REVIEW

Integrating Early Intervention for Borderline Personality Disorder and Mood Disorders

Andrew M. Chanen, MBBS (Hons), BMedSci (Hons), MPM, PhD, FRANZCP, Michael Berk, MBBCh, MMed(Psych), FF(Psych)SA, FRANZCP, PhD, and Katherine Thompson, BAppSci, PhD, BTheol, BSW

Abstract: Borderline personality disorder (BPD) has been demonstrated to be a reliable and valid construct in young people (adolescents and young adults). Both borderline- and mood-related psychopathology become clinically apparent from puberty through to young adulthood, frequently co-occur, can reinforce one another, and can be difficult to differentiate clinically. This Gordian knot of overlapping clinical features, common risk factors, and precursors to both BPD and mood disorders complicates clinical assessment, prevention, and treatment. Regardless of whether an individual crosses an arbitrary diagnostic threshold, a considerable proportion of young people with borderline- and mood-related psychopathology will develop significant and persistent functional, vocational, and interpersonal impairment and disability during this critical risk and developmental period. There is a clear need for early intervention, but spurious diagnostic certainty risks stigma, misapplication of diagnostic labels, inappropriate treatment, and unfavorable outcomes. This article aims to integrate early intervention for BPD and mood disorders in the clinical context of developmental and phenomenological change and evolution. "Clinical staging," similar to disease staging in general medicine, is presented as a pragmatic, heuristic, and trans-diagnostic framework to guide prevention and intervention. It acknowledges that the early stages of these disorders cannot be disentangled sufficiently to allow for disorder-specific preventive measures and early interventions. Clinical staging defines an individual's location along the continuum of the evolving temporal course of a disorder. Such staging aids differentiation of early or milder clinical phenomena from those that accompany illness progression and chronicity, and suggests the application of appropriate and proportionate intervention strategies.

Keywords: adolescence, bipolar disorder, borderline personality disorder, clinical staging, depression, early intervention, prevention, risk factor

Seventy-five percent of all mental disorders have their onset by the age of 25 years. The peak period of onset for depression, bipolar disorder, and borderline personality disorder (BPD) occurs from puberty through to young adulthood.[1–5] Mental disorders often do not present fully formed, however, and young people frequently present with evolving mixtures of symptoms. Our limited understanding of the prospective relationships between these often nonspecific symptoms and the major mental disorder syndromes implies a more complicated picture. Diagnostic precision is frequently possible only in retrospect. Nevertheless, even when a clear diagnosis cannot be made, the existence of distress and psychopathology can have negative developmental consequences for education, work, and family and peer relationships. This is especially so when treatment is delayed,[2,6] which can risk persistent functional deficits.

Concordant with the nosology of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), discussion about the relationship between BPD and mood disorders has principally been described in terms of their phenomenology and treatment, rather than their etiology or pathogenesis.[7] Most phenomenological studies have been undertaken in adults, when the disorders are "formed" and have mostly "run their course." These studies have often used retrospective reports, thereby introducing recall bias, which makes the timing of the onset of symptoms or disorders uncertain.[2] Many other studies have used clinical samples,[8,9] leading to inflated levels of co-occurrence of psychopathology.[10]

From the Centre for Youth Mental Health, University of Melbourne; Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne; Orygen Youth Health, Northwestern Mental Health, Melbourne (Dr. Chanen); IMPACT Strategic Research Centre, School of Medicine, Deakin University (Dr. Berk); Department of Psychiatry, University of Melbourne (Dr. Berk); Florey Institute for Neuroscience and Mental Health, Melbourne (Dr. Berk) (all Australia).

Original manuscript received 7 September 2014; revised manuscript received 29 April 2015, accepted for publication subject to revision 24 May 2015; revised manuscripts received 30 June and 8 September 2015.

Supported by National Health and Medical Research Council Senior Principal Research Fellowship no. 1059660 (Dr. Berk).

Correspondence: Prof. Andrew M. Chanen, Orygen, the National Centre of Excellence in Youth Mental Health, Locked Bag 10, Parkville, Victoria 3052, Australia. Email: andrew.chanen@orygen.org.au

DOI: 10.1097/HRP.0000000000000105

Clinical assessment tends to rely upon eliciting phenomenology and risk factors in the context of the patient's life narrative. This article highlights the task of early detection and intervention for BPD and mood disorders in the real-world clinical context of rapid developmental changes, phenomenological instability and evolution, and the multiple clinical outcomes that can result from the same risk factors, especially environmental ones (i.e., multifinality).[11] It principally draws upon available prospective, longitudinal data concerning the development of BPD and mood disorders, and suggests a pragmatic and heuristic early-intervention framework.

ANTECEDENTS AND EARLY SIGNS OF PSYCHOPATHOLOGY IN YOUNG PEOPLE

Borderline Personality Disorder

Although the consensus has been for many decades that personality disorder has its origins in childhood and adolescence,[12] diagnosing personality disorder prior to age 18 years has been more controversial than diagnosing personality disorder in adults.[13] Recent data suggest, however, that borderline personality and mood disorders in youth can be diagnosed with similar levels of confidence.[14–16] BPD has been shown to be recognizable early in life, evolves continuously across the lifespan, and is more plastic than previously believed.[3,16] BPD has similar reliability and validity in adolescence or adulthood,[17,18] and can be identified in day-to-day clinical practice.[19] Moreover, it has incremental validity (unique explanatory value) over and above other mental state (Axis I) disorders in regard to psychopathology, functioning, suicidal ideation, and self-harm.[20,21]

In fact, BPD is arguably better considered as a disorder of younger people, with evolving risks in childhood, a rise in prevalence from puberty, and a steady decline with each decade from young adulthood.[22–24] Limited data suggest that BPD occurs in up to 3% of community-dwelling,[25–27] and up to 22% of outpatient,[19,28] adolescents and young adults. BPD (or dimensional representations of BPD) in young people defines a group with high morbidity and potentially poor outcomes. BPD independently predicts current psychopathology, poor general functioning, poor self-care, and poor relationships with family, peers, and significant others.[20,29] BPD also predicts poor outcomes prospectively over two decades. These outcomes include a future BPD diagnosis, increased risk for mental state disorders (especially substance use and mood disorders), interpersonal problems, distress, and diminished quality of life.[4,30,31]

It is now clear that dimensional representations of personality pathology, including borderline personality pathology, have similar stability in adolescence and adulthood.[16] The underlying dimensions of BPD features (conceptualized as impulsivity, negative affectivity, and interpersonal aggression) also appear to be moderately stable in children.[32,33] Only the Children in the Community study has specifically measured childhood or adolescent personality disorder features as predictors of later personality disorder over multiple waves of assessment from childhood to adulthood.[4] In that study, childhood or adolescent personality disorder symptoms were the strongest long-term predictors of later DSM-IV Cluster A, B, or C personality disorders, over and above disruptive behavior disorders and depressive symptoms.[4,34–36] Overall, the Children in the Community study data support a normative increase in BPD traits following puberty. These traits decline in early adulthood, in part due to socialization or maturational processes,[4] revealing a group that is progressively deviant when compared with their peers[37] and that perhaps corresponds more to the "adult" BPD phenotype.[38] These data, supported by other studies, suggest that the adult BPD phenotype principally arises from the group of young people presenting with BPD features.[17]

The heritability of BPD is estimated to be .67,[39] which is akin to or higher than heritability estimates for other major psychiatric disorders. Childhood abuse or neglect, difficult family environment, and low socioeconomic status are all additional significant risk factors for developing BPD, but they are also risk factors for other personality pathology,[38] along with many other psychiatric disorders, including mood and substance use disorders. Prospective, longitudinal data show that certain temperamental characteristics and early-onset mental state or behavioral phenomena that are analogous to characteristics of BPD are precursors to the emergence of the BPD phenotype, but they do not predict its onset with certainty.[3] These phenomena include attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, substance use, depression, and self-harm, along with the features of BPD.[38] These are not true risk factors,[40] however, because each of these disorders has trait-like features, which are misleadingly classified as mental state phenomena in the DSM nosology. These same phenomena are subsequently used to define BPD. For this reason, they are better termed *precursor signs and symptoms*.[41]

Example precursor signs and symptoms include maternal reports of childhood temperament, which are prospectively related to increased risk for adolescent or adult BPD up to 30 years later.[42,43] Substance use disorders during adolescence, especially alcohol use disorders, also predict risk for young adult BPD,[44,45] and disturbances in attention, emotional regulation, and behavior—especially the disruptive behavior disorders (ADHD, conduct disorder, oppositional defiant disorder) in childhood or adolescence—independently predict young adult BPD.[43,46,47] Furthermore, findings from one study suggest that emotion-regulation and relationship difficulties might precede impulse-control problems in the development of adolescent BPD.[46]

Self-harm is a central feature of BPD,[48] and in retrospective reports from adults with BPD, self-harm commenced in childhood in over 30% of individuals and in adolescence in a further 30%.[49] Yet, self-harm is surprisingly underresearched as a potential precursor to BPD. Self-harm is relatively common among youth[50] and is associated with several clinical syndromes. Repetitive self-harm is less frequent,

however, and appears to differ from occasional self-harm.[51] BPD can be diagnosed in the majority of female adolescent inpatients with self-harm,[52] and it is more likely that adolescents will be diagnosed with BPD if they endorse both self-harm and suicide attempts, compared with individuals reporting either self-harm or suicide attempts alone.[53] Also, the greater the number of BPD criteria in adolescents, the more likely they are to have engaged in self-harm or attempted suicide.[54] Self-harm also occurs, however, in people with bipolar disorder, especially mixed states,[55] although the diagnostic boundaries between mixed states and BPD are ill defined.[56]

The findings outlined above demonstrate that BPD features can be detected at least from puberty onward, with reliability and validity that is comparable to other disorders. Nonetheless, BPD features are often heralded by, accompany, or follow signs and symptoms that are also associated with other "comorbid" mental state disorders, such as mood, anxiety, disruptive behavior, eating, and substance use disorders.[20,29,57] All told, these signs and symptoms appear from childhood through to adolescence, and many of these look like aspects of the BPD phenotype and herald its later appearance in adolescence or emerging adulthood. However, the specificity of these factors for BPD, other personality disorders, or mental state disorders is limited.

Bipolar Disorder

Research on precursor signs and symptoms of bipolar disorder also shows considerable overlap with BPD in regard to the patterns and types of symptoms that occur prior to the onset of the full disorder. However, research on the early signs and symptoms of mental disorders tends to be confined to discrete "silos," meaning that studies in young people that focus on bipolar disorder rarely measure BPD, and vice versa.

Advocacy for prevention and early intervention for bipolar disorder arises from concern about the consequences of delay in diagnosis and treatment, especially in view of the potential and specific neuroprotective properties of agents such as lithium.[58] Around 70% of individuals diagnosed with bipolar disorder will experience their first symptoms before age 25, with the peak onset at age 17, but a formal diagnosis is often preceded by a lengthy delay.[59] More than half of patients are diagnosed in the first year of illness, but some studies report that a diagnosis can take up to eight years following the first episode.[60,61] There is also often considerable delay between the onset of bipolar disorder and the introduction of mood-stabilizing medication. Delayed treatment has been linked with unfavorable outcomes, such as cognitive and neurostructural evidence of neuroprogression, poor psychosocial adjustment, increased rates of hospitalization and suicide, substance use, forensic problems, and failure to achieve developmental milestones.[60] When considered along with the potential neuroprotective effects that mood stabilizers might exert—limiting or averting structural brain changes associated with bipolar disorder—the rationale for early intervention is strong.[58]

Offspring of individuals with bipolar disorder are more liable to develop a variety of mental disorders, especially mood disorder.[62,63] In the Dutch bipolar offspring study 12-year follow-up, participants meandered over time between asymptomatic, subthreshold anxiety, substance abuse, and depressive and bipolar-like phenotypes, with very poor temporal diagnostic stability.[64] It is noteworthy that this study did not even measure personality disorder as an outcome. Yet, many of the risk factors associated with BPD are also risk factors for a later diagnosis of bipolar disorder. These factors include childhood or familial ADHD,[65,66] traumatic or stressful life events and childhood abuse,[63,67,68] and substance abuse.[69] Certain personality traits, such as high harm avoidance and high novelty seeking,[70] as well as impulsive aggression,[63] are also associated with later bipolar disorder.

A review of 13 retrospective and 12 prospective studies covering the period prior to the onset of first-episode mania[61] highlighted that depression is more commonly the initial polarity of first-presentation illness.[60] Retrospective studies have pointed to subthreshold mania, irritability and anger, lack of sleep, grandiosity, periods of depression, and mood changes (to a smaller extent). Prospective studies highlight racing thoughts, irritability, anger, periods of depression, mood swings, anxiety, and, in some cases, psychotic symptoms.[61,71,72] In these studies the prodromal period ranged from weeks to 15 years, in part due to study design, because studies that use "enriched" bipolar risk samples, compared with general samples, report a shorter time to transition. The symptoms of irritability, anger, depression, and mood changes are also present in BPD. The distinguishing symptoms for bipolar disorder were hypomania, grandiosity, and sleep disturbance.

The largest and most rigorous study to examine the incidence of hypomanic and depressive symptoms prospectively from adolescence through to adulthood drew a random representative sample of 14- to 24-year-olds living in Munich, Germany.[73] The findings show that hypomanic and depressive symptoms were commonly experienced once (almost 40% of 1565 participants) over the follow-up period. Multiple experiences of these symptoms, however, were less likely. The persistence of symptoms was predictive of transition to clinically relevant outcomes (i.e., hypomanic episodes or accessing mental health care) in a dose-dependent manner. Clinical bipolar disorder is relatively rare and might be seen as the poorest outcome of these developmental processes. The study's authors suggest that a nonclinical bipolar phenotype, usually transitory, might be developmentally common during adolescence. As with BPD, the period between adolescence and young adulthood thus sees the emergence of affective and behavioral psychopathology that is of uncertain clinical significance. It is the quantity, persistence, and qualities of this psychopathology that become important in distinguishing between syndromes.

The Course and Outcome of Bipolar Youth study followed 413 7- to 17-year-olds with "bipolar spectrum" (bipolar I, II, or not otherwise specified [NOS]) disorder prospectively over

a four-year period.[74] This study was designed to measure affective symptoms (i.e., mania and depression) but not features of other disorders, such as BPD. The study found that the greatest proportion of symptomatology was due to mixed/cycling and depressive symptoms. The study frequently found rapid mood changes, and almost all of the chronic symptoms reported were subsyndromal depressive symptoms. The study's authors stress that early onset gives rise to a greater likelihood of a chronic and fluctuating course. While they argue that their findings support the presence of clinically relevant, brief episodes of manic or hypomanic symptoms, the failure to measure BPD or other personality pathology as an outcome is a substantial limitation.

Although affective dysregulation is characteristic of both bipolar disorders and BPD, some evidence suggests differences in terms of goal regulation, threat sensitivity, and emotion-relevant impulsivity. In a sample of college students, elevated risk for mania was associated with greater reward sensitivity and intense goal pursuit. By contrast, risk for BPD was associated with impulsivity driven by negative affect and sensitivity to perceived threat.[75]

Some authors have proposed that bipolar disorder in children differs from that in adults by its non-episodic course and the far greater presence of irritability, rather than mania,[76,77] which has led to changes in diagnostic practices in the United States, in particular, and to a substantial increase in diagnoses of child and adolescent bipolar disorder. In reaction to this increase, Leibenluft[78] reviewed the link between mood dysregulation, irritability, and bipolar disorder in young people. Overall, she concluded that children presenting with non-episodic severe irritability do not have mania; in studies of youth with severe mood dysregulation, 84% also met criteria for lifetime oppositional defiant disorder, 86% for lifetime ADHD, 58% for lifetime anxiety disorder, and 16% for lifetime major depressive disorder (MDD). She also noted that young people with irritability do not have high rates of bipolar disorder in their families and that, compared with young people with bipolar disorder, they have a different pathophysiology. Finally, she concluded that severe mood dysregulation does not lead to bipolar disorder. Rather, irritability predicts adult unipolar depression and anxiety disorders. These syndromes have been previously noted to comprise precursor signs and symptoms of BPD.[38] Moreover, mood dysregulation and irritability are also characteristic of BPD, which was not measured in the cited studies.

These studies highlight the problem that the symptoms that precede first-episode mania have poor sensitivity and specificity.[79] Depressive symptoms have high sensitivity but low specificity for bipolar disorder, whereas low-grade elevation of mood is more specific but is not present in all young people who will go on to develop bipolar disorder. Bechdolf and colleagues[61] developed a "close-in" strategy (combining identified risk factors to "close in" on the target population)[80] in order to balance the need for sensitivity and specificity. They evaluated the validity of Bipolar At-Risk (BAR) Criteria (defined as subthreshold mania, depression plus cyclothymic features, or depression plus first-degree relative with bipolar disorder) in young people aged 15 to 24 years presenting for intake assessment at a psychiatric service with nonpsychotic disorders. In their sample, 22.7% of the BAR group developed bipolar disorder, compared with only 0.7% in the non-BAR group. BAR criteria appear to have some predictive validity in the proximal prodrome of bipolar disorder. The authors are currently testing these criteria in a new prospective study.[61] A comparison of the "signature" of bipolar and unipolar depression suggested that features of psychomotor retardation, melancholia, and atypical depression were more common in bipolar disorder and had some predictive capacity.[81]

The above studies suggest that BPD and bipolar disorder share numerous distal risk factors and precursor signs and symptoms. Even specific childhood and adolescent bipolar disorder symptoms, such as depression, irritability, mood changes, and an episode of hypomania, do not robustly predict the development of bipolar disorder per se. Some of these precursors for bipolar disorder overlap with the precursors for BPD. Strategies to identify young people at risk of developing bipolar disorder have had some success in closing in on the risk factors associated with the onset of bipolar disorder in young people, but these strategies require further investigation.

Unipolar Depression

There is a marked rise in the incidence of depressive symptoms during and after the pubertal period. Twenty percent of young people will have a diagnosable depressive episode prior to 18 years of age.[82] Half of all first depressive episodes occur during adolescence, with an average onset of 15 years of age.[83] Depression during this developmental period has also been associated with greater risk for subsequent episodes and a more chronic course.[84,85] Similar to BPD and bipolar disorder, depression in adolescence is associated with unfavorable long-term functional and psychopathological outcomes[86] that include impairments in education, vocation, interpersonal relationships, substance use, and suicide.

Various retrospective studies have investigated risk factors and other characteristics of individuals whose first depressive episode occurred during adolescence. These studies require cautious interpretation—first because of the potential for recall bias, and second because of the marked heterogeneity of the depressive construct. A study of 198 depressed women attending primary care practices found that those whose first episode of depression occurred prior to age 16 years were more likely to have had a suicide attempt, self-harm, a history of alcohol abuse, teenage pregnancy, pervasive personality dysfunction, inattention and hyperactivity, and poor relationships with their peers.[87] This group was also more likely to have been exposed to poor parental care, physical abuse, childhood sexual abuse, and interpersonal violence. Another study compared 372 adult patients with depression according to whether their first depressive episode occurred in childhood,

adolescence, or adulthood.[88] The group reporting adolescent-onset depression was significantly more likely to meet criteria for personality disorders. Avoidant personality disorder was the most common, followed by BPD.

There is notable overlap among risk factors for depression, BPD, and bipolar disorder, including substance use, social disadvantage, poverty, exposure to violence, childhood maltreatment, inter-parental conflict, parental overinvolvement, and parental aversiveness. The basis for claims of specificity for risk factors for youth depression (e.g., having a parent with a depressive illness, low self-esteem, female sex, negative body image, poor social support, and ineffective coping)[86] seems to be weak; for example, parental depressive illness is also associated with later bipolar or anxiety disorders.[63,89] Likewise, many protective factors, such as healthy diet and sleep, the presence of supportive adults, strong family and peer relationships, coping and emotion-regulation skills, and focusing on age-appropriate developmental tasks, appear to be nonspecific.[86,90]

Vulnerability to depression is associated with individual differences in temperament, such as high negative emotionality, which prospectively predicts depression.[91] Furthermore, personality disorder and depression have been shown to be mutually reinforcing throughout adolescence and young adulthood.[4] For example, BPD features identified between ages 14 and 22 years were prospectively associated with dysthymic or MDD at mean age 33 years, even after adjusting for a history of unipolar depression or other psychiatric disorder.[92]

The evidence above suggests that it is not surprising that unipolar depression shares many risk factors and precursor signs and symptoms with BPD and bipolar disorder, as well as other disorders, such as substance use. Depressive symptoms are common among adolescents and lead to outcomes that might include depression, BPD, or bipolar disorder but that might also include good mental health. Crucially, the initial polarity of first-presentation bipolar disorder is most commonly depressive,[60] making treatment initiation (especially pharmacotherapy) for first-presentation depressive illness clinically challenging. Compounding the challenge is the heterogeneous nature of the current definition of depression, which incorporates diverse and, arguably, poorly specific forms of dysphoria.[93]

CLINICAL "COMORBIDITY" AND BORDERLINE PERSONALITY DISORDER

Mental state disorder, personality traits, and personality disorder are significantly overlapping constructs.[94] The frequency and extent of co-occurring mental state and personality pathology present challenges for clinical diagnosis. This is especially true for BPD, where the phenotypic expression of personality disorder commonly includes varying forms of dysphoria, such that co-occurring mental state and personality disorder are the norm.[95,96] In a US, nationally representative survey of adults aged 18 years and over, 84.5% of those with BPD met criteria for at least one mental state disorder in the previous 12 months, with the mean number of mental state disorders being 3.2.[97] Conversely, 25.2% of individuals who had a mental state disorder in the previous 12 months also met criteria for at least one personality disorder. In addition to being an artifact of a symptom-based diagnostic system, this co-occurrence might be a predictable consequence of the involvement of common risk and vulnerability factors for multiple disorders.[98]

This pattern of co-occurrence of mental state and personality disorder has been found to be similar in young people in community and clinical settings. The Children in the Community study found that the long-term outcomes for mental state and personality disorders were of similar magnitude and often additive when they co-occurred.[30] Both mental state (mood, anxiety, disruptive behavior, and substance use disorders) and personality disorders in adolescence showed risks for adverse outcomes for 20 years following first assessment. Co-occurring mental state and personality disorders consistently presented the greatest risk, which was at least the sum of the risks for both mental state and personality disorders but could also be several times the risk for either disorder alone.

In a comparison among adolescent outpatients with BPD, with other personality disorders, and with no personality disorder, those with BPD had the greatest burden of co-occurring mood (59%), anxiety (46%), disruptive behavior (70%), and substance use (35%) disorders.[20] The same was true for female adolescent inpatients with BPD, where the most frequent co-occurring mental state disorders were mood (22%), eating (16%), dissociative/somatoform (13%), and substance use (10%).[29] Thirty-nine percent of patients also had one or more co-occurring personality disorders, most commonly Cluster C (avoidant, dependent, obsessive-compulsive), followed by Cluster A (paranoid).[29] These studies show that the normative clinical presentation of BPD is the presence of dysphoric anxiety, affective dysregulation symptoms, and other psychopathology.

Both the prominence of affective criteria and the co-occurrence of affective disorders (including bipolar I, bipolar II, MDD, and dysthymic disorder) in patients with BPD have driven debate about whether BPD should be viewed as a mood disorder.[99] Relevant literature will be covered relating to this issue in young people.

Borderline Personality Disorder and Bipolar Disorder

One source of clinical controversy regarding BPD and bipolar disorder might be the diagnostic criteria themselves. Many of the criteria for BPD and bipolar disorder in DSM-5 and its forerunners are related to mood instability.[100] A comprehensive exploration of the hypothesis that BPD is actually a bipolar spectrum disorder concluded that, more frequently than not, BPD remains both cross-sectionally and temporally distinct from bipolar disorders.[99] Others have argued that the debate about overlap is scientifically false because mood lability and impulsivity are neither specific nor fundamental to either disorder.[101] Proponents of this latter argument suggest that bipolar

disorder is principally a disorder of psychomotor activation and that the BPD criteria of abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, and dissociative symptoms distinguish BPD from bipolar disorder.

Others have highlighted that affective changes have a different time course and quality in BPD compared with bipolar disorder. In contrast to the presence of distinct and relatively persistent blocks of affective symptoms and a slower time course of affective change in bipolar disorder, BPD affect is subject to rapid and chaotic changes over minutes, hours, or days,[102] more usually shifts between euthymia and anger,[103] and is often triggered by environmental (especially interpersonal) factors.[102]

Little research actually supports the hypothesis (largely based on the observation of unstable mood) that BPD is a bipolar spectrum disorder.[7] One study of 87 depressed young people, recruited from consecutive referrals to a psychiatric clinic,[104] aimed to compare BPD pathology during an index depressive episode in three diagnostic groups: bipolar disorder (n = 14), "bipolar spectrum disorder" (n = 27), and MDD (n = 46). None of the participants met full diagnostic criteria for a personality disorder. Compared with the MDD group, both of the bipolar-depressed groups reported significantly higher median levels of borderline characteristics. Three borderline characteristics were proposed as potentially useful for differentiating bipolar depression from unipolar depression: "I've never threatened suicide or injured myself on purpose"; "I have tantrums or angry outbursts"; and "Giving in to some of my urges gets me into trouble." The authors concluded that certain BPD screening questions—which they believe reflect cyclothymic characteristics or depressive mixed states—might be useful for differentiating bipolar from unipolar depression in young adults, and that BPD in early-onset depression is predictive of ultimate bipolar outcome. This study had significant limitations, however, including the reliance on the International Personality Disorders Examination screening questionnaire (which does not perform well in young outpatients),[19] the absence of any case-level BPD, and the use of nonvalidated diagnostic criteria for "bipolar spectrum disorder."

Another study that investigated 100 adolescents and young adults (aged 15–36 years) with early onset of bipolar disorder found that a co-occurring diagnosis of BPD significantly increased the risk for self-harm but not suicide attempts.[105] The most important finding from this study was that, compared with later onset, early onset of bipolar disorder was associated with the highest risk of self-harm and suicide attempts. This finding is supported by data showing that anxiety, concentration difficulties, antisocial behavior, and substance use are present in the early stages of bipolar disorder and are associated with an unfavorable course.[106,107]

Fundamental to the need to distinguish BPD and bipolar disorder is the ability of clinicians to disentangle symptoms and to actively investigate whether either disorder might be present. Failure to look for BPD in adults presenting with mood symptoms might be seen as a form of diagnostic myopia[108] that risks favoring bipolar disorder diagnosis over BPD. This problem is potentially amplified by treatment-seeking patients' greater awareness of bipolar disorder compared with BPD,[109] and also by the greater stigma of BPD, especially among clinicians.[110] The problem appears to be exacerbated in young people because of clinicians' reluctance to make, or even antagonism toward making, the diagnosis of BPD among adolescents.[111,112] Reasons cited in defense of this failure include the mistaken beliefs that personality pathology is transient or normative among young people, or that the diagnosis is not allowed in adolescence. While some of these concerns can be moderated by evidence, the diagnosis is undoubtedly stigmatizing, and stigma remains a key barrier to clinicians' acceptance of the BPD diagnosis in young people.[3]

These studies imply that assessment should consider all available clinical data; the particular character and context of mood-regulation difficulties are critical to distinguishing these disorders from one another and to initiating disorder-specific treatments. Certain characteristics might be especially salient, such as mood elevation, atypical depressive features, or alternating, persistent and stable blocks of psychomotor activation/retardation for bipolar disorder, or abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, and dissociative symptoms for BPD. Co-occurrence of bipolar disorder and BPD is also possible and appears to heighten the risk of self-harm and suicide attempts.

Borderline Personality Disorder and Unipolar Depression

DSM-5 includes suicidal ideation or attempts in the diagnostic criteria for both BPD and MDD. The high frequency of these and other depressive symptoms in young patients with BPD[20] can contribute to a hasty diagnosis of depression or uncertainty about the presence of personality disorder.

A great deal of research has been conducted over many decades on the subject of BPD and depression in adults.[113] When the two syndromes co-occur in adults, BPD negatively influences both the functioning of depressed patients and the risk for the relapse, recurrence, and new onset of depression.[114–116] This subject has received comparatively little attention in young people, however, especially in clinical samples, and it is unclear how the findings in adults with BPD might apply to young people. A differential diagnosis of BPD needs to be entertained in any young person presenting with depression (and vice versa), but diagnosing BPD is uncommon not only because of clinicians' reluctance or antagonism concerning the diagnosis, as mentioned above,[111,112] but also because of the lack of developmentally appropriate diagnostic criteria for BPD in the major diagnostic manuals.[28] As with the comparison between bipolar disorder and BPD, it is possible that the nature of affective symptoms is different in young people with BPD, compared with their adult counterparts, and the relevant differences are likely to have significant consequences for both treatment and prognosis.

In a comparison of depressed adult patients with and without BPD, the Rhode Island Methods to Improve Diagnostic

Assessment and Services study found that depressed patients with BPD had a younger age of onset, more depressive episodes, a greater likelihood of experiencing atypical symptoms, a higher prevalence of comorbid anxiety and substance use disorders, and more previous suicide attempts.[9] This picture is similar to that for comparisons of bipolar depression to unipolar depression (e.g., Mitchell et al.[81] and Akiskal et al.[117]) and suggests that many of the features used to validate the bipolar spectrum are not specific to bipolar disorder.

Studies in adults with BPD also provide some insight into how the nature of depression in this group might differ from MDD. The McLean Study of Adult Development[118] studied the time to remission of 24 BPD symptoms in a sample of 290 patients over a ten-year period. Symptoms reflecting affective instability, impulsivity, and some interpersonal difficulties, such as stormy relationships, showed patterns of sharp decline over time. By contrast, affective symptoms reflecting chronic dysphoria, intense anger, and interpersonal symptoms, such as intolerance of aloneness or abandonment fears, were more stable, albeit still showing substantial declines over the follow-up period. The more stable symptoms included chronic feelings of depression, helplessness, hopelessness, worthlessness, guilt, anger, anxiety, and loneliness, which overlap with the diagnostic criteria for MDD. The authors suggest that it is the chronic nature of these symptoms and their resistance to change that causes poor psychosocial adjustment in BPD. Importantly, this study showed that, unlike MDD, chronic dysphoria in BPD occurs in the context of symptoms reflecting abandonment and dependency issues, such as intolerance of aloneness, chronic anger, and dependency. Equally, depression in bipolar disorder has been shown to have subtle differences from unipolar depression, with the former including more atypical features (especially hypersomnia), a seasonal pattern, abrupt onset and offset, less tearfulness, and fewer somatic symptoms.[81]

A qualitative study of seven individuals with BPD suggests that although chronic dysphoria in BPD appears to mimic depression, it might actually comprise an undifferentiated set of painful negative affects related to emotional suffering, rather than sadness.[119] These affects occur in the context of aggression or the breaking off of a relationship (by another person), are accompanied by reactive aggressive impulses, but do not appear to involve an explicit articulation of loss.

It is unclear how these findings relate to young people with BPD. The link between dysphoria and aggression, however, is supported by a nonclinical study of 226 adolescent and young adult students.[120] In the young adult students, maladaptive emotional coping significantly mediated the relationship between borderline pathology and reactive aggression, and maladaptive avoidant coping mediated the relationship between borderline pathology and proactive aggression. Another study of 196 girls (mean age = 10 years) found that borderline pathology is associated with aggression as a strategy to cope with the overwhelming experience of intense negative affect associated with stressful peer interactions.[121]

In short, while there is considerable phenomenological overlap between BPD and MDD, understanding symptom relationships in the early stages of these disorders is hampered by a lack of evidence. Preliminary evidence from samples of adults with BPD suggests that the chronic dysphoria that characterizes BPD has a longer time course and occurs in a relational context; rather than sadness, it might actually be overwhelming negative affect that is externalized as irritability and aggression. This interpretation has received some support in community samples of young people.

CLINICAL STAGING: A PRAGMATIC HEURISTIC FRAMEWORK FOR CLINICAL INTERVENTION

In adult psychiatric practice, debate has been previously framed around the underrecognition of bipolar disorder or BPD in people presenting for treatment of depression.[122] The reification of each DSM-5 syndrome leads, in turn, to insinuations that clinicians might be missing obvious cases or foolishly applying the wrong treatment or withholding much-needed treatments.[7,123]

A crucial problem in youth is the disproportionate focus placed upon bipolar disorder, unipolar depression, and BPD as separate domains of risk, especially in retrospective studies. For example, in both bipolar disorder and BPD, patients might present as depressed, experience mood changes, have early age of onset and a history of abuse, engage in substance abuse, impulsive behaviors, and self-harm, and have other comorbid disorders.[124] Youth frequently present clinically with blends of symptoms in the context of a dynamic, evolving, and unpredictable clinical picture. In that context, especially when symptoms are subthreshold, early application of a concrete and specific diagnosis might be inappropriate. The need for some form of treatment, however, often precedes reaching a diagnostic threshold,[6] and intervention often cannot wait until the trajectory of these symptoms, with time, eventually becomes clear.

Another fundamental issue is that interventions (usually pharmacotherapeutic) for adult disorder phenotypes are often used as first-line interventions in youth, whereas psychosocial interventions are largely deemphasized or ignored.[125] This focus on medication is implicit in discussions of potential interventions for mood dysregulation and irritability,[78] and has been explicit in discussions about the use of mood-stabilizing medications for pediatric bipolar disorder. Timely use of mood-stabilizing medications is desirable because delay might diminish potential neuroprotective effects, and the presence of any active symptoms disrupts developmental trajectories.[58] There is a risk, however, that premature use will medicate what might be a developmentally common, and usually short-lived, nonclinical bipolar phenotype.[73] And whatever the reasons for introducing such medications, they might entail longer-term harms that might outweigh any benefits for young people, especially second-generation antipsychotics.[126] What is absent from this calculus is a thorough evaluation of the potential role for less "toxic" interventions, especially psychosocial interventions.

Keeping the risks of treatment delay in mind, psychosocial interventions such as mental health literacy, family and individual psychoeducation, parenting skills and family interventions, substance use reduction, supportive counseling, and problem solving provide valid, but generic, methods for moderating the risk factors for progression to diagnosable disorder (outlined earlier) that are common to BPD and mood disorders, and for potentially averting significant disruption to normal development caused by mental disorders in this age group.

An alternative approach to focusing on diagnostic categories to guide prevention and early intervention in youth is to develop a range of risk syndromes, or warning signs for particular types of disorders.[6,127] Fundamental to this cross-diagnostic, "clinical staging"[128] approach is eschewing diagnostic categories and arbitrary age restrictions in favor of a focus on the severity and persistence of symptoms, the need for care, and the proportionality of any intervention. Once a convincing clinical phenotype has evolved, appropriate specific therapy can be initiated.

Clinical staging in the assessment of, and intervention for, mood disorders and BPD is illustrated in Table 1.

This model outlines a response to each stage of disorder that is proportionate to the presenting clinical picture. Proposed interventions are simpler and more benign during early stages of disorder (Stages 0 and 1), and increase in intensity (and potential adverse effects) with disorder progression. In later-stage disorder (Stages 3 and 4), the risk of more severe adverse effects potentially outweighs the risk of not treating the disorder. Interventions can also be combined when syndromes are found to genuinely co-occur.

In this model, Stage 0 comprises asymptomatic individuals with increased risk of disorder. Appropriate interventions might include health education campaigns or self-help interventions regarding substance use, diet and healthy weight, negative coping strategies, and sleep patterns.[90] Stage 1 comprises nonspecific or subthreshold BPD, potentially with hypomanic or depressive symptoms. Later stages would be characterized by the first onset of a disorder, by subsequent relapses and remissions, or by co-occurrence of other disorders (e.g., BPD or MDD).[9]

While generic psychosocial interventions apply to the early stages of this model, more specific psychosocial interventions are proposed for early stages of disorder, including the Helping Young People Early (HYPE) program for BPD[130] and psychosocial interventions for bipolar disorder[131] and unipolar depression.[132] Low-toxicity, novel pharmacotherapies might also be appropriate for Stages 1b and 2. Examples include N-acetylcysteine for bipolar disorder, substance abuse, and

Table 1

A Potential Clinical-Staging Model for Bipolar Disorder and Borderline Personality Disorder

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder or borderline personality disorder (e.g., family history, exposure to abuse or neglect, substance use). No specific current symptoms	Mental health literacy Self-help
1a	Mild or nonspecific symptoms of mood disorder or borderline personality disorder (e.g., disturbances in attention, emotion regulation, and behavior)	Formal mental health literacy; family psychoeducation, parenting skills; substance abuse reduction; supportive counseling/problem solving
1b	Subthreshold features of mood disorder or borderline personality disorder	Stage 1a interventions plus phase-specific psychosocial intervention (e.g., cognitive-behavioral therapy, HYPE early intervention for borderline personality disorder[129])
2	First episode of threshold mood disorder or borderline personality disorder	Stage 1b interventions plus case management, educational/vocational intervention/rehabilitation, family psychoeducation and support, specific time-limited psychotherapy, specific and targeted pharmacotherapy (e.g., mood stabilizer)
3a	Recurrence of subthreshold mood or borderline personality disorder symptoms	Stage 2 interventions plus emphasis on maintenance medication and psychosocial strategies for full remission
3b	First threshold relapse of mood disorder or borderline personality disorder	Stage 3a interventions plus relapse-prevention strategies
3c	Multiple relapses of mood disorder or borderline personality disorder	Stage 3b interventions plus combination of mood stabilizers and intensive psychosocial interventions (e.g., dialectical behavior therapy)
4	Persistent, unremitting disorder	Stage 3c interventions plus clozapine and other tertiary therapies, and social participation despite disability

Adapted from Berk et al. (2013)[58] and McGorry et al. (2006).[129]

depression,[133–135] and omega-3 fatty acids, which evidence suggests might be useful in both mood disorders and BPD from Stage 2 onward.[136–138]

This clinical-staging model for mood disorders and BPD will necessarily evolve and become more sophisticated with increased knowledge about the disorders' developmental pathways (including likely biological and endophenotypic markers), potentially also leading to novel interventions. The model provides a starting point for developing more nuanced diagnoses and treatments, and it constitutes, in effect, an algorithm for determining how to intervene early in the course of these disorders in young people.

INTEGRATING BPD INTO PREVENTION AND EARLY-INTERVENTION STRATEGIES FOR MOOD DISORDERS

BPD in adolescents and young adults appears to be as reliable and valid a disorder as many other major psychiatric disorders. Both borderline and mood-related psychopathology become clinically prominent from puberty through to young adulthood, overlap phenomenologically, and frequently co-occur. BPD and mood disorders share numerous common risk factors and precursors, complicating this aspect of clinical assessment. Although the outcomes for individuals presenting with such psychopathology are extremely variable, borderline- and mood-related psychopathology can intensify or mutually reinforce one another across this developmental period, possibly crossing the threshold to become a "case" of either or both disorders. Regardless of whether an individual crosses such an arbitrary threshold for caseness, a significant proportion of individuals will develop clinically important and persistent functional, vocational, and interpersonal impairment and disability.

There is a clear need for intervention early in the course of these disorders. Balancing the sensitivity and specificity of early-detection programs presents challenges, however, especially given that such symptoms overlap with what might be developmentally normal and that they often resolve without clinical intervention. Effective early intervention has the potential to improve developmental and functional outcomes for those affected, but this provisional benefit must be balanced against the risk of premature diagnosis at an age when diagnostic instability is normative—a situation that can lead to stigma, mistaken diagnostic labels, inappropriate treatment, and other adverse outcomes.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602.
2. de Girolamo G, Dagani J, Purcell R, Cocchi A, McGorry PD. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. Epidemiol Psychiatr Sci 2012;21:47–57.
3. Chanen AM, McCutcheon LK. Prevention and early intervention for borderline personality disorder: current status and recent evidence. Br J Psychiatry Suppl 2013;54:s24–9.
4. Cohen P, Crawford TN, Johnson JG, Kasen S. The children in the community study of developmental course of personality disorder. J Pers Disord 2005;19:466–86.
5. Paris J. Personality disorders begin in adolescence. J Can Acad Child Adolesc Psychiatry 2013;22:195–6.
6. McGorry PD. Early clinical phenotypes and risk for serious mental disorders in young people: need for care precedes traditional diagnoses in mood and psychotic disorders. Can J Psychiatry 2013;58:19–21.
7. Paris J. Personality disorders and mood disorders: phenomenological resemblances vs. pathogenetic pathways. J Pers Disord 2010;24:3–13.
8. Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH; BRIDGE Study Group. The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatr Scand 2013;128:376–83.
9. Galione J, Zimmerman M. A comparison of depressed patients with and without borderline personality disorder: implications for interpreting studies of the validity of the bipolar spectrum. J Pers Disord 2010;24:763–72.
10. Berkson J. Limitations of the application of fourfold table analysis to hospital data. Biom Bull 1946;2:47–53.
11. Cicchetti D, Toth SL. The past achievements and future promises of developmental psychopathology: the coming of age of a discipline. J Child Psychol Psychiatry 2009;50:16–25.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed.Washington, DC: APA, 1980.
13. Chanen AM, McCutcheon LK. Personality disorder in adolescence: the diagnosis that dare not speak its name. Pers Ment Health 2008;2:35–41.
14. National Collaborating Centre for Mental Health. Borderline personality disorder: treatment and management. London: National Institute for Health and Clinical Excellence, 2009.
15. National Health and Medical Research Council. Clinical practice guideline for the management of borderline personality disorder. Melbourne, Australia: NHMRC, 2012.
16. Newton-Howes G, Clark LA, Chanen AM. Personality disorder across the life course. Lancet 2015;385:727–34.
17. Chanen AM, Jovev M, McCutcheon L, Jackson HJ, McGorry PD. Borderline personality disorder in young people and the prospects for prevention and early intervention. Curr Psychiatry Rev 2008;4:48–57.
18. Miller AL, Muehlenkamp JJ, Jacobson CM. Fact or fiction: diagnosing borderline personality disorder in adolescents. Clin Psychol Rev 2008;28:969–81.
19. Chanen AM, Jovev M, Djaja D, et al. Screening for borderline personality disorder in outpatient youth. J Pers Disord 2008; 22:353–64.
20. Chanen AM, Jovev M, Jackson HJ. Adaptive functioning and psychiatric symptoms in adolescents with borderline personality disorder. J Clin Psychiatry 2007;68:297–306.
21. Sharp C, Green KL, Yaroslavsky I, Venta A, Zanarini MC, Pettit J. The incremental validity of borderline personality disorder relative to major depressive disorder for suicidal ideation and deliberate self-harm in adolescents. J Pers Disord 2012;26: 927–38.
22. Ullrich S, Coid J. The age distribution of self-reported personality disorder traits in a household population. J Pers Disord 2009;23:187–200.
23. Johnson JG, Cohen P, Kasen S, Skodol AE, Hamagami F, Brook JS. Age-related change in personality disorder trait levels

between early adolescence and adulthood: a community-based longitudinal investigation. Acta Psychiatr Scand 2000; 102:265–75.
24. Samuels J, Eaton WW, Bienvenu O, Brown C, Costa PT, Nestadt G. Prevalence and correlates of personality disorders in a community sample. Br J Psychiatry 2002;180:536–42.
25. Zanarini MC, Horwood J, Wolke D, Waylen A, Fitzmaurice G, Grant BF. Prevalence of DSM-IV borderline personality disorder in two community samples: 6,330 English 11-year-olds and 34,653 American adults. J Pers Disord 2011;25:607–19.
26. Bernstein DP, Cohen P, Velez CN, Schwab-Stone M, Siever LJ, Shinsato L. Prevalence and stability of the DSM-III-R personality disorders in a community-based survey of adolescents. Am J Psychiatry 1993;150:1237–43.
27. Moran P, Coffey C, Mann A, Carlin JB, Patton GC. Personality and substance use disorders in young adults. Br J Psychiatry 2006;188:374–9.
28. Chanen AM, Jackson HJ, McGorry PD, Allott KA, Clarkson V, Yuen HP. Two-year stability of personality disorder in older adolescent outpatients. J Pers Disord 2004;18:526–41.
29. Kaess M, von Ceumern-Lindenstjerna I-A, Parzer P, et al. Axis I and II comorbidity and psychosocial functioning in female adolescents with borderline personality disorder. Psychopathology 2012;46:52–62.
30. Crawford TN, Cohen P, First MB, Skodol AE, Johnson JG, Kasen S. Comorbid Axis I and Axis II disorders in early adolescence: prognosis 20 years later. Arch Gen Psychiatry 2008;65: 641–8.
31. Winograd G, Cohen P, Chen H. Adolescent borderline symptoms in the community: prognosis for functioning over 20 years. J Child Psychol Psychiatry 2008;49:933–41.
32. Stepp SD, Pilkonis PA, Hipwell AE, Loeber R, Stouthamer–Loeber M. Stability of borderline personality disorder features in girls. J Pers Disord 2010;24:460–72.
33. Crick NR, Murray-Close D, Woods K. Borderline personality features in childhood: a short-term longitudinal study. Dev Psychopathol 2005;17:1051–70.
34. Cohen P. Childhood risks for young adult symptoms of personality disorder: method and substance. Multivariate Behav Res 1996;31:121–48.
35. Bernstein DP, Cohen P, Skodol A, Bezirganian S, Brook J. Childhood antecedents of adolescent personality disorders. Am J Psychiatry 1996;153:907–13.
36. Kasen S, Cohen P, Skodol AE, Johnson JG, Brook JS. Influence of child and adolescent psychiatric disorders on young adult personality disorder. Am J Psychiatry 1999;156:1529–35.
37. Crawford TN, Cohen P, Johnson JG, et al. Self-reported personality disorder in the children in the community sample: convergent and prospective validity in late adolescence and adulthood. J Pers Disord 2005;19:30–52.
38. Chanen AM, Kaess M. Developmental pathways toward borderline personality disorder. Curr Psychiatry Rep 2012;14:45–53.
39. Torgersen S, Myers J, Reichborn-Kjennerud T, Roysamb E, Kubarych TS, Kendler KS. The heritability of cluster B personality disorders assessed both by personal interview and questionnaire. J Pers Disord 2012;26:848–66.
40. Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Coming to terms with the terms of risk. Arch Gen Psychiatry 1997;54:337–43.
41. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Am J Psychiatry 1995;152:967–72.
42. Crawford TN, Cohen PR, Chen H, Anglin DM, Ehrensaft M. Early maternal separation and the trajectory of borderline personality disorder symptoms. Dev Psychopathol 2009;21: 1013–30.
43. Carlson EA, Egeland B, Sroufe LA. A prospective investigation of the development of borderline personality symptoms. Dev Psychopathol 2009;21:1311–34.
44. Rohde P, Lewinsohn PM, Kahler CW, Seeley JR, Brown RA. Natural course of alcohol use disorders from adolescence to young adulthood. J Am Acad Child Adolesc Psychiatry 2001; 40:83–90.
45. Thatcher DL, Cornelius JR, Clark DB. Adolescent alcohol use disorders predict adult borderline personality. Addict Behav 2005;30:1709–24.
46. Stepp SD, Burke JD, Hipwell AE, Loeber R. Trajectories of attention deficit hyperactivity disorder and oppositional defiant disorder symptoms as precursors of borderline personality disorder symptoms in adolescent girls. J Abnorm Child Psychol 2012;40:7–20.
47. Burke JD, Stepp SD. Adolescent disruptive behavior and borderline personality disorder symptoms in young adult men. J Abnorm Child Psychol 2012;40:35–44.
48. Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. Lancet 2011;377:74–84.
49. Zanarini MC, Frankenburg FR, Ridolfi ME, Jager-Hyman S, Hennen J, Gunderson JG. Reported childhood onset of self-mutilation among borderline patients. J Pers Disord 2006;20:9–15.
50. Nock MK. Self-injury. Annu Rev Clin Psychol 2010;6:339–63.
51. Brunner R, Parzer P, Haffner J, et al. Prevalence and psychological correlates of occasional and repetitive deliberate self-harm in adolescents. Arch Pediatr Adolesc Med 2007;161:641–9.
52. Nock MK, Joiner JTE, Gordon KH, Lloyd-Richardson E, Prinstein MJ. Non-suicidal self-injury among adolescents: diagnostic correlates and relation to suicide attempts. Psychiatry Res 2006;144:65–72.
53. Muehlenkamp JJ, Ertelt TW, Miller AL, Claes L. Borderline personality symptoms differentiate non-suicidal and suicidal self-injury in ethnically diverse adolescent outpatients. J Child Psychol Psychiatry 2011;52:148–55.
54. Jacobson CM, Muehlenkamp JJ, Miller AL, Turner JB. Psychiatric impairment among adolescents engaging in different types of deliberate self-harm. J Clin Child Adolesc Psychol 2008;37: 363–75.
55. Tidemalm D, Haglund A, Karanti A, Landen M, Runeson B. Attempted suicide in bipolar disorder: risk factors in a cohort of 6086 patients. PLoS One 2014;9:e94097.
56. Berk M, Dodd S, Malhi GS. 'Bipolar missed states': the diagnosis and clinical salience of bipolar mixed states. Aust N Z J Psychiatry 2005;39:215–21.
57. Cohen P, Chen H, Kasen S, Johnson JG, Crawford T, Gordon K. Adolescent cluster A personality disorder symptoms, role assumption in the transition to adulthood, and resolution or persistence of symptoms. Dev Psychopathol 2005;17: 549–68.
58. Berk M, Berk L, Dodd S, et al. Stage managing bipolar disorder. Bipolar Disord 2014;16:471–7.
59. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31:281–94.
60. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord 2007;100:279–81.
61. Bechdolf A, Ratheesh A, Wood SJ, et al. Rationale and first results of developing at-risk (prodromal) criteria for bipolar disorder. Curr Pharm Des 2012;18:358–75.
62. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997;42:623–31.

63. Oquendo MA, Ellis SP, Chesin MS, et al. Familial transmission of parental mood disorders: unipolar and bipolar disorders in offspring. Bipolar Disord 2013;15:764–73.
64. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. Am J Psychiatry 2013;170:542–9.
65. Ryden E, Thase ME, Straht D, Aberg-Wistedt A, Bejerot S, Landen M. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr Scand 2009;120:239–46.
66. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry 1997; 36:1378–87; discussion 87–90.
67. Marchand WR, Wirth L, Simon C. Adverse life events and pediatric bipolar disorder in a community mental health setting. Community Ment Health J 2005;41:67–75.
68. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. Br J Psychiatry 2005;186:121–5.
69. Strakowski SM, DelBello MP. The co-occurrence of bipolar and substance use disorders. Clin Psychol Rev 2000;20:191–206.
70. Young LT, Bagby RM, Cooke RG, Parker JD, Levitt AJ, Joffe RT. A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. Psychiatry Res 1995;58:139–43.
71. Thompson KN, Conus PO, Ward JL, et al. The initial prodrome to bipolar affective disorder: prospective case studies. J Affect Disord 2003;77:79–85.
72. Conus P, Ward J, Hallam KT, et al. The proximal prodrome to first episode mania. Bipolar Disord 2008;10:555–65.
73. Tijssen MJ, van Os J, Wittchen HU, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. Br J Psychiatry 2010;196:102–8.
74. Birmaher B, Axelson D, Goldstein B, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry 2009;166:795–804.
75. Fulford D, Eisner LR, Johnson SL. Differentiating risk for mania and borderline personality disorder: the nature of goal regulation and impulsivity. Psychiatry Res 2015;227: 347–52.
76. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995;34: 867–76.
77. Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Pediatric mania: a developmental subtype of bipolar disorder? Biol Psychiatry 2000;48:458–66.
78. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry 2011;168:129–42.
79. Ratheesh A, Berk M, Davey CG, McGorry PD, Cotton SM. Instruments that prospectively predict bipolar disorder—a systematic review. J Affect Disord 2015;179:65–73.
80. Bell RQ. Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. Psychiatry 1992;55:370–81.
81. Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry 2001;62:212–6; quiz 7.
82. Allen NB, Hetrick S, Simmons JG, Hickie IB. Early intervention for depressive disorders in young people: the opportunity and the (lack of) evidence. Med J Aust 2007;187:S15–S7.
83. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–27.
84. Costello EJ, Pine DS, Hammen C, et al. Development and natural history of mood disorders. Biol Psychiatry 2002;52: 529–42.
85. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol Psychiatry 2013;18:595–606.
86. Gladstone TR, Beardslee WR, O'Connor EE. The prevention of adolescent depression. Psychiatr Clin North Am 2011;34: 35–52.
87. Hill J, Pickles A, Rollinson L, Davies R, Byatt M. Juvenile- versus adult-onset depression: multiple differences imply different pathways. Psychol Med 2004;34:1483–93.
88. Fernando K, Carter JD, Frampton CM, et al. Childhood-, teenage-, and adult-onset depression: diagnostic and individual characteristics in a clinical sample. Compr Psychiatry 2011;52: 623–9.
89. Vandeleur C, Rothen S, Gholam-Rezaee M, et al. Mental disorders in offspring of parents with bipolar and major depressive disorders. Bipolar Disord 2012;14:641–53.
90. Cairns KE, Yap MB, Pilkington PD, Jorm AF. Risk and protective factors for depression that adolescents can modify: a systematic review and meta-analysis of longitudinal studies. J Affect Disord 2014;169:61–75.
91. Hankin BL. Future directions in vulnerability to depression among youth: integrating risk factors and processes across multiple levels of analysis. J Clin Child Adolesc Psychol 2012; 41:695–718.
92. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorder traits associated with risk for unipolar depression during middle adulthood. Psychiatry Res 2005;136:113–21.
93. Berk M, Berk L. Is 'depression' the new 'neurosis'? Aust N Z J Psychiatry 2013;47:297–8.
94. Dolan-Sewell RT, Krueger RF, Shea M. Co-occurrence with syndrome disorders. In: Livesley WJ, ed. Handbook of personality disorders: theory, research, and treatment. New York: Guilford, 2001:84–104.
95. Barrachina J, Pascual JC, Ferrer M, et al. Axis II comorbidity in borderline personality disorder is influenced by sex, age, and clinical severity. Compr Psychiatry 2011;52:725–30.
96. Eaton NR, Krueger RF, Keyes KM, et al. Borderline personality disorder co-morbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychol Med 2011;41:1041–50.
97. Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;62:553–64.
98. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol 2006;2:111–33.
99. Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders. Compr Psychiatry 2007;48:145–54.
100. Benazzi F. A relationship between bipolar II disorder and borderline personality disorder? Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1022–9.
101. Barroilhet S, Vöhringer PA, Ghaemi SN. Borderline versus bipolar: differences matter. Acta Psychiatr Scand 2013;128: 385–6.
102. Renaud S, Corbalan F, Beaulieu S. Differential diagnosis of bipolar affective disorder type II and borderline personality

disorder: analysis of the affective dimension. Compr Psychiatry 2012;53:952–61.
103. Bassett D. Borderline personality disorder and bipolar affective disorder. Spectra or spectre? A review. Aust N Z J Psychiatry 2012;46:327–39.
104. Smith DJ, Muir WJ, Blackwood DHR. Borderline personality disorder characteristics in young adults with recurrent mood disorders: a comparison of bipolar and unipolar depression. J Affect Disord 2005;87:17–23.
105. Moor S, Crowe M, Luty SE, Carter JD, Joyce PR. Effects of comorbidity and early age of onset in young people with bipolar disorder on self harming behaviour and suicide attempts. J Affect Disord 2012;136:1212–5.
106. Baethge C, Baldessarini RJ, Khalsa HM, Hennen J, Salvatore P, Tohen M. Substance abuse in first-episode bipolar I disorder: indications for early intervention. Am J Psychiatry 2005;162: 1008–10.
107. Berk M, Dodd S, Callaly P, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. J Affect Disord 2007;103:181–6.
108. Zimmerman M. Improving the recognition of borderline personality disorder in a bipolar world. J Pers Disord 2015 Apr 20 [Epub ahead of print].
109. Richardson E, Tracy DK. The borderline of bipolar: opinions of patients and lessons for clinicians on the diagnostic conflict. BJPsych Bulletin 2015;39:108–13.
110. Aviram RB, Brodsky BS, Stanley B. Borderline personality disorder, stigma, and treatment implications. Harv Rev Psychiatry 2006;14:249–56.
111. Laurenssen EM, Hutsebaut J, Feenstra DJ, Van Busschbach JJ, Luyten P. Diagnosis of personality disorders in adolescents: a study among psychologists. Child Adolesc Psychiatry Ment Health 2013;7:3.
112. Griffiths M. Validity, utility and acceptability of borderline personality disorder diagnosis in childhood and adolescence: survey of psychiatrists. Psychiatrist 2011;35:19–22.
113. Gunderson JG, Stout RL, Shea MT, et al. Interactions of borderline personality disorder and mood disorders over 10 years. J Clin Psychiatry 2014;75:829–34.
114. Skodol AE, Grilo CM, Pagano ME, et al. Effects of personality disorders on functioning and well-being in major depressive disorder. J Psychiatr Pract 2005;11:363–8.
115. Gunderson JG, Stout RL, Sanislow CA, et al. New episodes and new onsets of major depression in borderline and other personality disorders. J Affect Disord 2008;111:40–5.
116. Grilo CM, Stout RL, Markowitz JC, et al. Personality disorders predict relapse after remission from an episode of major depressive disorder: a 6-year prospective study. J Clin Psychiatry 2010;71:1629–35.
117. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995;52:114–23.
118. 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.
119. Briand-Malenfant R, Lecours S, Deschenaux E. What does sadness mean to BPD patients? J Pers Disord 2012;26:939–55.
120. Gardner KJ, Archer J, Jackson S. Does maladaptive coping mediate the relationship between borderline personality traits and reactive and proactive aggression? Aggress Behav 2012;38:403–13.
121. Banny AM, Tseng WL, Murray-Close D, Pitula CE, Crick NR. Borderline personality features as a predictor of forms and functions of aggression during middle childhood: examining the roles of gender and physiological reactivity. Dev Psychopathol 2014;26:789–804.
122. Zimmerman ME, Morgan TA. The relationship between borderline personality disorder and bipolar disorder. Dialogues Clin Neurosci 2013;15:155–69.
123. Matza LS, Rajagopalan KS, Thompson CL, de Lissovoy G. Misdiagnosed patients with bipolar disorder: comorbidities, treatment patterns, and direct treatment costs. J Clin Psychiatry 2005;66:1432–40.
124. Zimmerman ME, Galione JN, Ruggero CJ, et al. Screening for bipolar disorder and finding borderline personality disorder. J Clin Psychiatry 2010;71:1212–7.
125. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry 2007;64: 1032–9.
126. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 2009;302:1765–73.
127. McGorry PD, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity. Lancet 2013;381:343–5.
128. McGorry PD. Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. Schizophr Res 2010;120:49–53.
129. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 2006;40:616–22.
130. Chanen AM, McCutcheon L, Germano D, Nistico H, Jackson HJ, McGorry PD. The HYPE Clinic: an early intervention service for borderline personality disorder. J Psychiatr Pract 2009;15:163–72.
131. Macneil CA, Hallam K, Conus P, Henry L, Kader L, Berk M. Are we missing opportunities for early intervention in bipolar disorder? Expert Rev Neurother 2012;12:5–7.
132. Garber J, Clarke GN, Weersing VR, et al. Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA 2009;301:2215–24.
133. Berk M, Copolov DL, Dean O, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry 2008; 64:468–75.
134. Prado E, Maes M, Piccoli LG, et al. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. Redox Rep 2015;20:215–22.
135. Berk M, Dean OM, Cotton SM, et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2014;75:628–36.
136. Amminger GP, Chanen AM, Ohmann S, et al. Ω-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: a post-hoc subgroup analysis of a double-blind randomised controlled trial. Can J Psychiatry 2013;58:402–8.
137. 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; 160:167–9.
138. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 2012;73:81–6.