have been reported in patients with BPD[100,101]. Indeed, individuals with BPD consistently choose smaller rewards delivered within a short timeframe over larger rewards delivered at a later timeframe compared with healthy individuals. In a monetary incentive delay task in which three different objects predicted a reward, loss or a neutral outcome, individuals with BPD had reduced activation of the ventral striatum to cues predicting reward and loss, compared with healthy individuals and activation was negatively correlated with impulsivity, suggesting that patients might have a poor ability to predict aversive outcomes[102]. In an affective go/no-go task, (in which participants were instructed to respond if the presented facial affect was consistent with the target affect for that epoch and to inhibit motor response to those inconsistent with the target affect), BPD was characterized by alterations in ventrolateral prefrontal or orbitofrontal activity, indicating an interference between the motor inhibition task and the processing of emotional stimuli[103]. Notably, the control of emotional interference at motor inhibition tasks involves brain areas that overlap with the affect regulation circuit, such as the orbitofrontal and subgenual anterior cingulate cortex[104]. Under high levels of stress (e.g. anger induction), females with BPD had decreased activity of the inferior frontal cortex compared with healthy controls during a go/no-go task, which challenges the capability to inhibit prepotent motor responses[105]. Accordingly, abnormalities in the inferior frontal cortex may be a neurobiological correlate of motor impulsivity in BPD[105]. Importantly, in contrast to previous assumptions, a failure of response inhibition beyond situations of intense stress is not characteristic of BPD, but is inherent to ADHD (a highly prevalent comorbid condition of BPD)[100]. Regarding the specificity of findings within the

externalizing spectrum of psychopathology, impairments in delay discounting and a close interaction between behavioral dyscontrol and negative emotional states in BPD differs from individuals with antisocial personality disorder, who have less impairment in delay discounting but a generally deficient response inhibition[100].

[H3] Pain processing circuit. The non-suicidal self-injurious behavior in those with BPD serves as a stress relief and is associated with diminished affect-related pain processing. Increased pain thresholds in patients with BPD might be based on two mechanisms[106]. First, deactivation of the amygdala and enhanced negative coupling between limbic and medial prefrontal areas might reflect an enhanced inhibitory top-down modulation in BPD. Consistent with this theory, amygdala activity decreased more in individuals with BPD than in healthy controls, and functional connectivity with the superior frontal gyrus normalized in BPD after an incision in the forearm[107]. Second, enhanced coupling between the posterior insula (involved in the processing of affect-related pain), and the dorsolateral prefrontal cortex might reflect an abnormal evaluation of pain that contributes to hypoalgesia in BPD[108]. Indeed, the experience of pain — not the tissue damage — leads to subjective stress reduction in patients with BPD[109]. Interestingly, dialectical behavior therapy (DBT) focuses on improving affect regulation strategies (see Management) and decreased inhibitory top-down modulation[110]. However, low self-worth and a self-critical cognitive style might also constitute a significant mediator between hypoalgesia and non-suicidal self-injurious behavior,[111] although the significance of this mechanism for BPD is not yet clear. Further studies may improve our understanding of what mechanisms act in each individual in which

context and how the pain circuit interferes with key regions of the self-processing and self-valuation systems of the brain.

[H2] Hormones

Dysfunction of the HPA axis has a central role in the development of BPD. Indeed, most studies have demonstrated increased levels of stress hormones, such as basal cortisol[112], a steeper cortisol awakening response (that is, a sharp increase in cortisol levels after awakening) [113] and reduced feedback sensitivity[112] in patients with BPD. Additionally, increased memory retrieval (memory of words, working memory and most pronounced of autobiographical memory) following cortisol administration in patients with BPD suggests alterations in the sensitivity of glucocorticoid receptors to stress hormones; in healthy individuals, cortisol administration was followed by impaired memory retrieval[114]. In addition, increased HPA activity correlated with early life maltreatment in BPD[112]. Interestingly, the extent of the cortisol stress response in a parent–young adult conflict discussion was modulated by the quality of parental protection, at least as perceived by individuals with BPD[115].

Peripheral oxytocin levels are decreased in adults with BPD[116], particularly in those with a history of early life maltreatment[116], and disorganized attachment representations[117]. Oxytocin is thought to act as a counterpart to cortisol and buffers chronic stress responses, particularly in the social context[118]. In BPD, oxytocin seems to dampen subjective and psychophysiological stress responses[119] as well as hypersensitivity to social threat[74] and other negative emotional stimuli[120] by modulating amygdala activity. Variants of *OXTR*, which encodes the oxytocin receptor (namely the

rs53576 single nucleotide polymorphism), are modulated by the environment; thus, gene-environmental interactions related to the oxytocin receptor modulate vulnerability to psychopathology in general[121] and BPD[122]. Importantly, these effects might be sex-sensitive[123].

Few studies have investigated sex hormones in BPD. Testosterone concentrations appear to be increased in female and male patients with BPD, whether assessed as short-term testosterone in saliva[113] or long-term testosterone in hair (a cumulative measure representing excretion levels over several months)[124]. Interestingly, testosterone has been shown to be involved in prefronto-amygdalar inhibition in a social approach-avoidance task whereby participants are instructed to approach and avoid emotional faces by pulling and pushing a joystick, respectively, and therefore, might favor social approach and dominant behavior [124,125]. Furthermore, changes in female sex hormones (such as estradiol and progesterone) during the menstrual cycle might affect BPD symptom expression[126].

[H1] DIAGNOSIS, SCREENING, AND PREVENTION

[H2] DSM-5 and ICD-10 diagnostic criteria

The DSM-5[127] Section II diagnostic criteria for BPD can be divided into four phenotypes, consistent with the general criteria for a personality disorder (Figure 2); diagnosis is made by a polythetic model requiring at least 5 of the 9 criteria (Box 2). Like

other psychiatric illnesses in the DSM, the BPD diagnostic criteria define an independent category although this category overlaps with other disorders.

Meeting increasing numbers of the BPD criteria in the DSM-5 up to a total of five criteria is associated with more-severe illness [128]. The presence of even one BPD criterion distinguishes patients with respect to concurrent other mental disorders, current suicidal ideation and past attempts, history of psychiatric hospitalization, and functional impairment[129]. Although all criteria for BPD are weighted equally for diagnosis, the unstable relationships criterion has the best combined sensitivity and specificity for BPD two years later[44] and had the highest familial aggregation in one study[41].The criterion of chronic feelings of emptiness was most strongly related to psychosocial morbidity, including history of suicide attempts, hospitalization, social and work dysfunction, and comorbidity with other mental disorders[130].

In the International Classification of Diseases, 10th Revision (ICD-10) [131], BPD is called emotionally unstable personality disorder and is characterized by unstable sense of self, unstable relationships with other people, and unstable emotions[131].

[H2] Clinical assessment

Patients with BPD frequently present for treatment in the midst of an episode of another mental disorder, such as depressive disorders, anxiety disorders, trauma-related disorders, or substance use disorders. Patients might also present after a suicide attempt or other impulsive, self-destructive actions, or might have a current interpersonal crisis (such as a relationship break-up) or other crisis (such as a job loss or school failure) that leads them to seek help.

In most clinical settings, assessment of patients with suspected BPD will be conducted by interview. As personality is the way people see, relate to, and think about themselves, others, and the environment, the perception of one's own personality is affected by it and accordingly, the assessment of personality pathology has unique challenges. Indeed, individuals with personality pathology are frequently unreliable observers of their own personality problems and might recognize problems only when they affect their interactions and relationships with others. Rather than directly questioning individuals about their personality, clinicians often look for patterns in the way patients describe themselves, their interpersonal relationships, and their work functioning. Common questions a clinician would pose to an individual with a suspected personality disorder include "how would you describe yourself as a person?", "how do you think others would describe you?", "who are the most important people in your life?" and "how do you get along with them?". In addition, clinicians often also rely on how individuals interact with them during the interview and may interview other individuals close to the patient to gather additional information and perspectives. Several additional factors should be considered during the assessment of a patient for BPD (Box 3).

Clinical assessments of borderline personality pathology are challenging. For example, clinicians might overgeneralize their experiences with patients during evaluation to other life situations without sufficient evidence. In addition, clinicians might have a general impression of the patients personality but with inadequate information to evaluate the specific criteria for BPD[132]. Clinicians will often deviate from their judgments about individual criteria and overdiagnose or underdiagnose BPD without a basis[133]. These sources of diagnostic unreliability – interpretation, information, and

551 criterion variance – have led to the development and use of semi-structured[134] and fully-
552 structured diagnostic interviews and self-report questionnaires for the diagnosis of BPD
553 and other personality disorders. Indeed, self-report instruments and semi-structured
554 interviews are more reliable and valid than routine clinical assessments for the
555 diagnosis of personality pathology[135] and the combined use of interview and self-report
556 optimally identifies BPD[136].

557

558 **[H3] Clinical interviews.** Most semi-structured interviews include questions to elicit
559 information to determine whether or not a subject or patient meets each of the
560 diagnostic criteria and apply diagnostic algorithms for all DSM-IV and DSM-5
561 personality disorders. These interviews differ primarily in the arrangement of the
562 questions, either by type of disorder or by area of functioning (Table 1). All semi-
563 structured interviews are meant to be administered by trained clinicians who have
564 experience evaluating patients with mental disorders in general and, specifically,
565 patients with personality pathology. Examples of clinical interviews include the
566 Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), the Structured
567 Interview for DSM-IV Personality Disorders (SIDP-IV), the Revised Diagnostic Interview
568 for Borderlines (DIB-R), and the Childhood Interview for DSM-IV Borderline Personality
569 Disorder (CI-BPD); the latter two assessments are specific to BPD. Some tools were
570 designed for use by non-clinical, lay interviewers in large epidemiological studies (such
571 as Alcohol Use Disorder and Associated Disabilities Interview Schedule-5), which
572 includes questions to assess the criteria for BPD. Other, short interval interviews such
573 as the Borderline Personality Disorder Severity Index-IV and the Zanarini Rating Scale

for Borderline Personality Disorder are used to track severity and change in BPD pathology over time.

[H3] Self-report questionnaires. Although patients with personality disorders have difficulty accurately observing themselves, a plethora of self-report instruments have been developed to expedite diagnostic assessments and as first-stage screening assessments (Table 1). Self-report instruments differ in their structure, length, and specificity for BPD. In addition, several self-report instruments are particularly suited for BPD screening in large populations. Of note, the affective instability criterion is the most sensitive and specific manifestation for BPD diagnosis and might be useful for screening[137]. Other self-report instruments do not assess personality disorders but assess problems in personality functioning.

[H2] Differential diagnosis and comorbidities

As individuals with BPD frequently present for treatment due to an exacerbation of another co-occurring mental disorder, careful assessment of a broad range of psychopathology is indicated in an individual with suspected BPD[138,139]. Several other disorders might also be present in patients with BPD including mood (e.g., major depressive disorder or bipolar disorder), anxiety, stressor-related (e.g., acute stress disorder, PTSD), substance-related, dissociative, disruptive behavior, somatoform, neurodevelopmental (e.g., attention-deficit/hyperactivity disorder) and other personality disorders[10]. Indeed, rates of lifetime major depressive disorder range from 61% to 83%, with a median of 71%[140–142], and the lifetime rate of anxiety disorders is 88% in patients

with BPD[141] in several large patient samples. A history of trauma, central to the diagnosis of PTSD, is also common in patients with BPD. ADHD has been reported in ~20% of patients with BPD [143]. The differential diagnosis between BPD with comorbid major depressive disorder and bipolar disorders is complex (Box 4).

The type and frequency of co-occurring disorder depends on the population assessed (i.e., patient or general population), clinical setting (e.g., inpatient, outpatient, sub-specialty clinic), the prevalence of the disorders in the population, the duration of the disorders, and the methods of assessment, among other factors. [10] Co-occurring disorders are unlikely to be comorbid in the sense of a disorder that is distinct from the index disease or condition[144]. Indeed, some patients with BPD do not respond to antidepressants and depressive symptoms can remit with improvement of BPD [145,146], suggesting that depression is linked to patient's dissatisfaction with life rather than a comorbid depressive disorder. Similarly, remission of BPD usually prompts remission of anxiety disorders[147]. In addition, the tendency of the DSM to split up psychopathology into different disorders encourages the diagnosis of multiple disorders to describe a patient's psychopathology and virtually ensures that patients receive more than one diagnosis. This, in turn, has encouraged polypharmacy (see Management). As BPD complicates the treatment of other mental disorders and is associated with a more chronic course for many disorders [148,149] and as effective treatment of BPD can diminish associated psychopathology, [147,150] distinguishing BPD from other mental disorders may be less important than setting priorities among disorders for treatment.

BPD is also associated with non-psychiatric disorders, including arthritis, gastrointestinal conditions, and, in young adults, cardiovascular disease.[151]

[H2] Prevention

Data is relatively scarce on the prevention of BPD development, including universal prevention, selective prevention (in high-risk populations, such as individuals who have been sexually or physically abused), or indicated prevention (in individuals with signs of BPD or underlying pathological personality traits in childhood or early adolescence). Universal prevention is not practical owing to the relatively low prevalence of BPD in all age groups. Risk factors lack sufficient specificity for BPD to support use in selective prevention. The identification of a BPD prodrome consisting of increased emotionality, hyperactivity or impulsivity, depression and inattention has been supported in one large prospective follow-up study of young girls[37]. Programs designed for early intervention in young people with precursor signs or a diagnosis of BPD have been developed[12,152,153] and sometimes implemented for example, in Australia, Germany and the Netherlands. Certainly, individuals at any age who meet criteria for BPD should receive treatment[154].

[H1] MANAGEMENT

The treatment of patients with BPD should begin with disclosure of the diagnosis and education about the expectable course, genetics, and treatment of the disorder. This approach can diminish distress and establish an alliance between the patient and the clinician [155]. Treatment should also inform patients that effective therapies have been developed, which involve learning to take care of oneself, and that medications

643 serve only an adjunctive role. Often patients with BPD will be misdiagnosed[132,156],
644 disliked[157], and overmedicated [158,159]. Such practices persist despite considerable
645 knowledge about how patients can be treated effectively.
646
647 **[H2] Evidence-based therapies**
648 Five general principles characterizing evidence-based effective treatments for
649 BPD have been developed[160,161]. First, treatment should be carried out by a primary
650 clinician who develops the treatment plan and goals, oversees the risk of suicide and
651 monitors progress. Second, management should have structure, such that therapies
652 have identifiable goals, the roles of both the patients and treater are specified,
653 boundaries about the availability of the treater have been determined and guidelines for
654 managing safety are established. Third, management should be collaborative and
655 clinicians should solicit their patients' involvement in setting the treatment goals and,
656 safety plans and within-session participation. Indeed, the patients sense of responsibility
657 for change and self-care is emphasized. Fourth, clinicians should be actively
658 responsive, reassuring patients that they are listening and interested, while also being
659 contained, not being overly emotional or activating. Finally, clinicians should be self-
660 aware, and colleagues should be used to diminish the hazards of personalized
661 reactions of patients. Of particular note is the principle, important for patients with BPD,
662 of reminding clinicians to be aware of how their reactions to patients requires attention
663 because they can be harmful.
664 13 forms of psychological therapy have demonstrated efficacy for the treatment
665 of BPD in at least one randomized controlled trial, although DBT has the most research

support. The availability of these therapies varies worldwide from being not available at all to at best being only inconsistently available. Nowhere is their availability sufficient to meet the public health needs. Four of these therapies have attained widespread recognition along with being grounded in substantive theories about BPD and sustained training opportunities offered by credentialed and committed trainers (Table 2). These therapies — dialectical behavioural therapy (DBT), mentalization-based treatment (MBT), transference focused psychotherapy (TFP) and General ("Good") psychiatric management (GPM) — all decrease suicidality and self-harm, depression, anxiety, and use of hospitals and emergency rooms in patients with BPD [3,4,162–165].

DBT, MBT and TFP are psychotherapies, and intend to change patient's psychological functions (such as self-awareness, empathy and social skills) through insights, instruction, and corrective interpersonal experiences. DBT is a type of cognitive-behavioral therapy that focuses on diminishing the observable symptoms of BPD. [2] MBT and TFP are psychodynamic therapies that focus on improving patients' understanding of their motives and feelings that are often unconscious and are thought to prompt symptoms[3,166]. With all these psychotherapies, the relationship between the patient and the therapist is often a central focus, and these require considerable training and time to learn.

The three main psychotherapies have been compared with less intensive manualized approaches that are less challenging to learn, more supportive, and more suitable for non-specialist, generalist providers [167,168]. GPM is a case management-based therapy that medicalizes BPD and focuses on the patient's situational stressors. This generalist

approach is intended to improve patients' social functioning with the expectation that this improvement will improve self-esteem, self-confidence, and social/interpersonal skills[169]. The development of a generalist model for the treatment of BPD offers a treatment modality that can be taught to clinicians using standard training programs. GPM is also well suited for integration with stepped care models of health care[170]. Non-intensive interventions administered by non-specialists are well-suited for early intervention and patients with less-severe BPD[171]. Such a model has been introduced in Australia with encouraging results[171].

[H2] Effect of co-morbidities

The management of patients with BPD is frequently confounded by co-occurring psychiatric disorders. Unlike with other personality disorders, the treatment of BPD should take priority in patients with comorbid major depressive disorder, panic disorder, adult-onset PTSD, intermittent substance abuse or bulimia, as these disorders remit with remission of BPD[169]. As anxious dysphoria is almost universal in patients with BPD [172] and a high proportion of patients have comorbid major depressive disorder, patients often are prescribed anti-depressants[159,173].

The treatment of comorbid bipolar I disorder, early-onset complex PTSD, severe substance abuse and anorexia should be prioritized over the treatment of BPD, as effective treatment of BPD requires the remission of these disorders. The co-occurrence of impulse control disorders (such as severe substance abuse) or severe antisocial personality disorder makes the successful treatment of BPD improbable. Milder forms of these disorders can interfere with the treatability of BPD, but treatment of BPD is

possible and will secondarily prompt improvement in those disorders[174,175]. In comorbid bipolar I disorder, a manic episode should always be treated before BPD; BPD and bipolar disorder should be treated as independent disorders as they have little effect the course of the other disorder[150]. Questioning whether treating comorbid PTSD should take priority is common. The treatment of early onset complex PTSD take priority over treatment of BPD, but otherwise BPD treatment usually improves PTSD and this effect can be augmented by concurrent exposure techniques[176,177].

[H2] Psychoactive medication

Patients with BPD who were diagnosed before they received trials with psychoactive medications, often multiple types extending over many years, are uncommon[14,15,158]. Approximately 40% of patients with BPD were prescribed ≥3 psychotropic medications, ~ 20% were prescribed ≥4 medications, and ~10% were prescribed ≥5 medications concurrently after diagnosis of BPD in a 16 year follow up study[158]. The most common types of medication administered to patient with BPD are selective serotonin reuptake inhibitors, atypical antidepressants, anxiolytics, antipsychotics and mood stabilizers, in that order[158]. This practice has developed despite that the usefulness of medications has not been established, no class of psychoactive medication is consistently or dramatically effective, and no medications are FDA approved for BPD[159,173,178,179,180]. Medications are often initiated by clinicians aiming to relieve the patient's presenting complaints of depression, moodiness, or anxiety; patients do not present asking for personality change. The National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom state that

psychotropic medications should not be used to treat the symptoms of BPD but can be prescribed for comorbid disorders for the shortest period possible [179]. Once medications are started, patients with BPD typically resist discontinuing them, even when the target symptoms are unchanged or exacerbated. In one study, a high percentage of patients with BPD reported using psychotropic medications at each of eight two-year follow-up periods[158]. Augmentation of medications is common, but is without empirical support[158].

A cautious empirical approach to medication management, recognizing their adjunctive role in treating some patients with BPD, can be helpful. This should include informing patients that the benefits of medication are variable and usually modest, encouraging patients to read about prescribed medications, enlisting patients as collaborators to evaluate whether target symptoms alter and tapering or discontinuing ineffective medications before starting another trial. This approach might disappoint patients who had hoped for a more beneficial role of medications, but it is a relief for patients who understand that their illness can be successfully treated by other means after disappointing results from medications.

[H2] Sociotherapies

The support of families, including spouses is often essential for enlisting the collaboration of patients with BPD. Attaining the families' supportive involvement begins with disclosure of the BPD diagnosis and a discussion about the disorder's genetics, expectable course, and its treatment. Families are often willing to modify the usual ways of responding to the patient with BPD, and to learn to accommodate the specific sensitivities and problems that characterize individuals with this disorder. Specifically,

this means learning to validate the distress of the patient with BPD, listening without challenging the patient's anger, and using professionals to help manage threats of suicide or self-endangering behaviors[181,182]. Family therapy is usually contraindicated until members are motivated and able to see each other's perspectives. Family Connections is a consumer-led group therapy that has proven very helpful to many[181].

The social learning processes within group therapies are often very helpful and cost-beneficial for patients with BPD who typically have problems with listening, sharing, and understanding others. Indeed, the group therapy component accounts for much of the effectiveness of DBT[163] and MBT[183]. However, patients usually resist such treatment, so making individual therapy (which patients desire) contingent on participation in groups might be necessary.

[H2] Overview

Great steps forward have occurred in the treatment of BPD. Indeed, combining treatment with informing patients about their likelihood of recovery, patients can have much higher expectations than previously thought. However, challenges remain to develop psychoactive medications that can directly address the emotional reactivity and interpersonal hypersensitivity of BPD, and that can improve persisting social and vocational problems (see Quality of Life). Therapies that target the persisting functional problems of patients are required.

[H1] QUALITY OF LIFE

[H2] Course of disease and prognosis

Two major prospective longitudinal studies (The McLean Study of Adult Development (MSAD) and the Collaborative Longitudinal Personality Disorders Study (CLPS)) yielded unexpectedly encouraging perspectives on the symptomatic course of BPD. In the CLPS study, ~85% of patients with BPD had a remission for at least 12 months, of which, relapse rates were 12% (Figure 4)[6]. In the MSAD study, 99% of patients had a remission period for at least 2 years and 78% of patients had remission for at least 8 years, over the 16 year follow-up[5]. However, symptomatic recurrence occurred at higher rates in the MSAD study (between 10 and 36%, depending on the length of the remission, with lower rates associated with longer periods of symptomatic remission), compared with CLPS.[5] Baseline predictors of a poor outcome in the CLPS study at two-year follow-up were more severe borderline psychopathology, functional impairment, and the quality of relationships.[184] At 10-year follow-up, the CLPS study found younger age and more education to be associated with good outcomes.[6] Predictors of remission by 10-year follow-up in the MSAD study were baseline younger age, absence of childhood sexual abuse, no family history of substance abuse, good vocational record, absence of an anxious cluster personality disorder, lower neuroticism, and higher agreeableness.[185]

Interestingly, some symptoms of BPD were demonstrated to remit more rapidly than others which are more enduring in both the MSAD and CLPS studies[186–188]. Most impulsive symptoms are acute and have relatively rapid remission, whereas all affective/emotional symptoms are more enduring[187]. Cognitive/self symptoms are both acute (such as, quasi psychotic thought and serious identity disturbance) and enduring

(such as, odd thinking, unusual perceptual experiences and non-delusional paranoia). Similarly, interpersonal symptoms can be acute or enduring; stormy relationships, devaluation, and demandingness are more acute, whereas fear of aloneness, undue dependency, and masochism are more enduring[186]. In the MSAD study, the more rapid and stable remission of acute symptoms and the less rapid remission and higher recurrence of temperamental symptoms was demonstrated after 16-years of follow-up[187]. However, after 10-years of follow-up in the CLPS study, the prevalence of all BPD criteria had declined at similar rates[6].

[H2] Social and Vocational Functioning

Individuals with BPD living in the community are often seriously impaired functionally.[11,22,189] Prospective studies of the course of BPD have determined the stability of these impairments for some patients. In the CLPS study, individuals with BPD had significantly worse employment functioning than individuals with Cluster C personality disorders (avoidant and obsessive-compulsive personality disorders) and had significantly worse Global Assessment of Functioning (GAF) scores than individuals with Cluster C personality disorders or major depressive disorder, at the two-year follow-up point [190]. Similarly, in the MSAD study, [191] patients reported poorer social and vocational functioning than those with other personality disorders at the six-year follow-up period[191]. However, remitted borderline patients reported better social and vocational functioning than non-remitted borderline patients, and the percentage of patients receiving disability payments was ~35% for those in remission, but increased from 56% to 73% for patients who had not remitted.[191] In addition, 43% of patients in remission

had a GAF score of ≥61 representing good overall functioning at the six-year follow-up period, compared with no patients not in remission.[191]

In the MSAD study, survival analyses showed that patient functioning was quite unstable, with some subjects losing their good psychosocial functioning and others attaining it for the first time.[192] However, 50% of patients attained recovery (defined as a concurrent remission from BPD and good social and good full-time vocational functioning) after 10 years of prospective follow-up, and 60% of patients attained recovery after 16 years of prospective follow-up. [193]Although patients with BPD improved in both the social and vocational realms, they continued to function more poorly than individuals with other personality disorders or major depressive disorders in the CLPS study after 10 years of follow up[6]. The MSAD findings concerning recovery rates indicate that there are subgroups of borderline patients—a high functioning group and a more poorly functioning group. They also suggest that studies that rely on overall results may inadvertently hide these important differences.

Patients with BPD who had recovered at some point during the course of disease were significantly more likely to have entered into a marriage or prolonged cohabitation relationship, and become a parent than patients who have never recovered in the MSAD study after 16 years of follow up[194]. Recovered patients are also significantly older when starting these relationships. Moreover, patients who had recovered were significantly less likely to have divorced or ended a cohabiting relationship, and were less likely to have given up or lost custody of a child (7% vs. 51%). Taken together,

these results suggest that patients with BPD can have stable intimate relationships and become competent parents. In addition, success in these areas is more likely if patients have recovered symptomatically and have achieved stable psychosocial functioning in other areas.

[H2] Other health and lifestyle issues

After six-year follow-up, patients who had not been in remission were significantly more likely to have a “syndrome-like” condition (e.g., chronic fatigue, fibromyalgia), obesity, diabetes, osteoarthritis, hypertension, back pain, and urinary incontinence than patients who had been in remission.[195] They were also significantly more likely to report daily consumption of alcohol, smoking one packet of cigarettes per day, daily use of sleep medications, overuse of pain medications, and lack of regular exercise. In addition, non-remitted patients with BPD were significantly more likely than remitted patients with BPD to have had at least one medically-related emergency room visit, medical hospitalization, or both. At 16-year follow-up, these same variables distinguished ever and never-recovered borderline patients.[196]

A large epidemiological study found elevated rates of a number of conditions among borderline persons living in the community. These conditions were: arteriosclerosis or hypertension, hepatic disease, cardiovascular disease, gastrointestinal disease, arthritis, venereal disease, and any assessed medical condition.[197]

[H2] Mortality

By the time of the 16-year follow-up in the MSAD study, 4.5% of borderline patients had died by suicide and 4.5% had died of other causes[187]. Although patients with BPD have a known increased risk of suicide, data from the MSAD study suggest that suicide might not be as common as previously estimated. For patients with other personality disorders, 1.4% had died from suicide and 1.4% had died from another cause [187]. The average age of non-suicidal deaths was 39 years of age, suggesting that patients with BPD died up to 40 years prematurely, compared with the life expectancy norms of 78 or 79 years of age in the United States.[198]

[H1] OUTLOOK

One of the major challenges is that we still do not have a satisfactory understanding of what comprises the core psychopathology of BPD. As suggested within this Primer, this core psychopathology could be within the affect/emotion dysregulation phenotype and/or within social processes, reflecting both the interpersonal and self phenotypes. Like for other major mental illnesses, the search for the core psychopathology of BPD identified by specific biomarkers or specific genetic alterations associated with BPD is ongoing, but such markers have not yet been found. The ambiguity inherent in the name “borderline” persists largely as a fall-back option until the core psychopathology has been successfully identified.

Growing evidence suggests that BPD is related to a general personality disorder factor (‘g’) that is common to all personality disorders and reflects the severity of personality psychopathology[199]. General features of personality disorders have less stability than specific trait features, consistent with the notion that personality functioning

is the more dynamic and changeable aspect of personality pathology, whereas personality traits are stable, but general features are also more closely related to impairment in psychosocial functioning[200]. The National Institute for Mental Health Research Domain Criteria (RDoC) include 'perception and understanding of self' encompassing self-awareness, self-monitoring, and self-knowledge, and 'perception and understanding of others' related to social cognitive functions, as two subdomains of 'Social Processes' [201], in addition to affiliation and attachment, which are moderated by social information processing including the detection of and attention to social cues.

The definition of BPD also faces challenges. The DSM-5 retained the definition for BPD that it has largely sustained since its conception, but an alternative proposal, named the Alternative Model for Personality Disorders (AMPD; Box 5) was developed by the DSM-5 personality disorders working group in 2011. The AMPD model appears in the DSM-5 section III[202]. In this model, the traditional criteria for BPD are parsed into impairments in personality functioning (self and interpersonal functioning) and into pathological personality traits (negative affectivity, disinhibition and antagonism). These personality trait domains were developed to represent personality disorders based on meta-analyses[203] and a field trial survey[204]. The AMPD criteria for BPD are highly correlated (correlation coefficient of 0.80) with the standard crtieria[205], such that application of either criteria to clinical observations made by trained diagnosticians will lead to the reliable identification of BPD . Establishing the reliability, validity, and clinical utility of the AMPD is undergoing active research. The AMPD has several potential advantages over standard DSM-5 criteria. First, it emphasizes the centrality of the self and interpersonal sectors of the psychopathology of BPD, thereby helping identify what

best distinguishes BPD from other disorders with which it can be confused. Second, the AMPD bridges the definition of BPD to trait structures of normal and abnormal personality and, therefore, links BPD with the known anatomy of personality and will help reflect that most personality disorders do not have discrete boundaries between normal and abnormal functioning. Although these advantages for changing the definition of BPD are substantial, reasons for moving slowly are also apparent[206]. For example, the heritability of BPD is high compared with other personality disorders, BPD combines externalizing and internalizing symptoms, and has clinical priority over other major psychiatric disorders. Moreover, it doesn't load on any specific personality factors, rather it is distinguished by loading on a general factor. At this point in the development of the BPD construct it seems important to retain multiple points of view regarding the psychopathology of BPD.

A final challenge is that research in BPD is remarkably underfunded. Despite the prevalence of BPD in the general population the high prevalence within treatment facilities, high morbidity and high costs to society (Box 6), BPD comprises <1% of the National Institute for Mental Health funded research. Europe is the foremost leader in BPD-related research and within Europe, Germany stands out for establishing BPD as a major research priority. Reasons for the failure of BPD to gain traction within the research establishment in the United States might be the sustained stigma associated with this disorder. Indeed, patients with BPD are difficult and the temptation is to ignore or avoid these patients, justifying and aggravating their continued protests of being neglected and unheard.

This Primer has summarized the remarkable body of knowledge that has been acquired since the official recognition of BPD in 1980. Research into the genetic and neurobiological abnormalities of this disorder have earned its place within the biomedical community. However, still, the search for specificity in terms of biological or genetic markers remains as is the case with other mental illnesses. Research into the psychology, development, and response to psychological therapies of BPD have established the place of this disorder within the mental health field's clinical community. Here, the neurobiological correlates of change in BPD psychopathology and new therapies to better diminish persisting social and vocational impairment require further study. Research into the prevalence and its societal costs of BPD have established this disorder as a still inadequately addressed major public health problem. Increased public awareness, better training of health care professionals, and increased investment in research are needed.

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S.C.H. was the past president of the International Society for the Study of Personality Disorders. A.E.S. receives author and editor royalties from American Psychiatric

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Box 1. BPD in children and adolescents.

Although borderline personality disorder (BPD) is thought to start in childhood or early adolescence, it typically comes to clinical attention in early adulthood. However, clinicians have been reluctant to diagnose personality disorders in childhood and adolescence for several reasons: personality is considered to be in flux during this time; some immature attitudes and behaviours may be developmentally appropriate; and diagnosis could be stigmatizing.

A cumulative prevalence of BPD of 1.4% by 16 years of age and 3.2% by 22 years of age has been reported in the United States[9]. BPD diagnoses in childhood and adolescence have low to moderate diagnostic stability and moderate to high mean level (level of manifestations within a population) and rank order (an individual's position on manifestations within a group) stability [207]. From a systematic review of 10 studies, 14–40% of children or adolescents <19 years of age retained the BPD diagnosis after periods of between 2 and 20 years. [207] Thus, individuals with BPD pathology early in life can improve over time, but those with more-severe symptoms have a risk for BPD in early adult life and have substantial social, educational, work, and financial impairment in later life[208].

Complex comorbidity of BPD and other mental disorders is found in adolescents similar to in adults with BPD[209]. In a large community sample of girls at risk of BPD, the development of BPD symptoms was associated with impairment in eight domains of psychosocial functioning (for example, academic achievement, self-perception, social skills, sexual behavior) in the age range 14-17 years[210]. Taken together, these data suggest that BPD should be recognized and treated in children and early adolescence,

and early intervention may prevent BPD chronicity and persistent associated psychosocial morbidity[211,212].

Box 2. DSM-5 criteria for BPD.

Five or more of the following nine criteria are required for the diagnosis of borderline personality disorder (BPD) according to the Diagnosis and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) [127].

- Frantic efforts to avoid real or imagined abandonment
- A pattern of unstable and intense interpersonal relationships that are characterized by alternating between the extremes of idealization and devaluation
- Markedly and persistently unstable self image or sense of self (identify disturbance)
- Impulsivity in at least two areas that are potentially self-damaging (for example, spending, sex, substance abuse, reckless driving or binge eating) [a]
- Recurrent suicidal behaviour, gestures or threats, or self-mutilating behaviour
- Affective instability due to a marked reactivity of mood (for example, intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely lasting for more than a few days)
- A chronic feeling of emptiness
- Inappropriate, intense anger or difficult controlling anger (for example, frequent displays of temper, constant anger or recurrent physical fights)
- Transient, stress-related paranoid ideation or severe dissociative symptoms

[a]Does not include suicidal or self-mutilating behaviour .

BOX 3. Additional factors to be considered in evaluating patients with BPD.

Emotional intensity, anger, neediness, demanding behaviour, and tendencies to either overvalue or devalue the clinician should be anticipated during evaluations of patients with borderline personality pathology [10]. Clinicians should elicit information about how the patient views themself and interacts with others, and they must establish that the features of borderline personality pathology are pervasive (manifest in many different life contexts and with many people) and inflexible (persist despite evidence that they are inappropriate, ineffective, or maladaptive). Focusing on maladaptive personality traits such as impulsivity and specific problematic behaviors, such as self-mutilation, is useful for documenting pervasiveness, as by definition personality traits are tendencies or predispositions to think, feel, or behave in patterned ways.

Personality pathology is often evident by adolescence or early adulthood, as individuals encounter major life transitions, such as leaving home, becoming financially independent, and forming intimate relationships with people outside their families. Although personality pathology has traditionally been considered as stable and enduring, more recent, rigorous, longitudinal follow-along studies demonstrated that the most patients with BPD can substantially improve over time[5,6]. As patients with BPD frequently present for care due to an episode of another co-occurring mental disorder the clinician should distinguish signs and symptoms of the more acute disorder (states) from the manifestations of BPD (traits). Valid diagnoses of BPD can be made in individuals with concurrent major depressive disorder[213].

BOX 4. Bipolar disorders and BPD.

A differential diagnostic dilemma that has befuddled clinicians and researchers is between bipolar disorder – especially bipolar II disorder – and borderline personality disorder (BPD) with comorbid major depressive disorder. Bipolar disorders and BPD co-occur in ~10-20% of patients with either disorder, but most patients have only one of these disorders[214]. Many patients with BPD have been mistakenly diagnosed as having a bipolar disorder at some time[215]. Episodes of mood disturbances in bipolar disorders last longer and are less connected to external events than the labile affective states of BPD that are commonly triggered by stressful life events. Patients with major depressive disorder and comorbid BPD have significantly higher rates of post-traumatic stress disorder, substance use disorders, somatoform disorders, and other personality disorders than patients with bipolar II disorder without BPD [216]. Patients with major depressive disorder and BPD also have more-severe impairment in global and social functioning, and have an increased number of suicide attempts. First-degree relatives of patients with bipolar II disorder have a higher morbid risk for bipolar disorder than patients with major depressive disorder and BPD.

Box 5. DSM-5 Alternative Model for Personality Disorders Diagnostic Criteria for BPD.

Moderate or greater impairment in personality functioning, manifested by characteristic difficulties in two or more of the following four areas:

1. Identity: markedly impoverished, poorly developed, or unstable self-image that is often associated with excessive self-criticism, chronic feelings of emptiness or dissociative states under stress.
2. Self-direction: instability in goals, aspirations, values, or career plans.
3. Empathy: compromised ability to recognize the feelings and needs of others associated with interpersonal sensitivity (i.e., prone to feel slighted or insulted) or the perceptions of others are selectively biased toward negative attributes or vulnerabilities.
4. Intimacy: intense, unstable, and conflicted close relationships, marked by mistrust, neediness, and anxious preoccupation with real or imagined abandonment; close relationships often viewed in extremes of idealization and devaluation and alternate between overinvolvement and withdrawal.

A. Four or more of the following seven pathological personality traits, at least one of which must be impulsivity, risk taking, or hostility:
   1. Emotional lability (an aspect of negative affectivity): unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances.
   2. Anxiousness (an aspect of negative affectivity): intense feelings of nervousness, tenseness, or panic, often in reaction to interpersonal stresses;

worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fears of falling apart or losing control.

3. Separation insecurity (an aspect of negative affectivity): fears of rejection by and/or separation from significant others, associated with fears of excessive dependency and complete loss of autonomy.
4. Depressivity (an aspect of negative affectivity): frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feelings of inferior self-worth; thought of suicide and suicidal behavior.
5. Impulsivity (an aspect of disinhibition): acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behavior under emotional distress.
6. Risk taking (an aspect of disinhibition): engagement in dangerous, risky and potentially self-damaging activities, unnecessarily and without regard for consequences; lack of concern for one's limitations and denial of the reality of personal danger.
7. Hostility (an aspect of antagonism): persistent or frequent angry feelings; anger or irritability in response to minor slights of insults.

Note: Both criterion A and B must be met. Not all facets of a criterion need to be present for a criterion to be met, if one or two manifestations are strikingly descriptive of the

patient. For diagnosis, impairments in personality functioning and the individual's personality trait expression are also relatively inflexible and pervasive across a range of personal and social situations, are relatively stable over time and can be traced back to at least adolescence or early adulthood, are not better explained by another mental disorder, are not solely attributable to the physiological effects of a substance or another medical condition, and are not better understood as normal for an individual's developmental stage or sociocultural environment. Adapted from DSM-5 [127].

Box 6. Costs to society.

Multiple studies have documented the high direct costs associated with treatment of borderline personality disorder (BPD)[217,218]. The frequent use of high cost hospital and emergency room services by patients accounts for a higher proportion of these direct costs than outpatient therapies[217]. Patients who have been in remission[195] or who receive evidence-based interventions[218] diminish these costs. The estimated reduction in yearly healthcare costs for those who receive evidence-based treatments is $4,139 per patient compared with costs for BPD patients receiving usual care in Australia[218]. Accompanying the direct costs for BPD are indirect costs associated with patients' persistent failures in social adaptation, most significantly the lack of vocational productivity. Indirect costs are estimated to be two to four times higher than the costs of direct health care usage[217,219].

Less easy to document are the costs associated with increased divorce rates, custody battles, automobile accidents, medical disability, and compensatory childcare of patients. The burden of patients with BPD on those who love or care for them is higher than for other major mental illnesses[220]. This burden is evident in altered lifestyles[221], and in feelings of powerlessness, anxiety, hopelessness, and depression of caregivers[222,223].

Figure 1. Milestones in BPD diagnosis, underlying mechanisms and treatment. Patients who in retrospect had BPD were first described by the problem they caused their physicians in both office practice and hospitals [224,225]. Contributions from a psychoanalyst, Otto Kernberg[226], a scientist, Seymour Kety[227], and a distinguished leader in psychiatry, Roy Grinker[228], legitimized the significance of these patients to psychiatry >50 years ago. The diagnostic criteria for BPD arose by the identification of what best distinguished this disorder from schizophrenia and depression[124,229,230]. In 1980, BPD was classified in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III)[202], followed 10 years later by its adoption into the International Classification of Diseases (ICD-10) as emotionally unstable personality disorder)[131]. CLPS. Collaborative Longitudinal Personality Disorders Study; MSAD, The McLean Study of Adult Development; PSA, psychoanalysis**.**

Figure 2. Symptoms of BPD.

In the interpersonal instability phenotype, individuals with borderline personality disorder (BPD) have unstable and conflicted relationships, and patients alternate between over involvement with others and social withdrawal. Patients can become deeply involved and dependent on some individuals, but they become manipulative and demanding when they feel like their needs are not met. Indeed, patients have dramatic shifts in their views toward people with whom they are emotionally involved, leading them to idealize these individuals when they feel that their needs are being met and devaluating them at other times when they feel disappointed, neglected, or uncared for. Patients have difficulty recognizing the feelings and needs of other individuals and are hypersensitive

to social threat, particularly real or perceived interpersonal rejection. Patients also fear abandonment by others and go to great lengths to avoid abandonment whether it is real or imagined by, for example, showing provocative behaviours such as clinginess, or threatening or demanding behaviour. In the cognitive/self disturbance phenotype, individuals with BPD have markedly impoverished, poorly developed, or unstable self-image (such as self-contempt) that is often associated with a chronic feeling of emptiness. Patients also have low self-esteem, are prone to self-criticism and feelings of shame, and can harbor self-contempt or self-hatred. Personal goals, aspirations, values, and career plans are inconsistent, frequently change, and are pursued without conviction. Patients can also experience disturbed cognition, such as transient paranoid ideation or dissociative symptoms when under stress. In terms of the affective/emotional dysregulation phenotype, patients are emotionally labile and react strongly, particularly in interpersonal contexts, with intensely experienced and expressed dysphoric emotions, such as depression, anxiety, or irritability. Patients are prone to intense, inappropriate outbursts of anger, and can engage in physical fights. Behavioral dysregulation in BPD involves problems with excessive behaviors that put the patient at risk for harm and problems with poor impulse control. Individuals with BPD can engage in impulsive spending; indiscriminate sex; substance abuse; reckless driving; binge eating; self-injurious behavior (e.g., cutting, burning); and recurrent suicide gestures, threats, and attempts. Impulsivity in BPD typically occurs in negative, distressing emotional states.

Figure 3: Alterations of brain circuits in BPD.

Functional alterations in midline structures such as the medial prefrontal cortex, the temporoparietal junction, the posterior cingulate cortex, and the precuneus seem to underlie distorted self thinking and thoughts about others in BPD[61,62]. Enhanced connectivity between the amygdala and midline structures might be associated with hypermentalizing (that is excessive interpretation of mental states) about the self and others. Low activity in midline structures and reduced activity of the superior temporal sulcus might have a role in deficient reasoning about the mental states of others[66,68,70,231] whereas a non-reflective, intense sharing of others' emotions is associated with overactive insular activity[67]. Alterations of the affect regulation circuit might be involved in amygdala hyper-reactivity to negative stimuli[77], particularly to social threat cues, dysfunctional prefrontal processes[90–93] and deficient prefronto-limbic connectivity[93]. Although affect dysregulation is a central clinical feature of BPD, this mechanism might reflect the trait of negative affectivity that is shared by individuals with the broad spectrum of internalizing disorders and/or be sequelae of early life maltreatment. Impulsivity is based on alterations in the reward and control circuits, delay discounting being mediated in the ventral striatum[102] and deficient behavioral inhibition in prefrontal areas[103,104]. The affective pain processing pathway, which has a major role in non-suicidal self-injurious behavior in BPD, might be based on two mechanisms: a negative functional coupling between the amygdala and the medial prefrontal areas[107], and an enhanced coupling between the posterior insula and the dorsolateral prefrontal cortex[108]. In addition, preliminary data suggest impairments of coordinated activities between social cognition and emotion regulation areas[69].

INS: insula; DLPFC: dorsolateral prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; OFC: orbitofrontal cortex; DACC: dorsal anterior cingulate cortex; HIP: hippocampus; AMY: amygdala; MPFC: medial prefrontal cortex; PCu/PCC: precuneus/posterior cingulate cortex; STS: superior temporal sulcus; TPJ: temporoparietal junction; VS: ventral striatum.

Figure 4. Rates of Symptomatic Remission of BPD. Remission of borderline personality disorder (BPD) in the Collaborative Longitudinal Personality Disorders study. 2 months and 12 months refers to the two definitions of remission; 2 months refers to remission for 2 or more months with 2 or fewer BPD criteria, 12 months refers to remission for 12 or more months with 2 or less BPD criteria**.** Adapted from [6].

Table 1. Illustrative Interview and Self-Report Measures.

Name (abbreviation)	Scope	Comments	Refs
Semi-structured clinical interviews or clinician rated instruments			
Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)	All personality disorders	Items grouped by type of personality disorder .	232
Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV)	All personality disorders	Items grouped by type of personality disorder.	233
International Personality Disorders Examination (IPDE)	All personality disorders DSM-IV + ICD-10	Items grouped by topic, such as work, self, interpersonal, affect, reality testing (that is, assessing for psychotic-like symptoms), impulse control.	234
Structured Interview for DSM-IV Personality Disorders (SIDP-IV)	All personality disorders	Items grouped by type of personality disorder or by topic.	235
Structured Clinical Interview for the DSM-5 Alternative Model for Personality Disorders Module III (SCID-5-AMPD)	BPD + 5 other personality disorders	Items grouped by type of personality disorder. Based on DSM-5 AMPD.	236
Revised Diagnostic Interview for Borderlines (DIB-R)	BPD only	Items grouped by areas of functioning (impulsive actions, affect, cognition and interpersonal relations).	237,238
Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD)	BPD only	Designed specifically for adolescents.	239
Borderline Personality Disorder Severity Index-IV (BPDSI-IV)	BPD only	Dimensional, short interval change measure that has adolescent and parent versions.	240
Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)*	BPD only	Dimensional, short interval change measures.	241,242
Structured Interview for Lay Person Administration			
Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5)	BPD, ASPD, STPD	Used in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	243
Self-Report Instruments for Diagnosis			

Personality Diagnostic Questionnaire-4 (PDQ-4)	All personality disorders	Includes clinical significance questions.	[244]
Personality Assessment Inventory (PAI)	BPD and ASPD	Identity problems, negative relationships, affective instability, self-harm. This measure includes validity scales and has an adolescent version.	[245]
Borderline Symptom List (BSL)	BPD	Full and short versions available.	[246]
Five Factor Borderline Inventory (FFBI)	BPD	Based on the five-factor model of personality traits.	[247]
Self-Report Instruments to Assess Pathological Personality Traits			
Schedule for Nonadaptive and Adaptive Personality-II (SNAP-II)	All personality disorders and traits	Higher order factors and lower order traits. Can be scored for diagnoses. Has youth version.	[248]
Dimensional Assessment of Personality Pathology – Basic Questionnaire (DAPP-BQ)	BPD and OPD traits	Identity problems, insecure attachment, affective lability, self-harm scales.	[249]
Minnesota Multiphasic Personality Inventory-2-Restructured Form (MMPI-2-RF)	Personality disorder traits	Dimensional.	[250]
Personality Inventory for DSM-5 (PID-5)	BPD and OPD traits	Based on the DSM-5 AMPD.	[251]
Self-Report Instruments for Screening			
McLean Screening Instrument for BPD (MSI-BPD)	BPD	10 items. Translated into multiple languages and has been used in adults and adolescents.	[252]
Borderline Personality Questionnaire (BPQ)	BPD	Has been used for screening in adults and adolescents.	[253]
Borderline Personality Features Scale for Children (BPFSC)	BPD	Dimensional measure deigned to assess children and adolescents. Has child and parent versions and has been used for screening.	[254]
Self-Report Instruments to Assess Impairment in Personality Functioning			
Severity Indices of Personality	Personality	Includes 5 domains of	[255]

Problems (SIPP-118)	Functioning	personality functioning.	
General Assessment of Personality Disorder (GAPD)	Personality Functioning	Measures self or identity problems and interpersonal dysfunction.	[256]
Level of Personality Functioning Scale Self-Report (LPFS-SR)	Personality Functioning	Measures severity of impairment in personality functioning. Based on the DSM-5 AMPD.	[257]

* Semi-structured, clinical interview and self-report. AMPD, Alternative Model for Personality Disorders; ASPD, antisocial personality disorder; BPD, borderline personality disorder; DSM, Diagnosis and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; OPD, other personality disorder; STPD, schizotypal personality disorder.

Table 2. Major evidence-based treatments.

Type of therapy	Description	Frequency of treatment (Hrs/week)	Training
Dialectical behaviour therapy (DBT)	Individual and group components using a cognitive-behavioural model. Emphasizes patients to build skills for self-harm and emotional regulation. Therapies coach, are active, directive, and validating.	1hr individual / 2 hr group / 24/7 availability / 2hr therapist consultation (>5 hr/wk)	Two 5-day workshops
Mentalization-based treatment (MBT)	Individuals and group components using a developmental model. Emphasizes patients to consider the effects of the self on others and vice versa. Therapists are active, curious and validating.	1hr individual / 2hr group / 1hr therapist consultation (4hr/wk)	3-day workshop

Transference focused psychotherapy (TFP)	Individual psychotherapy using a psychoanalytic model. Focuses on the integration of disowned ("split off") aggression, especially as it occurs within the therapy relationship. Therapists are active, neutral and challenging.	2hr individual / when necessary consultation (2hr/wk)	Two 3-day workshops and one year group supervision
General ("Good") psychiatric management (GPM)	Individual case management-orientated therapy focusing on situational stressors and social adaptation. Medication, family and group interventions are added as needed. Therapists are active, directive and challenging.	1hr individual / when necessary consultation (1hr/wk)	One-day workshop, when necessary supervision