

## Borderline personality disorder

Falk Leichsenring, Eric Leibling, Johannes Kruse, Antonia S New, Frank Leweke

Lancet 2011; 377: 74–84

Department of Psychosomatics and Psychotherapy, University of Giessen, Germany (Prof F Leichsenring DSc, Prof J Kruse MD, Prof F Leweke MD); Department of Psychosomatic Medicine and Psychotherapy, University of Goettingen, Germany (Prof E Leibling DSc); Mental Illness Research, Education and Clinical Center, James J Peters VA Medical Center, Department of Veterans Affairs and Mount Sinai School of Medicine, New York, NY, USA (A S New MD)

Correspondence to: Prof Falk Leichsenring, Department of Psychosomatics and Psychotherapy, University of Giessen, Ludwigstrasse 76, 35392 Giessen, Germany falk.leichsenring@psycho.med.uni-giessen.de

Recent research findings have contributed to an improved understanding and treatment of borderline personality disorder. This disorder is characterised by severe functional impairments, a high risk of suicide, a negative effect on the course of depressive disorders, extensive use of treatment, and high costs to society. The course of this disorder is less stable than expected for personality disorders. The causes are not yet clear, but genetic factors and adverse life events seem to interact to lead to the disorder. Neurobiological research suggests that abnormalities in the frontolimbic networks are associated with many of the symptoms. Data for the effectiveness of pharmacotherapy vary and evidence is not yet robust. Specific forms of psychotherapy seem to be beneficial for at least some of the problems frequently reported in patients with borderline personality disorder. At present, there is no evidence to suggest that one specific form of psychotherapy is more effective than another. Further research is needed on the diagnosis, neurobiology, and treatment of borderline personality disorder.

### Introduction

Borderline personality disorder is a common mental disorder associated with high rates of suicide, severe functional impairment, high rates of comorbid mental disorders, intensive use of treatment, and high costs to society.<sup>1–5</sup> In recent years, research findings have contributed to an improved understanding and therapy of these difficult-to-treat patients. In this Seminar, we provide an up-to-date review of recent research on the diagnosis, epidemiology, course, causes, and treatment of borderline personality disorder in adults.

### Epidemiology

In epidemiological studies of adults in the USA, prevalences for borderline personality disorder were between 0.5% and 5.9% in the general US population<sup>6,7</sup> with a median prevalence of 1.35 as assessed by Torgersen and colleagues.<sup>8</sup> There is no evidence that borderline personality disorder is more common in women.<sup>7,9</sup> In clinical populations, borderline personality disorder is the most common personality disorder, with

a prevalence of 10% of all psychiatric outpatients and between 15% and 25% of inpatients.<sup>9,10</sup> In a study of a non-clinical sample,<sup>7</sup> a high rate of borderline personality disorder was reported (5.9%), indicating that many individuals with this disorder do not seek psychiatric treatment. In primary care, the prevalence reported for borderline personality disorder was four-times higher than that in the general population, suggesting that individuals with this disorder are frequent users of general medical care.<sup>11</sup>

### Diagnosis

According to the current psychiatric classification system in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), borderline personality disorder is characterised by a pervasive pattern of instability in interpersonal relationships, identity, impulsivity, and affect (panel).<sup>12</sup> For a diagnosis of borderline personality disorder, at least five of the nine criteria must be met. However, suicidal tendency or self-injury are the most useful indications for a correct diagnosis,<sup>13</sup> whereas suicidal tendency or self-injury and unstable relationships have been the most predictive features in follow-up studies.<sup>14</sup> Accordingly, the rank ordering of criteria as most prototypical of this disorder in DSM-IV was not supported by the evidence. Further research is needed to establish whether some criteria should be given more emphasis than others.<sup>5</sup> The nine DSM-IV criteria of borderline personality disorder seem to indicate a statistically coherent construct.<sup>15</sup> Because factor analyses have established both a one-factor model and a three-factor model (disturbed relatedness, behavioural dysregulation, affective dysregulation), an underlying multidimensional structure of borderline personality disorder consisting of three homogeneous components might exist.<sup>5,15</sup> With nine DSM-IV criteria and a threshold for five positive criteria of a diagnosis of borderline personality disorder, however, there are 151 theoretical possible ways of diagnosing this disorder.<sup>2,3</sup> Thus, despite conceptual coherence, borderline personality disorder seems to be a heterogeneous diagnostic

### Search strategy and selection criteria

We searched Medline, PsycINFO, and Current Contents from their start dates to Dec 31, 2009, with the database-specific search terms such as “borderline personality disorder”, “borderline personality”, or “borderline disorder”. The search was updated in Aug 30, 2010. We mainly selected publications from the past 5 years. Studies had to meet criteria of recent Cochrane reviews on borderline personality disorder;<sup>79,107</sup> for example, participants had to be aged 18 years or older, diagnosis of borderline personality disorder was made by use of operational criteria such as that described by DSM-IV or comparable approaches (eg, revised diagnostic interview for borderlines); and outcome measures for which reliability has been indicated were used. In studies of psychotherapy, studies had to also report a clear purpose (eg, pre-defined therapeutic benefits), define a rationale for participant inclusion or exclusion, and include a detailed description of the intervention (eg, treatment manuals or manual-like guidelines).<sup>79,107</sup> Pharmacological interventions targeting cognitive-perceptual, affective, and impulsive-behavioural areas of borderline personality disorder were included. With respect to treatment, only randomised controlled trials (RCTs) were included. Two authors (FaL, FrL) independently extracted the necessary information from each article. In cases of disagreement, a third author was included (EL) and disagreements were resolved by consensus.

category, which can include subtypes of patients, such as those with or without stress-related paranoid ideations or chronic feelings of emptiness.<sup>3</sup>

### Course

Although more stable than major depressive disorder, borderline personality disorder seems to be less stable over time than expected for personality disorders.<sup>5,16,17</sup> High rates of remission were reported in both short-term and long-term follow-up studies.<sup>16</sup> The rate of remission does not seem to be affected by major depressive disorder. By contrast, the rate of remission of major depressive disorder does seem to be significantly reduced by co-occurring borderline personality disorder.<sup>18</sup> Affective features (eg, anger, anxiety, depression) and interpersonal features indicative of abandonment and dependency were the most prevalent and stable, whereas impulsive symptoms (eg, suicide efforts, self-injury) and interpersonal features indicative of treatment regressions were the least prevalent and consistent.<sup>19</sup> Features of this disorder decline over time and this process seems to be partly affected by temperament.<sup>19</sup> With fewer features over time, personality disorders such as borderline personality disorder become more correlated with each other and less distinct as individual disorders.<sup>20</sup> Changes in personality traits (defined by the five-factor model) seem to be followed by changes in the personality disorder psychopathology of borderline personality disorder, but not vice versa.<sup>21</sup> Traits were more unstable in patients with borderline personality disorder than in patients with other personality disorders indicating a “stable instability”,<sup>22</sup> a term introduced by Schmideberg.<sup>23</sup> Data from most studies show that patients with borderline personality disorder are not at higher than average risk for schizophrenia or bipolar disorder.<sup>24,25</sup>

### Comorbidity

Borderline personality disorder is regularly associated with comorbid axis I and axis II disorders.<sup>5-7</sup> 84·5% of patients with borderline personality disorder met criteria for having one or more 12-month axis I disorders, and 73·9% met criteria for another lifetime axis II disorder.<sup>6,7</sup> Borderline personality disorder is most frequently associated with mood disorders, anxiety disorders, and disorders associated with substance misuse.<sup>5-7</sup> With a lifetime prevalence of 39·2%, post-traumatic stress disorder is common but not universal in patients with borderline personality disorder,<sup>7</sup> which questions the view of borderline personality disorder as a complex form of post-traumatic stress disorder.<sup>26</sup> With respect to comorbid mental disorders, differences between female and male patients with borderline personality disorder have been reported, with disorders associated with substance misuse being more common in men and eating disorders being more common in women.<sup>7</sup>

Borderline personality disorder is associated with severe and stable functional impairment<sup>5-7,27</sup> and characterised by a high risk of suicide.<sup>3,28</sup> The mortality rate from suicide is between 8% and 10%, which is

#### Panel: DSM-IV-TR diagnostic criteria for 301.83 borderline personality disorder

The essential feature of borderline personality disorder is that it has a pervasive pattern of instability of interpersonal relationships, self-image, and affect, with notable impulsivity that begins by early adulthood and is present in various contexts, as indicated by five (or more) of the following:

- 1 Frantic efforts to avoid real or imagined abandonment\*
- 2 A pattern of unstable and intense interpersonal relationships characterised by alternating extremes of idealisation and devaluation
- 3 Identity disturbance: notably and persistently unstable self-image or sense of self
- 4 Impulsivity in at least two areas that are potentially self-damaging (eg, spending, sex, substance misuse, reckless driving, binge eating)\*
- 5 Recurrent suicidal gestures, or threats or self-mutilating behaviour
- 6 Affective instability caused by a distinct reactivity of mood (eg, intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
- 7 Chronic feelings of emptiness
- 8 Inappropriate intense anger or difficulty controlling anger (eg, frequent displays of temper, constant anger, recurrent physical fights)
- 9 Transient, stress-related paranoid ideation or severe dissociative symptoms

\*Note: does not include suicidal or self-mutilating behaviour covered in criterion 5. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

50-times higher than in the general population.<sup>3,28</sup> However, there are reports of lower rates.<sup>29</sup> Patients with borderline personality disorder have more functional impairment and higher use of treatment than do patients with major depressive disorder.<sup>1,30</sup> However, some patients with borderline personality disorder have good psychosocial functioning (25·9%), but most of them (80%) lose this level of functioning over time and do not regain it.<sup>31</sup> Personality disorders have a negative effect on the treatment outcomes of various axis I disorders.<sup>2</sup>

### Psychosocial factors in the development of borderline personality disorder

Patients with borderline personality disorder report many negative events (eg, trauma, neglect) during childhood<sup>32</sup> and substantially more adverse events than do patients with other personality disorders.<sup>33</sup> However, no close association between these experiences and the development of psychopathological changes in adulthood has been identified.<sup>34,35</sup> For this reason, an interaction between biological (eg, temperamental) and psychosocial factors (eg, adverse childhood events) will probably provide the best explanation of how the condition develops,<sup>36</sup> consistent with results from recent studies of gene/environment interaction in this disorder.<sup>37,38</sup> The figure shows the biopsychosocial model of borderline personality disorder.

### Genetic factors and neurobiology

Evidence has emerged that genetic factors contribute to the development of borderline personality disorder;<sup>39-41</sup> however, no specific genes have yet been clearly identified as causative. For dimensional representations of

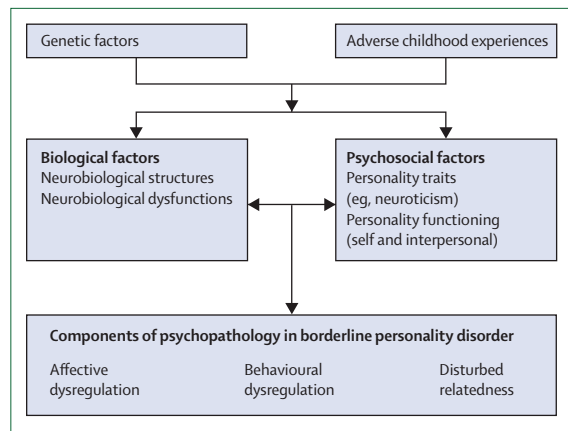


Figure: The biopsychosocial model of borderline personality disorder

borderline personality disorder traits (ie, their quantitative intensity), a moderate heritability has been reported.<sup>40</sup> In studies of twins, heritability scores for the full diagnosis were 0.65 to 0.75,<sup>42</sup> consistent with heritability estimates for personality disorders in general (40%–60%).<sup>43</sup> Impulsive aggression, common in patients with borderline personality disorder, is associated with reduced serotonergic responsiveness,<sup>44</sup> and some genes that might be linked to psychopathological changes in the disorder are involved in the serotonergic system.<sup>42</sup> Thus, the serotonin system is the neurotransmitter system of greatest interest in these patients, and is the assumed site of action for specific selective serotonin-reuptake inhibitors.<sup>42</sup> Data from a candidate gene study<sup>45</sup> showed an association between a haplotype containing the short allele in the serotonin transporter gene (the serotonin-transporter-linked promoter region [5-HTTLPR] in *SLC6A4*) and development of borderline personality disorder; however, no association between polymorphisms in 5-HTTLPR and this disorder were reported in another study.<sup>46</sup> Presence of the short allele of 5-HTTLPR can also indicate a poor treatment response to fluoxetine in patients with borderline personality disorder.<sup>47</sup> Polymorphisms in 5-HTTLPR might also modulate the association between serious life events and the development of impulsivity in patients.<sup>37</sup>

In a study of gene–gene interactions,<sup>48</sup> an interaction between the Met158 allele of the catecholamine-O-methyltransferase gene (*COMT*) and the short allele of 5-HTTLPR was reported in patients with borderline personality disorder, but no association between the 5-HTTLPR genotype alone and development of this disorder was reported. Although the results of these studies suggest a role for polymorphisms in 5-HTTLPR in these patients, there are undoubtedly complex gene–gene and gene–environment interactions, thus making the results inconclusive.<sup>42</sup>

Another gene that has been implicated in impulsive aggression and suicidal behaviour is the tryptophan hydroxylase gene (*TPH*), which encodes the first enzyme

in serotonin biosynthesis. Two isoforms are known—*TPH-1* and *TPH-2*. Patients with borderline personality disorder have a higher frequency of two of eight polymorphisms in *TPH-2* than do controls.<sup>49</sup>

Finally, in a recent case-control study,<sup>50</sup> patients with borderline personality disorder had a greater frequency of polymorphisms in the variable number tandem repeat of the high-activity monoamine oxidase A gene promoter allele than did healthy volunteers. Taken together, the published evidence suggests that there is an abnormality in serotonergic function, which underlies the impulsive aggressive symptoms, and that this defect might be associated with specific genetic risk factors, but the precise molecular nature of this abnormality is not yet clear. Data from early studies of dexamethasone-suppression tests<sup>51,52</sup> have suggested that this disorder was associated with excessive production of cortisol and hypothalamic-pituitary-adrenocortical hyperactivity, although this finding was reported in many patients who had post-traumatic stress disorder with severe histories of trauma. However, in more recent studies that investigated borderline personality disorder without comorbid post-traumatic stress disorder, there was evidence of hypersuppression of cortisol, interpreted as increased feedback inhibition of the hypothalamic-pituitary-adrenocortical axis.<sup>53</sup>

## Neuroimaging

### Anatomical MRI findings

Although CT studies of the brain did not detect any morphological changes in patients with borderline personality disorder, reduced volume in the amygdala has been reported in some studies with structural MRI.<sup>54,55</sup> Excitotoxicity in the course of this disorder was discussed as a possible cause of reduced amygdala volume. Similar to these findings, no morphological changes in the amygdala were reported after the first appearance of symptoms in teenagers.<sup>56</sup> Reduced hippocampal volumes,<sup>57</sup> but no reductions in the amygdala volume, were observed in patients with post-traumatic stress disorder.<sup>58</sup> Although results from a recent meta-analysis<sup>59</sup> indicated that the amygdala volume in patients with borderline personality disorder was smaller than that in healthy controls, data from studies not included in that analysis,<sup>60–63</sup> including some with hand-tracing of the amygdala, did not show a reduced amygdala volume in these patients. Data from these subsequent studies also highlight the importance of taking into account the effect of comorbid post-traumatic stress disorder on amygdala volume, because patients with borderline personality disorder without post-traumatic stress disorder might not have reduced amygdala volumes.<sup>60</sup> Thus, evidence about the specificity of reductions in amygdala volume in patients with borderline personality disorder is inconsistent.

Although there were no volumetric differences in the pituitary gland between patients with early-stage borderline personality disorder and controls,<sup>64</sup> the

pituitary gland volume in teenagers with first-presentation borderline personality disorder was positively correlated with the number of parasuicidal actions.<sup>65</sup> In psychosis, the volume of the pituitary gland seems to be positively correlated with the extent of activation of the hypothalamic-pituitary-adrenocortical axis.<sup>66</sup> Thus, an increased volume of the pituitary gland in patients with borderline personality disorder might be an indicator of increased activity of this axis.<sup>65</sup> Several reports have revealed morphological changes in other neuroanatomical structures in patients with borderline personality disorder. A reduction in grey matter volume in the anterior cingulate gyrus, posterior cingulate gyrus,<sup>63</sup> or hippocampus,<sup>55,67</sup> and a reduced size of the right parietal cortex in these patients<sup>67</sup> have been reported. Moreover, size abnormalities of the superior parietal cortices were correlated with dissociation in these patients.<sup>68</sup> Reduced grey matter volumes in the dorsolateral cortex and in the left orbitofrontal cortex were reported in an early stage of borderline personality disorder.<sup>69</sup> No differences in the grey matter volume between patients with borderline personality disorder and patients with other psychiatric disorders were reported.<sup>69</sup> The authors assumed an early morphological change in the prefrontal cortex of patients with borderline personality disorder; however, this change might be nonspecific.

#### PET

Results from most PET studies detected changes in frontal glucose metabolism in patients with borderline personality disorder. In these studies, a hypometabolism was more often reported than a hypermetabolism,<sup>70</sup> which lends support to the assumption of a frontolimbic dysfunction in these patients. Moreover, autobiographical memories of abuse events in traumatised women without borderline personality disorder were accompanied by large increases in blood flow of the prefrontal cortex (right anterior cingulate, left orbitofrontal, right dorsolateral prefrontal cortex) and a decrease in the left dorsolateral prefrontal cortex compared with traumatised women with borderline personality disorder.<sup>60</sup> These findings might be indicative of dysfunctions in prefrontal areas in this disorder. In a recent PET study<sup>71</sup> of aggression provocation, patients with borderline personality disorder activated orbital cortex more than did controls, whereas controls activated regions of prefrontal cortex more typically associated with emotion control than did those with borderline personality disorder. This result lends further support to the view that there is an abnormality in prefrontal brain regions associated with emotional control function in borderline personality disorder.

#### Functional MRI findings

The most consistent finding in patients with borderline personality disorder is increased amygdala activation compared with control individuals when viewing aversive emotion-inducing slides<sup>72</sup> or when viewing pictures of

human emotional facial expressions.<sup>73</sup> During the recall of an unresolved life event, only patients with borderline personality disorder (vs healthy controls) showed bilateral activations of the amygdala.<sup>74</sup> The amygdala is assumed to function as a key structure during the processing of anxiety and other affective states. As expected, there was no activation of the amygdala in patients with borderline personality disorder or in healthy individuals when positive visual material was presented.<sup>75</sup> Furthermore, activation of the prefrontal cortex was reported for patients with borderline personality disorder after inducing negative emotions, possibly indicating an attempt to control intensive emotions.<sup>74,76</sup> When asked to use a cognitive strategy to control their responses to unpleasant pictures by distancing themselves from the image, those with borderline personality disorder had less blood-oxygen-level dependent (BOLD) signal changes in the anterior cingulate and had greater activation in the superior temporal sulcus and superior frontal gyrus than did controls. Thus, patients with borderline personality disorder do not seem to engage the cognitive control regions to the extent that healthy individuals do, which might contribute to the affective instability of this disorder.<sup>75</sup> Further findings from functional MRI studies indicate different neuronal patterns of traumatic memory in patients with and without post-traumatic stress disorder.<sup>77</sup> Only in patients with post-traumatic stress disorder did a thermic pain-induction evoke a decreased amygdala activation.<sup>78</sup> These results might indicate the existence of different neural networks in subgroups of patients with borderline personality disorder.

These reports lend support to the assumption of a dysfunctional frontolimbic network in borderline personality disorder. This network seems to involve the anterior cingulate cortex, the orbitofrontal cortex, the dorsolateral prefrontal cortex, the hippocampus, and the amygdala. However, future studies are needed, including with individuals who do not have borderline personality disorder, including healthy controls, patients with axis I disorders or patients with other personality disorders to investigate the specificity of these findings.

#### Treatment

The American Psychiatric Association's practice guideline recommends psychotherapy as the main treatment of borderline personality disorder, with pharmacotherapy as an adjunctive component of treatment that targets state symptoms during periods of acute decompensation and trait vulnerabilities.<sup>28</sup> This guideline is a set of evidence-based best practice recommendations. The pharmacotherapy algorithms are directed towards three clusters of symptoms: cognitive-perceptual symptoms (with neuroleptics), affective symptoms (with selective serotonin-reuptake inhibitors), and impulsive-behavioural dyscontrol (with selective serotonin-reuptake inhibitors and low-dose neuroleptics).<sup>28</sup>

	Treatment	Mean dose
Bogenschutz et al <sup>89</sup>	Olanzapine vs placebo	6.9 mg per day
de la Fuente et al <sup>92</sup>	Carbamazepine vs placebo	Blood concentration 6.4–7.1 µg/mL
Frankenburg et al <sup>82</sup>	Sodium valproate vs placebo	850 mg per day
Goldberg et al <sup>87</sup>	Tiotixene vs placebo	8.7 mg per day
Hollander et al <sup>93</sup>	Sodium valproate vs placebo	Blood concentration 64.6 µg/mL
Hollander et al <sup>94</sup>	Sodium valproate vs placebo	1325 mg per day
Leone et al <sup>88</sup>	Loxapine vs placebo	14.4 mg per day
Leone et al <sup>88</sup>	Chlorpromazine vs placebo	110 mg per day
Pascual et al <sup>100</sup>	Ziprasidone vs placebo	81 mg per day
Reich et al <sup>96</sup>	Lamotrigine vs placebo	25–275 mg per day
Rinne et al <sup>95</sup>	Fluvoxamine vs placebo	150 mg per day
Salzman et al <sup>85</sup>	Fluoxetine vs placebo	40 mg per day
Schulz et al <sup>97</sup>	Olanzapine vs placebo	2.5–20 mg per day
Shafti and Shahveisi <sup>98</sup>	Olanzapine vs haloperidol	2.5–10 mg per day
Soloff et al <sup>84</sup>	Haloperidol vs amitriptyline vs placebo	4.8 mg per day; 149.1 mg per day
Soloff et al <sup>83</sup>	Haloperidol vs phenelzine sulfate vs placebo	3.9 mg per day; 60.45 mg per day
Zanarini et al <sup>90</sup>	Olanzapine vs placebo	5.3 mg per day
Zanarini et al <sup>95</sup>	Omega-3 fatty acids vs placebo	1 mg per day
Zanarini et al <sup>91</sup>	Olanzapine vs fluoxetine vs olanzapine plus fluoxetine	3.3 mg per day; 15.0 mg per day; 3.2 mg per day plus 12.7 mg per day
Ziegenhorn et al <sup>99</sup>	Clonidine vs placebo	0.45 mg per day

**Table 1: Randomised controlled trials of pharmacotherapy in patients with borderline personality disorder**

### Pharmacotherapy

Following the Cochrane criteria, evidence for the pharmacological treatment of BPD was reviewed in 2006;<sup>79</sup> only ten small randomised controlled trials (RCTs) were identified. The authors concluded that evidence for the pharmacological treatment of BPD was poor.<sup>79</sup> In the meantime, several RCTs on the pharmacological treatment of borderline personality disorder have been done and several reviews have been published.<sup>80,81</sup> Using the same Cochrane criteria as Binks and colleagues,<sup>79</sup> we identified 19 RCTs of pharmacotherapy alone in patients with borderline personality disorder (table 1).<sup>82–100</sup> Additionally, the combination of pharmacotherapy with psychotherapy was studied in four RCTs.<sup>101–104</sup> As stated by the UK National Institute for Health and Clinical Excellence (NICE) guideline group, funding has turned out to be unclear for five additional RCTs (references 75–82 in the webappendix).<sup>105</sup> For this reason, the NICE group deemed the evidence provided by these studies as unreliable and excluded them from analysis. Taking these caveats into account, we decided to exclude these five RCTs from this report. Herein, our review differs from that by Lieb and colleagues,<sup>81</sup> which was critically commented on by Kendall and colleagues.<sup>106</sup> According to the results of the RCTs included, evidence for the pharmacotherapy of borderline personality disorder is as follows.

The antidepressants amitriptyline and imipramine were more effective than placebo for some symptoms of

depression, but not for other symptoms of borderline personality disorder.<sup>84</sup> Few differences between monoamine oxidase inhibitors (phenelzine) and placebo were reported.<sup>83</sup> Phenelzine reduced hostility, but not depression.<sup>83</sup> In one RCT, fluoxetine was not clearly more effective than placebo for depression, but a beneficial effect on anger was reported.<sup>85</sup> In another RCT, beneficial effects of fluvoxamine on mood shifts were reported, but not on aggression or impulsivity.<sup>86</sup>

In some studies, the typical antipsychotic haloperidol was more effective than placebo for several symptoms, but results vary.<sup>83,84,87</sup> By contrast with their previous results,<sup>84</sup> Soloff and colleagues<sup>83</sup> did not find haloperidol more effective than placebo for most outcome measures. Haloperidol seems to be more effective than tricyclic antidepressants (amitriptyline) for hostility and schizotypal symptoms.<sup>84</sup> Phenelzine was more effective than haloperidol for some symptoms (eg, depression, anxiety, schizotypal symptoms), but not for others (eg, impulse control).<sup>83</sup> At present, there is no evidence that one typical antipsychotic is more effective than another (ie, loxapine vs chlorpromazine or tiotixene vs haloperidol).<sup>79,88</sup>

In two RCTs, the atypical antipsychotic olanzapine was more effective than placebo for several, but not all, symptoms;<sup>89,90</sup> however, in another RCT, no superiority of olanzapine over placebo was reported.<sup>97</sup> Olanzapine monotherapy and olanzapine combined with fluoxetine were more effective than fluoxetine alone for depression and impulsive aggression.<sup>91</sup> This combination had no advantage over olanzapine monotherapy.<sup>91</sup> Ziprasidone had no superiority over placebo.<sup>100</sup>

In a recent small RCT of 28 patients with borderline personality disorder, no differences between olanzapine and haloperidol were reported.<sup>98</sup> No studies comparing different atypical antipsychotics are available.

The mood stabiliser carbamazepine had no superiority over placebo.<sup>92</sup> No effects of sodium valproate were reported on depression.<sup>82,93</sup> Beneficial effects on interpersonal sensitivity were reported in one RCT.<sup>82</sup> In some, but not all, RCTs, a beneficial of sodium valproate was reported on anger or aggression.<sup>82,93,94</sup> Beneficial effects of lamotrigine on affective instability and impulsivity were reported in one RCT.<sup>96</sup> Improvements were reported for an omega-3 fatty acid treatment<sup>95</sup> in one small RCT of 30 patients with borderline personality disorder, and for clonidine in 18 patients in another small RCT.<sup>99</sup>

In summary, evidence for pharmacotherapy in borderline personality disorder varies. Beneficial effects on depression, aggression, and other symptoms were reported in some RCTs, but not in others. Many of the findings are based on single RCTs or on small samples of patients. Some studies (eg, of olanzapine) included only female patients. Only a few studies included long-term follow-ups. As stressed by the NICE group, some of the drugs are potentially harmful—eg, valproate semisodium, which is dangerous for women of child-bearing age.<sup>106</sup> Antipsychotics have many neurological side-effects and

See Online for webappendix



	Treatment	Comparison
Bateman and Fonagy <sup>109</sup>	Mentalisation-based treatment in a partial hospital setting	Treatment as usual
Bateman and Fonagy <sup>118</sup>	Mentalisation-based psychodynamic treatment	Structured clinical management
Blum et al <sup>120</sup>	Brief cognitive-behavioural therapy plus treatment as usual	Treatment as usual
Bohus et al <sup>121</sup>	Inpatient dialectical behaviour therapy	Treatment as usual
Clarkin et al <sup>122</sup>	Transference-focused therapy	Dialectical behaviour therapy as supportive therapy
Cottraux et al <sup>123</sup>	Cognitive-behavioural therapy	Client-centred therapy
Davidson et al <sup>119</sup>	Brief cognitive-behavioural therapy plus treatment as usual	Treatment as usual
Doering et al <sup>132</sup>	Transference-focused therapy	Community treatment by experienced therapists
Farrel et al <sup>124</sup>	Schema-focused therapy plus treatment as usual	Treatment as usual
Giesen-Bloo et al <sup>125</sup>	Schema-focused therapy	Transference-focused therapy
Gregory et al <sup>126</sup>	Dynamic deconstructive therapy	Treatment as usual
Harned et al <sup>127</sup>	Dialectical behaviour therapy	Community treatment by experts
Koons et al <sup>114</sup>	Dialectical behaviour therapy	Treatment as usual
Linehan et al <sup>110</sup>	Dialectical behaviour therapy	Treatment as usual
Linehan et al <sup>112</sup>	Dialectical behaviour therapy	Treatment as usual
Linehan et al <sup>111</sup>	Dialectical behaviour therapy	Comprehensive validation therapy plus a 12-step substance misuse programme
Linehan et al <sup>128</sup>	Dialectical behaviour therapy	Therapy by experts
McMain et al <sup>129</sup>	Dialectical behaviour therapy	Psychodynamically informed clinical management
Munroe-Blum et al <sup>116</sup>	Psychodynamic therapy	Interpersonal group therapy
Soler et al <sup>130</sup>	Dialectical behaviour therapy skills training	Standard group therapy
Tyrer et al <sup>117</sup>	Brief cognitive-behaviour therapy	Treatment as usual
Turner et al <sup>115</sup>	Dialectical behaviour therapy	Client-centred therapy
Verheul et al <sup>131</sup>	Dialectical behaviour therapy	Treatment as usual
Weinberg et al <sup>133</sup>	Brief cognitive-behavioural therapy plus treatment as usual	Treatment as usual

**Table 2: Randomised controlled trials of psychotherapy in patients with borderline personality disorder**

metabolic effects leading to weight gain and increased risk of diabetes.<sup>106</sup> Thus, more evidence is needed before definitive recommendations can be made about the pharmacological treatment of any symptoms of borderline personality disorder.

### Psychotherapy

Several methods of psychotherapy are available for patients with borderline personality disorder—eg, cognitive-behavioural, interpersonal, or psychodynamic treatments. Two formal reviews on the efficacy of psychotherapy for the disorder exist.<sup>107,108</sup> Following Cochrane criteria, Binks and colleagues<sup>107</sup> identified only seven RCTs published up to 2002.<sup>109–115</sup> Brazier and colleagues<sup>108</sup> included two additional RCTs.<sup>116,117</sup> In their review on borderline personality disorder, Lieb and colleagues<sup>4</sup> identified 11 RCTs. Since 2006, several RCTs on psychotherapy have been published. Following the Cochrane criteria used by Binks and colleagues,<sup>107</sup> we identified 24 RCTs on psychotherapy alone in borderline personality disorder (table 2).<sup>109–112,114–133</sup>

For cognitive behaviour therapy, the results can be summarised as follows. In studies comparing dialectical behaviour therapy with treatment as usual, dialectical behaviour therapy was more effective in several outcome measures (eg, self harm, parasuicidal behaviour, suicidal ideation).<sup>110–112,114,128,131</sup> However, the number of patients still

meeting the diagnostic criteria of borderline personality disorder did not differ. For depression, anxiety, admission to hospital, or drop outs, only two trials also reported superiority of dialectical behaviour therapy.<sup>121,128</sup> In another RCT,<sup>131</sup> dialectical behaviour therapy was more effective than treatment as usual in reducing self-mutilating behaviours and self-damaging impulsive acts, but not in reducing suicidal behaviour. The skills training component for dialectical behaviour therapy was superior to a non-manualised standard group therapy in several measures (eg, depression, anxiety).<sup>130</sup> Furthermore, dialectical behaviour therapy was superior to a community treatment by experts (not further specified non-cognitive behaviour therapy) with respect to remission of co-occurring substance-dependence disorders.<sup>127</sup> No superiority was identified for remission of other axis I disorders.<sup>127</sup> No clear differences were reported between dialectical behaviour therapy focusing on substance misuse and comprehensive validation therapy plus a 12-step substance misuse programme.<sup>111</sup> Compared with client-centred therapy, dialectical behaviour therapy was superior in reducing parasuicidal behaviour, suicidal ideation, and general psychiatric severity.<sup>115</sup> No superiority of dialectical behaviour therapy over client-centred therapy was identified for anxiety.<sup>115</sup> In the most recent RCT,<sup>129</sup> which was sufficiently powered to detect a medium effect size (sample sizes of 90 for both groups), both dialectical behaviour

therapy and a well specified and psychodynamically informed clinical management provided significant improvements with no differences between treatments. Results from another RCT indicated that schema-focused therapy was superior to transference-focused psychotherapy.<sup>125</sup> However, differences in therapist competence ratings indicate that transference-focused psychotherapy might have been less competently implemented than schema-focused therapy. Thus, replications are needed. Adding an 8-month schema-focused therapy group to treatment as usual was more effective than just treatment as usual.<sup>124</sup> Adding availability of a therapist by telephone outside office hours to schema-focused therapy did not lead to extra effects.<sup>134</sup> Client-centred therapy was as effective as cognitive behaviour therapy with respect to the response criterion, although cognitive behaviour therapy was superior in some other outcome measures.<sup>123</sup> Brief cognitive behaviour therapy was not superior to treatment as usual, but was more cost-effective.<sup>117</sup> In three studies, new and brief cognitive-behavioural treatments for patients with borderline personality disorder were tested in an add-on design.<sup>119,120,133</sup> When added to treatment as usual, these strategies were superior to treatment as usual alone in some, but not in all, outcome measures.<sup>119,120,133</sup>

Seven RCTs have studied psychodynamic psychotherapy.<sup>109,116,118,122,125,126,132</sup> In three studies, psychodynamic psychotherapy was more effective than treatment as usual for most outcome measures.<sup>109,126,132</sup> In one trial, the effects of mentalisation-based treatment in a partial hospital setting might have been confounded by duration of partial hospitalisation, which was longer in the mentalisation-based treatment condition.<sup>109</sup> In a recent RCT,<sup>118</sup> however, this treatment was superior to manual-driven structured clinical management for primary (suicidal and self-injurious behaviours, treatment in hospital) and secondary outcome measures (eg, depression, general symptom distress, interpersonal functioning). Psychodynamic psychotherapy was reported in one RCT to be as equally effective as an interpersonal group therapy.<sup>116</sup> In another RCT that compared transference-focused psychotherapy, dialectical behaviour therapy, and psychodynamic supportive psychotherapy,<sup>122</sup> transference-focused psychotherapy and dialectical behaviour therapy reduced suicidal tendency to the same extent. Transference-focused psychotherapy was superior to dialectical behaviour therapy in some measures of affect regulation, impulsivity, and attachment.<sup>122,135</sup>

In summary, dialectical behaviour therapy and specific forms of psychodynamic psychotherapy seem to be superior to treatment as usual in some clinically relevant problems of borderline personality disorder. Adding brief cognitive behaviour therapy to treatment as usual seems to be superior to treatment as usual alone. According to follow-up studies, effects of psychotherapy are stable over time.<sup>111,112,116,119,120,124,127,128,136–138</sup> At present, there is no clear evidence that one specific form of psychotherapy is

superior to another.<sup>139</sup> In several studies comparing specific forms of psychotherapy, however, power was not sufficient to detect possible differences.<sup>111,116,122</sup> In summary, there is evidence that psychotherapy is beneficial with respect to some clinically relevant problems of patients with borderline personality disorder. However, the available forms of psychotherapy do not yet lead to remission of borderline personality disorder for most patients (ie, no longer fulfilling the criteria of a diagnosis of borderline personality disorder). Thus, further research is needed.

### Pharmacotherapy with psychotherapy

The benefit of a combination of pharmacotherapy and psychotherapy in borderline personality disorder is unclear. Fluoxetine combined with dialectical behaviour therapy provided no additional benefit compared with dialectical behaviour therapy plus placebo.<sup>102</sup> In one study,<sup>103</sup> olanzapine added to dialectical behaviour therapy provided an additional benefit compared with dialectical behaviour therapy, although no differences were reported in another study in favour of the combined treatment.<sup>104</sup> The combination of interpersonal therapy and fluoxetine was superior to fluoxetine plus clinical management.<sup>101</sup>

### Future perspectives

Although much has been learned about borderline personality disorder in recent years, several questions remain. Despite conceptual coherence, borderline personality disorder seems to be a heterogeneous diagnostic category that is less stable and distinct over time than expected. These findings raise questions of both how to conceptualise this disorder and how to implement it in future versions of DSM as a form of personality pathology that is both enduring and distinct from other personality disorders.<sup>20</sup> Furthermore, the discussion on whether a categorical or a dimensional model best suits personality disorders is ongoing.<sup>140,141</sup> The results of the Collaborative Longitudinal Personality Disorders Study (CLPS)<sup>5,142</sup> suggest reconceptualising personality disorders as hybrids of stable personality traits and as intermittently expressed symptomatic behaviours that are attempts to cope with or defend against or compensate for these pathological traits (eg, self-harm to reduce affective tension). Further research is needed on the association between personality traits and personality disorder psychopathological changes as well as on the relation between personality disorders and personality functioning.<sup>21,143</sup> Personality might function differently at different ages and in response to different needs.<sup>143</sup> Future research on the causes of this disorder should investigate how genetic and psychosocial factors interact with neurotransmitter function to lead to cognitive and emotional regulations and specific traits.<sup>44</sup> The available findings of neuroimaging studies lend support to the assumption of a dysfunctional frontolimbic network in borderline

personality disorder. The exact molecular nature of this dysfunction is not yet clear. Future studies should include individuals who do not have borderline personality disorder (ie, healthy controls and patients with axis I disorders or other personality disorders) to establish the specificity of findings. Furthermore, further research is needed for childhood and adolescent precursor symptoms of adult borderline personality disorder as well as borderline personality disorder in elderly patients.<sup>42</sup> More work is also needed to understand the neurobiology of interpersonal dysfunction and attachment in borderline personality disorder.<sup>42</sup> Future studies on pharmacotherapy are needed to improve the empirical support for its use in patients with borderline personality disorder, including studies of long-term effects and studies of the combination of pharmacotherapy and psychotherapy. Psychotherapy is beneficial for some clinically relevant problems of patients with borderline personality disorder. However, further research is needed to also improve other core features of this disorder.<sup>5</sup> Improvements in borderline personality disorder are commonly followed by improvements in major depressive disorder.<sup>18</sup> Therefore, clinicians are recommended not to focus on the treatment of major depressive disorder in the hope that improvements in major depressive disorder will lead to improvements in borderline personality disorder; instead the personality disorder should be treated.<sup>18</sup> Changes in personality traits seem to be followed by changes in personality disorder psychopathology, but not vice versa.<sup>21</sup> For this reason, clinicians and future studies should focus on treating the personality traits associated with borderline personality disorder. Focusing on personality traits and on personality functioning associated with personality disorders is consistent with the recent proposals made for DSM-V.<sup>144</sup>

#### Contributors

All authors conceived the outline of the Seminar and co-wrote the body of the text.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### References

- Bender DS, Dolan RT, Skodol AE, et al. Treatment utilization by patients with personality disorders. *Am J Psychiatry* 2001; **158**: 295–302.
- Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley WJ, Siever LJ. The borderline diagnosis I: psychopathology, comorbidity, and personality structure. *Biol Psychiatry* 2002; **51**: 936–50.
- Oldham JM. Borderline personality disorder and suicidality. *Am J Psychiatry* 2006; **163**: 20–26.
- Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet* 2004; **364**: 453–61.
- Skodol AE, Gunderson JG, Shea MT, et al. The Collaborative Longitudinal Personality Disorders Study (CLPS): overview and implications. *J Pers Disord* 2005; **19**: 487–504.
- Lenzenweger M, Lane M, Loranger A, Kessler R. Personality disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007; **62**: 553–64.
- Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2008; **69**: 533–45.
- Torgersen S, Kringlen, E, Cramer V. The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry* 2001; **58**: 590–96.
- Torgersen J. Epidemiology. In: Oldham J, Skodol, AE, Bender, DS, eds. Textbook of personality disorders. Washington, DC: American Psychiatric Publishing, 2005: 129–41.
- Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. *Am J Psychiatry* 2009; **166**: 530–39.
- Gross R, Olfson M, Gameroff M, et al. Borderline personality disorder in primary care. *Arch Intern Med* 2002; **162**: 53–60.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fourth edn. Washington, DC: American Psychiatric Association, 1994.
- Grilo CM, Becker DF, Anez LM, McGlashan TH. Diagnostic efficiency of DSM-IV criteria for borderline personality disorder: an evaluation in Hispanic men and women with substance use disorders. *J Consult Clin Psychol* 2004; **72**: 126–31.
- Grilo CM, Sanislow CA, Skodol AE, et al. Longitudinal diagnostic efficiency of DSM-IV criteria for borderline personality disorder: a 2-year prospective study. *Can J Psychiatry* 2007; **52**: 357–62.
- Sanislow CA, Grilo CM, Morey LC, et al. Confirmatory factor analysis of DSM-IV criteria for borderline personality disorder: findings from the collaborative longitudinal personality disorders study. *Am J Psychiatry* 2002; **159**: 284–90.
- Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Prediction of the 10-year course of borderline personality disorder. *Am J Psychiatry* 2006; **163**: 827–32.
- Gunderson JG, Bender D, Sanislow C, et al. Plausibility and possible determinants of sudden “remissions” in borderline patients. *Psychiatry* 2003; **66**: 111–19.
- Gunderson JG, Morey LC, Stout RL, et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. *J Clin Psychiatry* 2004; **65**: 1049–56.
- Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. *Am J Psychiatry* 2007; **164**: 929–35.
- Sanislow CA, Little TD, Ansell EB, et al. Ten-year stability and latent structure of the DSM-IV schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. *J Abnorm Psychol* 2009; **118**: 507–19.
- Warner MB, Morey LC, Finch JF, et al. The longitudinal relationship of personality traits and disorders. *J Abnorm Psychol* 2004; **113**: 217–27.
- Hopwood CJ, Newman DA, Donnellan MB, et al. The stability of personality traits in individuals with borderline personality disorder. *J Abnorm Psychol* 2009; **118**: 806–15.
- Schmideberg M. The borderline patient. In: Arieti S, ed. American handbook of psychiatry New York: Basic Books, 1959: 398–416.
- Carpenter WT Jr, Gunderson JG. Five year follow-up comparison of borderline and schizophrenic patients. *Compr Psychiatry* 1977; **18**: 567–71.
- Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. *Compr Psychiatry* 2007; **48**: 145–54.
- Lewis KL, Grenyer BF. Borderline personality or complex posttraumatic stress disorder? An update on the controversy. *Harv Rev Psychiatry* 2009; **17**: 322–28.
- Skodol AE, Pagano ME, Bender DS, et al. Stability of functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder over two years. *Psychol Med* 2005; **35**: 443–51.
- American Psychiatric Association Practice Guidelines. Practice guideline for the treatment of patients with borderline personality disorder. *Am J Psychiatry* 2001; **158**: 1–52.
- Zanarini MC, Frankenburg FR, Vujanovic AA, Hennen J, Reich DB, Silk KR. Axis II comorbidity of borderline personality disorder: description of 6-year course and prediction to time-to-remission. *Acta Psychiatr Scand* 2004; **110**: 416–20.
- Skodol AE, Gunderson JG, McGlashan TH, et al. Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. *Am J Psychiatry* 2002; **159**: 276–83.



- 31 Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. The 10-year course of psychosocial functioning among patients with borderline personality disorder and axis II comparison subjects. *Acta Psychiatr Scand* 2010; **122**: 103–09.
- 32 Zanarini MC, Yong L, Frankenburg FR, et al. Severity of reported childhood sexual abuse and its relationship to severity of borderline psychopathology and psychosocial impairment among borderline inpatients. *J Nerv Ment Dis* 2002; **190**: 381–87.
- 33 Yen S, Shea MT, Battle CL, et al. Traumatic exposure and posttraumatic stress disorder in borderline, schizotypal, avoidant, and obsessive-compulsive personality disorders: findings from the collaborative longitudinal personality disorders study. *J Nerv Ment Dis* 2002; **190**: 510–18.
- 34 Fossati A, Madeddu F, Maffei C. Borderline personality disorder and childhood sexual abuse: a meta-analytic study. *J Personal Disord* 1999; **13**: 268–80.
- 35 Paris J. The nature of borderline personality disorder: multiple dimensions, multiple symptoms, but one category. *J Pers Disord* 2007; **21**: 457–73.
- 36 Gabbard GO. Mind, brain, and personality disorders. *Am J Psychiatry* 2005; **162**: 648–55.
- 37 Wagner S, Baskaya O, Lieb K, Dahmen N, Tadic A. The 5-HTTLPR polymorphism modulates the association of serious life events (SLE) and impulsivity in patients with borderline personality disorder. *J Psychiatr Res* 2009; **43**: 1067–72.
- 38 Wagner S, Baskaya O, Dahmen N, Lieb K, Tadic A. Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. *Genes Brain Behav* 2009; **9**: 97–102.
- 39 Siever LJ, Torgersen S, Gunderson JG, Livesley WJ, Kendler KS. The borderline diagnosis III: identifying endophenotypes for genetic studies. *Biol Psychiatry* 2002; **51**: 964–68.
- 40 Torgersen S, Czajkowski N, Jacobson K, et al. Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychol Med* 2008; **38**: 1617–25.
- 41 Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pföhl B, Widiger TA. The borderline diagnosis II: biology, genetics, and clinical course. *Biol Psychiatry* 2002; **51**: 951–63.
- 42 New AS, Goodman M, Triebwasser J, Siever LJ. Recent advances in the biological study of personality disorders. *Psychiatr Clin North Am* 2008; **31**: 441–61.
- 43 Cloninger CR. Genetics. In: J. Oldham JM, Skodol AE, Bender DS, eds. *Textbook of personality disorders*. Washington, DC: American Psychiatric Publishing, 2005: 143–54.
- 44 Coccaro EF, Siever LJ. Neurobiology. In: Oldham JM, Skodol AE, Bender DS, eds. *Textbook of personality disorders*. Washington, DC: American Psychiatric Publishing, 2005: 155–69.
- 45 Ni X, Chan K, Bulgin N, et al. Association between serotonin transporter gene and borderline personality disorder. *J Psychiatr Res* 2006; **40**: 448–53.
- 46 Pascual JC, Soler J, Barrachina J, et al. Failure to detect an association between the serotonin transporter gene and borderline personality disorder. *J Psychiatr Res* 2008; **42**: 87–88.
- 47 Silva H, Iturra P, Solari A, et al. Serotonin transporter polymorphism and fluoxetine effect on impulsiveness and aggression in borderline personality disorder. *Actas Esp Psiquiatr* 2007; **35**: 387–92.
- 48 Tadic A, Victor A, Baskaya O, et al. Interaction between gene variants of the serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT) in borderline personality disorder. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 487–95.
- 49 Ni X, Chan D, Chan K, McMain S, Kennedy JL. Serotonin genes and gene-gene interactions in borderline personality disorder in a matched case-control study. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 128–33.
- 50 Ni X, Sicard T, Bulgin N, et al. Monoamine oxidase a gene is associated with borderline personality disorder. *Psychiatr Genet* 2007; **17**: 153–57.
- 51 Lahmeyer HW, Reynolds CF 3rd, Kupfer DJ, King R. Biologic markers in borderline personality disorder: a review. *J Clin Psychiatry* 1989; **50**: 217–25.
- 52 Grossman R, Yehuda R, Siever L. The dexamethasone suppression test and glucocorticoid receptors in borderline personality disorder. *Ann N Y Acad Sci* 1997; **821**: 459–64.
- 53 Zimmerman DJ, Choi-Kain LW. The hypothalamic-pituitary-adrenal axis in borderline personality disorder: a review. *Harv Rev Psychiatry* 2009; **17**: 167–83.
- 54 Schmahl CG, Vermetten E, Elzinga BM, Bremner DJ. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res* 2003; **122**: 193–98.
- 55 Weniger G, Lange C, Sachsse U, Irle E. Reduced amygdala and hippocampus size in trauma-exposed women with borderline personality disorder and without posttraumatic stress disorder. *J Psychiatry Neurosci* 2009; **34**: 383–88.
- 56 Chanan AM, Velakoulis D, Carison K, et al. Orbitofrontal, amygdala and hippocampal volumes in teenagers with first-presentation borderline personality disorder. *Psychiatry Res* 2008; **163**: 116–25.
- 57 Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. *J Affect Disord* 2005; **88**: 79–86.
- 58 Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry* 1997; **41**: 23–32.
- 59 Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. *J Pers Disord* 2009; **23**: 333–45.
- 60 Schmahl C, Berne K, Krause A, et al. Hippocampus and amygdala volumes in patients with borderline personality disorder with or without posttraumatic stress disorder. *J Psychiatry Neurosci* 2009; **34**: 289–95.
- 61 Chanan AM, Velakoulis D, Carison K, et al. Orbitofrontal, amygdala and hippocampal volumes in teenagers with first-presentation borderline personality disorder. *Psychiatry Res* 2008; **163**: 116–25.
- 62 New AS, Hazlett EA, Buchsbaum MS, et al. Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology* 2007; **32**: 1629–40.
- 63 Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Frontolimbic structural changes in borderline personality disorder. *J Psychiatr Res* 2008; **42**: 727–33.
- 64 Garner B, Chanan AM, Phillips L, et al. Pituitary volume in teenagers with first-presentation borderline personality disorder. *Psychiatry Res* 2007; **156**: 257–61.
- 65 Jovev M, Garner B, Phillips L, et al. An MRI study of pituitary volume and parasuicidal behavior in teenagers with first-presentation borderline personality disorder. *Psychiatry Res* 2008; **162**: 273–77.
- 66 Garner B, Pariente CM, Wood SJ, Velakoulis D, Phillips L, Soulsby B. Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. *Biol Psychiatry* 2005; **58**: 417–23.
- 67 Irle E, Lange C, Sachsse U. Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. *Biol Psychiatry* 2005; **57**: 173–82.
- 68 Irle E, Lange C, Weniger G, Sachsse U. Size abnormalities of the superior parietal cortices are related to dissociation in borderline personality disorder. *Psychiatry Res* 2007; **156**: 139–49.
- 69 Brunner R, Henze R, Parzer P, et al. Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? *Neuroimage* 2010; **49**: 114–20.
- 70 Juengling FD, Schmahl C, Hesslinger B, et al. Positron emission tomography in female patients with borderline personality disorder. *J Psychiatr Res* 2003; **37**: 109–15.
- 71 New AS, Hazlett EA, Newmark RE, et al. Laboratory induced aggression: a positron emission tomography study of aggressive individuals with borderline personality disorder. *Biol Psychiatry* 2009; **66**: 1107–14.
- 72 Koenigsberg HW, Siever LJ, Lee H, et al. Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res* 2009; **172**: 192–99.
- 73 Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. *Psychiatry Res* 2007; **155**: 231–43.

- 74 Beblo T, Driessen M, Mertens M, et al. Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. *Psychol Med* 2006; **36**: 845–56.
- 75 Koenigsberg HW, Fan J, Ochsner KN, et al. Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. *Biol Psychiatry* 2009; **66**: 854–63.
- 76 Herpertz SC, Dietrich TM, Wenning B, et al. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry* 2001; **50**: 292–98.
- 77 Driessen M, Beblo T, Mertens M, et al. Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. *Biol Psychiatry* 2004; **55**: 603–11.
- 78 Kraus A, Esposito F, Seifritz E, et al. Amygdala deactivation as a neural correlate of pain processing in patients with borderline personality disorder and co-occurring posttraumatic stress disorder. *Biol Psychiatry* 2009; **65**: 819–22.
- 79 Binks CA, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database Syst Rev* 2006; **1**: CD005653.
- 80 Nose M, Cipriani A, Biancosino B, Grassi L, Barbui C. Efficacy of pharmacotherapy against core traits of borderline personality disorder: meta-analysis of randomized controlled trials. *Int Clin Psychopharmacol* 2006; **21**: 345–53.
- 81 Lieb K, Vollm B, Rucker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *Br J Psychiatry* 2010; **196**: 4–12.
- 82 Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry* 2002; **63**: 442–46.
- 83 Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch Gen Psychiatry* 1993; **50**: 377–85.
- 84 Soloff PH, George A, Nathan S, et al. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J Clin Psychopharmacol* 1989; **9**: 238–46.
- 85 Salzman C, Wolfson AN, Schatzberg A, et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmacol* 1995; **15**: 23–29.
- 86 Rinne T, van den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am J Psychiatry* 2002; **159**: 2048–54.
- 87 Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. *Arch Gen Psychiatry* 1986; **43**: 680–86.
- 88 Leone NF. Response of borderline patients to loxapine and chlorpromazine. *J Clin Psychiatry* 1982; **43**: 148–50.
- 89 Bogenschutz MP, George Nurnberg H. Olanzapine versus placebo in the treatment of borderline personality disorder. *J Clin Psychiatry* 2004; **65**: 104–09.
- 90 Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 2001; **62**: 849–54.
- 91 Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry* 2004; **65**: 903–07.
- 92 de la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. *Eur Neuropsychopharmacol* 1994; **4**: 479–86.
- 93 Hollander E, Allen A, Lopez RP, et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry* 2001; **62**: 199–203.
- 94 Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry* 2005; **162**: 621–24.
- 95 Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 2003; **160**: 167–69.
- 96 Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int Clin Psychopharmacol* 2009; **24**: 270–75.
- 97 Schulz SC, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. *Br J Psychiatry* 2008; **193**: 485–92.
- 98 Shafti SS, Shahveisi B. Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double-blind trial. *J Clin Psychopharmacol* 2010; **30**: 44–47.
- 99 Ziegenhorn AA, Roepke S, Schommer NC, et al. Clonidine improves hyperarousal in borderline personality disorder with or without comorbid posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2009; **29**: 170–73.
- 100 Pascual JC, Soler J, Puigdemont D, et al. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J Clin Psychiatry* 2008; **69**: 603–08.
- 101 Bellino S, Zizza M, Rinaldi C, Bogetto F. Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. *Can J Psychiatry* 2006; **51**: 453–60.
- 102 Simpson EB, Yen S, Costello E, et al. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J Clin Psychiatry* 2004; **65**: 379–85.
- 103 Soler J, Pascual JC, Campins J, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am J Psychiatry* 2005; **162**: 1221–24.
- 104 Linehan MM, McDavid JD, Brown MZ, Sayrs JH, Gallop RJ. Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder: a double-blind, placebo-controlled pilot study. *J Clin Psychiatry* 2008; **69**: 999–1005.
- 105 Borderline personality disorder. The NICE guideline on treatment and management. The British Psychological Society and The Royal College of Psychiatrists. <http://www.nice.org.uk/nicemedia/live/12125/43045/43045.pdf>; p218 (accessed Aug 30, 2010).
- 106 Kendall T, Burbeck R, Bateman A. Pharmacotherapy for borderline personality disorder: NICE guideline. *Br J Psychiatry* 2010; **196**: 158–59.
- 107 Binks CA, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev* 2006; **1**: CD005652.
- 108 Brazier J, Tumor I, Holmes M, et al. Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation. *Health Technol Assess* 2006; **10**: 1–117.
- 109 Bateman A, Fonagy P. Effectiveness of partial hospitalization in the treatment of borderline personality disorder: a randomized controlled trial. *Am J Psychiatry* 1999; **156**: 1563–69.
- 110 Linehan MM, Armstrong HE, Suarez A, Allmon D, Heard HL. Cognitive-behavioral treatment of chronically parasuicidal borderline patients. *Arch Gen Psychiatry* 1991; **48**: 1060–64.
- 111 Linehan MM, Dimeff LA, Reynolds SK, et al. Dialectical behavior therapy versus comprehensive validation therapy plus 12-step for the treatment of opioid dependent women meeting criteria for borderline personality disorder. *Drug Alcohol Depend* 2002; **67**: 13–26.
- 112 Linehan MM, Schmidt H, Dimeff LA, Craft JC, Kanter J, Comtois KA. Dialectical behavior therapy for patients with borderline personality disorder and drug-dependence. *Am J Addict* 1999; **8**: 279–92.
- 113 van den Bosch LM, Verheul R, Schippers GM, van den Brink W. Dialectical behavior therapy of borderline patients with and without substance use problems. Implementation and long-term effects. *Addict Behav* 2002; **27**: 911–23.
- 114 Koons CR, Robins CJ, Tweed JL, et al. Efficacy of dialectical behavior therapy in women veterans with borderline personality disorder. *Behavior Therapy* 2001; **32**: 371–90.
- 115 Turner R. Naturalistic evaluation of dialectical behavior therapy-oriented treatment for borderline personality disorder. *Cognitive and Behavioral Practice* 2000; **7**: 413–19.

- 116 Munroe-Blum H, Marziali E. A controlled trial of short-term group treatment for borderline personality disorder. *J Pers Disord* 1995; **9**: 190–98.
- 117 Tyrer PTS, Schmidt U, Jones V, et al. Randomized controlled trial of brief cognitive behaviour therapy versus treatment as usual in recurrent deliberate self-harm: the POPMACT study. *Psychol Med* 2003; **33**: 969–76.
- 118 Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. *Am J Psychiatry* 2009; **166**: 1355–64.
- 119 Davidson K, Norrie J, Tyrer P, et al. The effectiveness of cognitive behavior therapy for borderline personality disorder: results from the borderline personality disorder study of cognitive therapy (BOSCOT) trial. *J Pers Disord* 2006; **20**: 450–65.
- 120 Blum N, St John D, Pfohl B, et al. Systems Training for Emotional Predictability and Problem Solving (STEPPS) for outpatients with borderline personality disorder: a randomized controlled trial and 1-year follow-up. *Am J Psychiatry* 2008; **165**: 468–78.
- 121 Bohus M, Haaf B, Simms T, et al. Effectiveness of inpatient dialectical behavioral therapy for borderline personality disorder: a controlled trial. *Behav Res Ther* 2004; **42**: 487–99.
- 122 Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder: a multiwave study. *Am J Psychiatry* 2007; **164**: 922–28.
- 123 Cottraux J, Note ID, Boutitie F, et al. Cognitive therapy versus rogerian supportive therapy in borderline personality disorder. Two-year follow-up of a controlled pilot study. *Psychother Psychosom* 2009; **78**: 307–16.
- 124 Farrell JM, Shaw IA, Webber MA. A schema-focused approach to group psychotherapy for outpatients with borderline personality disorder: a randomized controlled trial. *J Behav Ther Exp Psychiatry* 2009; **40**: 317–28.
- 125 Giesen-Bloo J, van Dyck R, Spinhoven P, et al. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. *Arch Gen Psychiatry* 2006; **63**: 649–58.
- 126 Gregory R, Chlebowski S, Kang D, et al. A controlled trial of psychodynamic psychotherapy for co-occurring borderline personality disorder and alcohol use disorder. *Psychotherapy: Theory/Research/Practice/Training* 2008; **45**: 28–41.
- 127 Harned MS, Chapman AL, Dexter-Mazza ET, Murray A, Comtois KA, Linehan MM. Treating co-occurring axis I disorders in recurrently suicidal women with borderline personality disorder: a 2-year randomized trial of dialectical behavior therapy versus community treatment by experts. *J Consult Clin Psychol* 2008; **76**: 1068–75.
- 128 Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen Psychiatry* 2006; **63**: 757–66.
- 129 McMain SF, Links PS, Gnam WH, et al. A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. *Am J Psychiatry* 2009; **166**: 1365–74.
- 130 Soler J, Pascual JC, Tiana T, et al. Dialectical behaviour therapy skills training compared to standard group therapy in borderline personality disorder: a 3-month randomised controlled clinical trial. *Behav Res Ther* 2009; **47**: 353–58.
- 131 Verheul R, Van Den Bosch LM, Koeter MW, De Ridder MA, Stijnen T, Van Den Brink W. Dialectical behaviour therapy for women with borderline personality disorder: 12-month, randomised clinical trial in The Netherlands. *Br J Psychiatry* 2003; **182**: 135–40.
- 132 Doering S, Horz S, Rentrop M, et al. Transference-focused psychotherapy v. treatment by community psychotherapists for borderline personality disorder: randomised controlled trial. *Br J Psychiatry* 2010; **196**: 389–95.
- 133 Weinberg I, Gunderson JG, Hennen J, Cutter CJ Jr. Manual assisted cognitive treatment for deliberate self-harm in borderline personality disorder patients. *J Pers Disord* 2006; **20**: 482–92.
- 134 Nadort M, Arntz A, Smit JH, et al. Implementation of outpatient schema therapy for borderline personality disorder with versus without crisis support by the therapist outside office hours: a randomized trial. *Behav Res Ther* 2009; **47**: 961–73.
- 135 Levy KN, Meehan KB, Kelly KM, et al. Change in attachment patterns and reflective function in a randomized control trial of transference-focused psychotherapy for borderline personality disorder. *J Consult Clin Psychol* 2006; **74**: 1027–40.
- 136 Bateman A, Fonagy P. Treatment of borderline personality disorder with psychoanalytically oriented partial hospitalization: an 18-month follow-up. *Am J Psychiatry* 2001; **158**: 36–42.
- 137 Linehan MM, Heard HL, Armstrong HE. Naturalistic follow-up of a behavioral treatment for chronically parasuicidal borderline patients. *Arch Gen Psychiatry* 1993; **50**: 971–74.
- 138 Bateman A, Fonagy P. 8-year follow-up of patients treated for borderline personality disorder: mentalization-based treatment versus treatment as usual. *Am J Psychiatry* 2008; **165**: 631–38.
- 139 Zanarini MC. Psychotherapy of borderline personality disorder. *Acta Psychiatr Scand* 2009; **120**: 373–77.
- 140 Skodol AE, Oldham JM, Bender DS, et al. Dimensional representations of DSM-IV personality disorders: relationships to functional impairment. *Am J Psychiatry* 2005; **162**: 1919–25.
- 141 Widiger TA. Current controversies in nosology and diagnosis of personality disorders. *Psychiatric Annals* 2007; **32**: 93–99.
- 142 McGlashan TH, Grilo CM, Sanislow CA, et al. Two-year prevalence and stability of individual DSM-IV criteria for schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders: toward a hybrid model of axis II disorders. *Am J Psychiatry* 2005; **162**: 883–89.
- 143 Tyrer P, Coombs N, Ibrahim F, et al. Critical developments in the assessment of personality disorder. *Br J Psychiatry Suppl* 2007; **49**: s51–59.
- 144 American Psychiatric Association. DSM-5: The future of psychiatric diagnosis. <http://www.dsm5.org> (accessed Aug 30, 2010).