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REVIEW ARTICLE

The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid personality disorders

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BACKGROUND: The association between mood disorders and personality disorders (PDs) is complicated clinically, conceptually, and neurobiologically. There is a need for recommendations to assist clinicians in treating these frequently encountered patients.

METHODS: The literature was reviewed with the purpose of identifying clinically relevant themes. MedLine searches were supplemented with manual review of the references in relevant papers. From the extant evidence, consensus-based recommendations for clinical practice were developed.

RESULTS: Key issues were identified with regards to the overlap of PDs and mood disorders, including whether certain personality features predispose to mood disorders, whether PDs can reliably be recognized if there is an Axis I disorder present, whether personality disturbances arise as a consequence or are a *forme fruste* of mood disorders, and whether personality traits or disorders modify treatment responsiveness and outcome of mood disorders.

CONCLUSION: This paper describes consensus-based clinical recommendations that arise from a consideration of how signals from the literature can impact clinical practice in the treatment of patients with comorbid mood and personality pathology. Additional treatment studies of patients with the comorbid conditions are required to further inform clinical practice.

KEYWORDS: major depressive disorder, bipolar disorder, mood disorders, personality disorders, borderline personality disorder, clinical guidelines

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INTRODUCTION

There are numerous studies reporting the rates of comorbid personality disorders (PDs) in patients with mood disorders. PDs appear to be highly prevalent among patients with chronic depression,[1-11] with up to 50% of patients with dysthymic disorder reported to have a comorbid PD.[4,12,13] Rates of PDs are higher in early-onset chronic depression than in late-onset chronic depression,[14-16] with some evidence that early-onset dysthymia is more strongly associated with PD compared with episodic depression.[12,17] Some have suggested that up to 35% to 65% of patients with major depressive disorder (MDD) have a comorbid PD.[18]

PD comorbidity rates in bipolar disorder (BD), defined broadly to include BD I and BD II, as well as schizoaffective disorder, bipolar type, are in the range of 30% to 50%. In a pooled analysis of 7 studies, Brieger and colleagues[19] reported a prevalence rate of 46% in 393 BD patients. In their analysis, obsessive-compulsive personality disorder (OCPD), histrionic PD, and borderline PD each had a prevalence rate of approximately 15%.[19] The least common PD diagnoses associated with BD appear to be schizotypal (3%), schizoid (4.9%), and dependent PD (5.1%).

With the exception of the recognized and complex association between borderline PD and BD, comorbidity rates of PD in general appear to be lower in BD compared with MDD. Given that few studies have made direct assessments in both MDD and BD patients, it is difficult to specify with confidence which PDs occur at different frequencies in BD and unipolar depression. One study that assessed the frequency of borderline PD characteristics—not disorder—examined a sample of BD, bipolar spectrum, and unipolar young adults and reported that both bipolar groups had higher levels of borderline personality features than the unipolar group. Features that were endorsed more commonly in the BD and bipolar spectrum groups were primarily those related to impulsivity.

The investigators acknowledge that some of the bipolar spectrum patients might have entered that category in part because of high rates of impulsivity and corresponding behaviors, which may account for this distinction noted between the bipolar and unipolar group. They suggest, however, that the results support previous assertions by Akiskal and colleagues[3] that high rates of borderline pathology in the presence of early-onset depression should raise a high index of suspicion for BD. This type of symptom overlap exemplifies the challenges faced by clinicians attempting to diagnostically differentiate these conditions, and formulate illness-specific management plans.

The nature of the association and differentiation between borderline PD and BD continues to be debated, with evidence for negative ramifications of misdiagnosis in either direction.[21,22] With regard to the rate of BD in borderline PD, Gunderson and colleagues[23] used a prospective repeated-measures design with reliable independent diagnostic measures and 4 years of follow-up to assess 196 patients with borderline PD and 433 patients with other PDs. Patients with borderline PD had a significantly higher co-occurrence of BD (19.4%) at the beginning of the study than did patients with other PDs. They found that 8.2% of the borderline PD patients developed new-onset BD over the 4-year study. This rate was higher than in patients with other PDs.

The field remains divided with respect to whether patients whose diagnosis may be unclear will be better served if they are diagnosed with either BD or borderline PD. One group recently noted that once patients are labelled with a borderline PD diagnosis, health care professionals are more likely to see them as problematic and undeserving of medical care, leaving the patients feeling unsupported.[22]

In keeping with this view, a recent review concluded that when PD patients are viewed as experiencing a mood disorder, they do not receive the best treatment. Medications are freely prescribed and psychotherapies rarely offered.[24] It seems unlikely that the polarity inherent in these assumptions will be resolved until we relinquish the historical model that presupposes that treatment of Axis I disorders requires adherence to a model of biological reductionism that is uninformed by the influence of either the proximate or distal influences of the environment.

Conversely, there are also many recent studies examining brain functioning in patients with borderline PD that recognize the biological and social contributions to temperament and personality.[2] Certainly, a growing number of studies emphasize the significance of the social environment and the corresponding role of psychotherapy in the treatment of both mood disorders and PDs.

Despite the ongoing controversies regarding how best to conceptualize patients with features of mood disorders and PDs, the data suggest that clinicians must be

vigilant to the presence of comorbid PD in patients with either BD or MDD. Certainly, the presence of apparently refractory symptoms of illness should trigger a review for both Axis I and Axis II comorbidity that may be impeding treatment outcome.

A challenge to understanding the scope of the overlap between Axis I mood disorders and Axis II PDs is the limitations of the available data on rates of this comorbidity. The definitions of PD and mood disorders are operationalized in a variety of ways in extant studies. Many studies have small sample sizes, resulting in the number of individuals diagnosed with any one disorder on Axis II amounting to no more than a single case or even no cases. Researchers are forced to draw conclusions on prevalence and differences in prevalence rates, from a very small number of cases.

Do personality features predispose people to mood disorders?

Certain traits such as obsessionality, dependency, neuroticism, and interpersonal sensitivity are associated with depression. Some have suggested that specific PDs, such as borderline, avoidant, and dependent, are associated with elevated rates of depression.[25,26] Overall, patients with borderline PD are more likely than patients with non-borderline PD to have multiple Axis I diagnoses.[13,27] In a prospective, well-designed study of patients with borderline PD, 96% had a lifetime comorbid mood disorder, 9% had comorbidity with BD, 88% had an anxiety disorder, 55% had posttraumatic stress disorder, 53% had an eating disorder, and 64% had a substance use disorder.[28] Other investigators also have suggested that the high rate of mood disorders, particularly depression, in patients with a PD likely reflects the increased risk for development of depression in patients with problematic personality traits.[12,13] Personality pathology but not cognitive distortions have been linked to MDD recurrences.[29] Shea and Yen concluded that neuroticism increased the risk of depressive episode recurrence.[30]

In a recent thorough review, Klein and colleagues[31] summarized their findings on the relationship between personality and depression, noting that there are moderate-to-large cross-sectional associations between depression and 3 general personality traits—high levels of neuroticism/negative emotionality (N/NE), low levels of extraversion/positive emotionality (E/PE), and conscientiousness—as well as with a variety of related traits (eg, harm avoidance, rumination, and self-criticism) and personality types (depressive personality). Most of the personality traits associated with depression appeared to be related to other forms of psychopathology, particularly anxiety disorders. They noted that some traits (eg, N/NE and harm avoidance) are influenced by clinical state, whereas other traits (eg, E/PE) appear to be independent of mood state. They note a strong negative association between conscientiousness and depression, at least in cross-sectional studies.

However, Klein and colleagues[31] concluded that state effects cannot fully account for the associations between personality and depression, and that depressive personality and some traits, particularly N/NE, predict the subsequent onset of depressive disorders. It remains unclear whether personality traits are best conceptualized as precursors or predispositions, and there is evidence supporting both hypotheses. Other traits, such as low E/PE and low conscientiousness/effortful control, may moderate the relationship between N/NE and depression.

Klein and colleagues[31] concluded that it appears unlikely that depressive episodes produce enduring changes in most personality traits, but that personality traits predict, and in fact may influence, the course and treatment response of depression. They maintain that if personality is a precursor of, or predisposes to, the development of depressive disorders, it is critical to identify the moderating factors and mediating processes involved in these pathways. Their review indicates that there is some evidence suggesting that moderators may include sex, early adversity, and life stress, and mediators may include interpersonal deficits, depressotypic cognitions, maladaptive coping, and behavioral and neurobiological stress reactivity.[31]

The conclusions in this careful review help summarize a complicated literature on state/trait issues, confirming that certain traits are important influences in the course and treatment response of depression.

Are personality disorders state dependent?

Another approach to examining the association between PD and depression has been to explore whether PDs are state dependent. Mullen and colleagues[32] noted the treatment of MDD results in an improvement in maladaptive defences. Hirschfeld and colleagues[33] has suggested the treatment of MDD results in improvement in PDs, and Fava and colleagues[34] also described a significant reduction in the proportion of unipolar depressed patients having a comorbid PD after only 8 weeks of fluoxetine treatment.[12]

Morey and colleagues[35] examined whether patients diagnosed with a PD during depressive episodes had outcomes that were more similar to other patients with a PD or to depression patients without a comorbid PD. Six-year outcomes of >400 patients suggested that patients diagnosed with borderline, schizotypal, obsessive-compulsive, or avoidant PD while depressed had outcomes that were similar to pure PD patients and significantly worse than people with pure MDD. Although only 8% of patients with pure depression remained depressed at 6-year follow up, almost 1 in 3 (29%) comorbid patients remained depressed.

As Michels[36] noted in an accompanying editorial, it is unclear whether this reflects the fact that the PD interferes with recovery from MDD or whether the persistent symptoms actually reflects elements of the PD. The stability estimates of the PD diagnoses were similar for patients diagnosed with either a comorbid or a pure PD, suggesting that a PD diagnosed in the context of a mood episode generally reflect personality pathology and are not an artifact of the mood disorder.

This conclusion is dependent on formal assessment of PDs, which was done in this study. Overdiagnosis of PDs during a depressive episode remains a risk if a formal PD assessment is not conducted. Patients experiencing mood episodes sometimes appear to have a PD based on features that dominate the clinical presentation. The mood episode exacerbates what appear to be PD features, such as self-mutilative behaviors, inappropriate anger, affective dysregulation, and frantic efforts to avoid abandonment.

Clinicians may react to such MDD exacerbations of negative behaviors by assuming prematurely (ie, without a confirming longitudinal review of personality structure) that the patient has a PD. However, absent the longitudinal confirmation of a PD diagnosis, the more accurate diagnosis is the mood disorder, which may have exacerbated some personality vulnerabilities during the episode. Treatment of MDD in such patients may diminish the maladaptive personality expressions. This reflects what Mullen and colleagues[32] have noted—that MDD treatments may result in an improvement in maladaptive defenses.

Mulder and colleagues[37] reported on a follow-up study of 149 depressed outpatients who were systematically assessed for PDs at baseline and at 18 months. They concluded that PD diagnoses and symptoms demonstrated low-to-moderate stability and that in depressed outpatients, PD symptoms tend to improve significantly more in patients who recover from MDD but also improve in patients who have poor or modest response to their depression treatment. They concluded that aggressive treatment of mood symptoms appears to have a positive effect on personality pathology.

Clark[38] indicates that studies of PD stability have converged on the finding that PD features include both acute, dysfunctional behaviors that resolve in relatively short periods, and maladaptive temperamental traits that are relatively more stable—similar to normal range personality traits. Clark indicates that a PD defined by acute symptoms that are linked directly to maladaptive traits (eg, avoiding interpersonal occupational activity with social inhibition), and/or develop as defensive or compensatory behaviors (eg, self-mutilation) to cope with stress—both exogenous and self-created by one's own maladaptivity. These more changeable symptoms, together with the inherent lesser reliability of single-observation assessment, largely account for observed diagnostic instability. Personality traits, however, that are more extreme and maladaptive, account for the persistent dysfunction. Clark's conceptualization may be an important consideration in understanding whether and/or how personality has a state-dependent component.

To date, there are no psychometrically validated and widely-used short assessment tools for PD screening in patients with a comorbid mood disorder. A structured assessment process, including, for example, the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) or Neuroticism-Extroversion-Openness Personality Inventory may be helpful, particularly for patients with treatment-resistant mood disorders; however, clinical use currently is limited by the length of these instruments and lack of training in non-research settings. Some tools are under active development for screening PDs in clinical practice; for example, utility of the short form of the Coolidge Axis II Inventory, a 70-item scale, remains to be confirmed for use in clinical samples, particularly in comorbid mood disorders. Referring patients for systematic assessment, such as with the Minnesota Multiphasic Personality Inventory (MMPI) or other such measures may be useful, particularly with patients when it is difficult to establish the extent of PD traits by other means. Such referral is best done after the Axis I disorder has been stabilized and should be undertaken by a practitioner with adequate expertise to interpret the findings.

With the increased emphasis on personality dimensions anticipated in the DSM-5, it is hoped that clinically useful and well-validated screening tools will be developed. It also is hoped that the controversies regarding categorical vs dimensional views of personality and how these can be clinically operationalized, will also be clarified.[39-41]

Do personality disorders influence treatment response and outcome in mood disorders?

Many studies have found that compared with depressed patients without Axis II comorbidity, patients with PDs have a less complete or delayed response to pharmacotherapy alone[42-45] or to pharmacotherapy and psychotherapy together.[46] (Not all studies have supported this finding.[5,8,13,47,48]) Some have suggested that borderline PD predicts a decreased likelihood of response to treatment for chronic depression.[13,32] Dysthymic patients with a comorbid PD are less likely to recover than those without a PD.[49] Depressive personality traits, but not a comorbid PD, also are associated with higher nonresponse to antidepressants in patients with chronic major or double depression.[8,13,33]

Grilo and colleagues,[50] noting multiple shorter-term studies indicating that PDs negatively affect treatment outcome in MDD, reported on the 6-year follow-up of the Collaborative Longitudinal Personality Disorders Study, concluding that a PD at baseline, specifically borderline and obsessive-compulsive PDs, were robust predictors of accelerated relapse after remission from an episode of MDD.

In data from a US national epidemiologic survey, Skodol and colleagues[51] noted that presence of any PD elevated the risk for persistence of MDD; however, borderline PD remained the most robust predictor of MDD persistence after controlling for Axis I and II disorders, age of onset of MDD, number of episodes, family history, treatment, and duration of illness. Interestingly, the authors concluded that although borderline PD predicted MDD persistence, no PD predicted recurrence of MDD. This is in contrast to Grilo and colleagues,[50] who indicated that a PD was a predictor of recurrence. In an accompanying editorial, Weissman[52] concluded that borderline PD should be assessed in all depressed patients, considered in prognosis, and addressed in treatment.

A heuristic model provided by Gabbard and Simonsen[53] accounts for why depressed patients with a comorbid PD can show greater treatment refractoriness than depressed patients without a PD. The model focuses on the role of temperamental predispositions, early childhood adversity and resulting attachment disturbances, dysfunctional schemas, affect dysregulation, and deviant cognitive styles. The authors also comment on avoidance of the PD diagnosis, and difficulties PD patients may have in forming a treatment alliance.

In a meta-analysis, Newton-Howes and colleagues[54] concluded that a PD comorbid with depression was associated with double the risk of a poor outcome for depression compared with absence of a PD. All treatments except electroconvulsive therapy (ECT) showed this poor outcome, and the ECT group was small. They concluded that combined depression and PD is associated with a poorer outcome than depression alone. Mulder's[55] response to the Newton-Howes meta-analysis indicates that the heterogeneous nature of their data does not allow for definitive answers. He concludes that there is an absence of good evidence to indicate that targeting comorbid personality pathology is necessary or will result in better outcomes for MDD. However, in a study of 175 depressed outpatients, Mulder and colleagues[56] found that personality factors such as high harm avoidance and schizoid traits were associated with a worse outcome of MDD.

Several earlier meta-analyses regarding whether PDs negatively affect outcome have suggested differing conclusions. In contrast to Newton-Howes, other meta-analyses indicated that a PD does not worsen outcome of MDD. In a review of the literature on unipolar depression complicated by Axis II pathology, Mulder[57] concluded that Axis II pathology did not worsen the treatment outcome of MDD if optimal medication and psychotherapy were used. In a meta-analysis, Kool and colleagues[58] demonstrated that the presence of a PD did not significantly worsen outcome in MDD treatment.

Thus, although there are divergent signals from the literature, it is reasonable to conclude that the clinical observation that a comorbid PD worsens outcome in mood disorders is consistent with the more recent literature on this issue. The foregoing observation provides the basis for recommending that routine assessment of PDs in depressed patients is warranted.[52]

Personality traits, psychosocial factors, and treatment response

Although some studies have suggested that personality traits and temperaments, rather than a specific PD, may predict the response to antidepressant treatment, there is

no consistent finding regarding specific traits or specific antidepressant medications.[13,33,47,59-62] Other studies have found no relationship between personality traits or temperaments and treatment outcome.[13,63-65] There also is the question of whether the effects of selective serotonin reuptake inhibitors (SSRIs) on personality contributes to the antidepressant effects. For example, paroxetine may have a specific pharmacologic effect on personality that is distinct from its effect on depression.[66] This is an interesting observation that sometimes is observed clinically, but requires further research elaboration and clinical observation to confirm.

Kennedy and colleagues[67] observed that certain personality traits may have maladaptive implications for help-seeking, treatment compliance, and response, including increased side effects. Paying attention to personality issues can help clinicians address maladaptive attributional styles.

Considering the conceptual issues that may be involved, Reich[68] noted that PDs may reflect a long-lasting subgroup as well as a second subgroup that is "stress-induced" or "state" PD, which may be relatively transient. McGlashan and colleagues[69] also commented that within PDs, the relatively fixed criteria are more trait-like and attitudinal, whereas the relatively intermittent criteria are more behavioral and reactive. They suggest that PDs are hybrids of traits and symptomatic behaviors and that the interaction of these elements over time helps determine diagnostic stability.

Bagby and Quilty[70] suggest that personality trait dimensions underlying the PD may provide a more reliable and valid focus of clinical and research attention for the treatment of MDD and call for the use of the Five-Factor Model of Personality.

Howland and Thase[13] have considered how psychosocial issues impact medication response in persons with a PD. Individuals with a PD may be burdened by more factors that diminish the effectiveness of antidepressant treatments.[71] PDs beginning early in life are associated with many interpersonal difficulties and high rates of Axis I comorbidity, including anxiety and substance use disorders.[72,73] A PD negatively affects development, and causes interpersonal difficulties and social skills deficits, all of which negatively affect one's capacity to develop social supports. These difficulties also contribute to persistent adverse life events. Therefore, such individuals are more vulnerable to affective episodes because of a variety of adverse factors.[13]

Personality pathology and certain personality traits, such as sensation seeking, also are linked to antidepressant nonresponse through poor medication adherence.[74,75] Bock and colleagues[76] reported on 301 patients with a first depressive episode; 31% met criteria for a PD based on the SCID-II. The presence of a comorbid PD was associated with a 2-fold increase in the risk of non-remission for the first antidepressant medication tried. There was no significant impact of comorbid personality pathology on the risk of non-remission with a second antidepressant trial, but a high degree of neuroticism predicted non-remission with both a first and subsequent trial of antidepressant medications. Therefore, a number of predictors of antidepressant response overlap with the clinical and psychosocial features that characterize patients with PDs.[13,77,78]

Bieling and colleagues[79] used a life-charting method to determine the extent to which a range of Axis II dimensional features were associated with poor long-term outcome in 87 patients with BD I and BD II. Patients were followed regularly and treated according to published guidelines for pharmacologic treatment for an average of 3.4 years. Better outcomes on symptom severity and functioning were noted for patients with lower scores on 7 out of 10 PD categories. Cluster A symptoms (paranoid, schizoid, schizotypal) best distinguished euthymic and symptomatic patients. Consistent with findings in MDD, PD traits predicted negative outcome over this relatively long-term follow-up.

Although extant studies consistently suggest that comorbid PD exerts a negative effect on BD outcome, the quality of methodologies employed in the relevant studies varies considerably. Most of the studies use naturalistic designs, in which the presence of a PD is positively correlated with a dependent measure related to function. Use of DSM-defined PDs dismisses the impact that PD traits, even when subthreshold for diagnosis, might exert on outcome. Patients who do not meet criteria for the DSM diagnosis of a PD tend to be included in the "no PD" group, which may minimize the differences observed between the PD-positive and the "no PD" groups. Few studies define "no PD" as the absence of any or a few traits, which might be a more accurate representation of the outcome of people with healthy personality functioning despite a diagnosis of BD.

Although the shortcomings of this literature are important to note, we conclude that the clinical impression that PDs worsens outcome in mood disorders is generally supported by the literature in both MDD and BD.

Suicidality

Suicide risk is elevated in patients with mood disorders,[80] and the role of comorbid PDs in further increasing this risk has been examined. Leverich and colleagues[81] investigated correlates of serious suicide attempts over an average of 2.8 years of follow-up in 648 patients with BD followed through the Stanley Foundation Bipolar Network. In total, 34% of patients had a history of suicide attempts. In a hierarchical cluster analysis, having a Cluster B PD (antisocial, borderline, histrionic, and narcissistic) was a significant predictor of serious suicide attempt in addition to history of sexual abuse, lack of confidant prior to illness, hospitalizations for depression, and suicidal thoughts when depressed. Further analyses suggested that PD comorbidity had an effect on suicidality above and beyond the effects of other comorbid psychiatric illness (eg, anxiety and substance use disorders), loss of social supports, lack of health care access, and negative life events.[81]

Garno and colleagues[82] also examined the extent to which comorbid Cluster B PDs impacted course and outcome for patients with BD and the risk of lifetime suicide attempts. Overall, 30% of their sample met DSM-IV criteria for a Cluster B PD (17% borderline, 6% antisocial, 5% histrionic, 8% narcissistic), and this comorbidity was associated with significantly increased lifetime suicide attempts after controlling for current depression severity, lifetime substance abuse, and past sexual or emotional abuse.

Psychotherapy for personality disorders

Although it is difficult to conduct research on psychotherapy for PDs, there is an encouraging body of research emerging, primarily related to borderline PD. A Cochrane review of psychological therapies concluded that dialectical behavior therapy (DBT) seemed to be helpful for a wide range of outcomes, such as hospitalization; however, it was noted that the small size of the studies limits its confidence in these results.[83] This review also noted that psychoanalytically-oriented day hospital therapy also seemed to decrease admissions and use of medication and increase social improvement and adjustment. Concerns about sample size were similarly noted.

More recent reviews concluded that randomized controlled trials (RCTs) demonstrated favorable results for psychotherapies on symptomatology, social and interpersonal functioning, reduced frequencies of maladaptive behaviors, and decreased hospitalization.[84] Paris[24] concluded that the strongest evidence for psychotherapy for borderline PD favored DBT and mentalization-based treatments. Focus on predictable structure and methods that promote emotion regulation and problem solving was emphasized.

Zanarini[85] noted the main therapies for borderline PD include DBT, schema-focused therapy, transference-focused therapy, and mentalization-based treatment. Although acknowledging that these therapies significantly reduce severity of borderline symptomatology, Zanarini called for development of less intensive and less costly forms of treatment. In her 2008 review she noted that most borderline PD patients improve over time, but the reasons for this change are unclear. She observed that therapy and the reparations that adult life offers may be responsible for facilitating these changes.[86]

In a RCT using a relatively brief augmenting group therapy strategy, Blum and colleagues[87] described their work with Systems Training for Emotional Predictability and Problem Solving (STEPPS), a 20-week manual-based group treatment program for outpatients with borderline PD that combines cognitive-behavioral elements and skills training with a systems component. The authors compared STEPPS plus treatment as usual with treatment as usual alone in a RCT. The STEPPS plus treatment as usual group showed greater improvement in the Zanarini Rating Scale for borderline PD total score and subscales assessing affective, cognitive, interpersonal, and impulsive domains. STEPPS plus treatment as usual also led to greater improvements in impulsivity, negative affectivity, mood, and global functioning. These differences yielded moderate-to-large effect sizes. Fewer patients in the STEPPS plus treatment as usual group had emergency department visits during treatment and follow-up. The authors concluded that STEPPS is an adjunctive group treatment that can deliver clinically meaningful improvements in borderline PD-related symptoms and behaviors, enhance global functioning, and relieve depression. Black and colleagues[88] provide more detail on the clinical approach involved.

In an accompanying editorial, Silk[89] described the study by Blum and colleagues as intriguing in that it complements other therapies and need not replace or compete with them. He viewed it as a sensible adjunct, particularly to an intervention in which effectiveness is limited in areas where STEPPS has been shown to be beneficial.

While making similar observations on psychological therapies as noted above in the Cochrane review, the National Institute for Health and Clinical Excellence

(NICE) clinical guidelines for borderline PD cited the Blum and colleagues approach as an adjunctive treatment for borderline PD.[90] A recent Cochrane database review examined the role for psychological interventions in antisocial PD.[91] They examined data from 5 studies, including 276 participants with antisocial PD. None of the studies reported significant change in specific features of antisocial behaviors, and the investigators concluded that there currently is insufficient evidence to recommend use of any specific psychotherapeutic or behavioral approach in treating antisocial PD.

Pharmacotherapy for comorbid personality disorders

NICE clinical guidelines for borderline PD recommend that medication "should not be used specifically for borderline PD or for the individual symptoms or behavior associated with the disorder."[90] These guidelines noted, "There was some evidence that pharmacological treatments can help to reduce specific symptoms experienced by people with borderline personality disorder including anger, anxiety, depression symptoms, hostility and impulsivity, although this is largely based on single studies. However, there is no evidence that they alter the fundamental nature of the disorder in either the short or longer term. The evidence is weak, and it is far from clear if the effects found are the consequence of treating comorbid disorders."

Stoffers and colleagues[92] conducted a Cochrane Database Systematic Review of the use of medications to treat borderline PD. They reported on 28 trials involving 1,742 participants. Comparative effectiveness studies were rare, and therefore it was not possible to make recommendations regarding the relative superiority of one medication or class relative to others. There were small studies suggesting benefit with second-generation antipsychotics (SGAs), mood stabilizers, and omega-3 fatty acids, but insufficient evidence to support the use of antidepressant medications for borderline PD alone. Of note, there were no studies that suggested total severity was positively influenced by any class of medications, and concordant with this, there was little evidence that the core borderline PD symptoms were effectively controlled with medications. The applicability of these data to patients with comorbid mood disorders is unknown.

Another recent review provided recommendations for the pharmacologic treatment domains of borderline PD symptoms. In a Cochrane Collaboration systematic review and meta-analysis, Lieb and colleagues[93] concluded that current evidence from RCTs suggests that drug treatment, especially with mood stabilizers and SGAs, may be effective for treating a number of core symptoms and associated psychopathology; however, the evidence does not currently support effectiveness for overall severity of borderline PD. Most beneficial effects were found for the mood stabilizers topiramate, lamotrigine, and valproate, and the SGAs aripiprazole and olanzapine.

Lieb and colleagues[93] commented on the contrary findings of the NICE recommendations indicating, "It is of note that this comprehensive guideline recognizes evidence for the reduction of specific symptoms with some pharmacological treatments, but that the final recommendations do not reflect this evidence. Although more robust findings would certainly be desirable, and we appreciate concerns related to giving strong recommendations, we suggest considering a reassessment of these recommendations, as there actually is encouraging evidence of the effectiveness of drug treatment for individual symptoms of borderline personality disorder."

Lieb and colleagues[93] concluded that the mood stabilizers topiramate, valproate, and lamotrigine were effective first-line treatments for affective dysregulation symptoms, and that the SGAs aripiprazole and olanzapine as well as the first-generation antipsychotic (FGA) haloperidol, showed positive results. With respect to impulsive-behavioral dyscontrol symptoms, there is evidence for lamotrigine and topiramate. There are also favorable results for omega-3 fatty acid supplementation, and, to a lesser extent, for the FGA flupenthixol decanoate. In addition, the SGAs aripiprazole and olanzapine are described as the first choice for treating cognitive-perceptual symptoms. SSRIs lack high-level evidence of effectiveness in borderline PD. Pharmacotherapy should therefore be targeted at specific symptoms.[93]

Consistent with the view of Lieb and colleagues[93] but not the NICE findings,[76] Ingenhoven and colleagues[94] reported on a meta-analysis of 21 studies and concluded that drug therapy tailored to well-defined symptom domains can have a beneficial effect on patients with severe PD. The researchers evaluated studies on the effectiveness of psychoactive drugs on specific symptom domains for borderline and/or schizotypal PD. Placebo-controlled RCTs (PC-RCTs) on the efficacy of antipsychotics, antidepressants, and mood

stabilizers regarding cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, and affective dysregulation—with subdomains depressed mood, anxiety, anger, and mood lability—were selected in patients with well-defined borderline and/or schizotypal PD. Studies whose primary emphasis was on the treatment of Axis I disorders were excluded.

Ingenhoven and colleagues[94] concluded that antipsychotics have a moderate effect on cognitive-perceptual symptoms (5 PC-RCTs) and a moderate-to-large effect on anger (4 PC-RCTs). They also found that while antidepressants had no significant effect on impulsive-behavioral dyscontrol and depressed mood, they do have a small but significant effect on anxiety (5 PC-RCTs) and anger (4 PC-RCTs). Mood stabilizers have a very large effect on impulsive-behavioral dyscontrol (6 PC-RCTs) and anger (7 PC-RCTs), a large effect on anxiety (3 PC-RCTs), but a moderate effect on depressed mood (5 PC-RCTs). Mood lability as an outcome measure was seldom assessed. Mood stabilizers have a more pronounced effect on global functioning (3 PC-RCTs) compared to antipsychotics (5 PC-RCTs). The effect of antidepressants on global functioning is negligible, which was also consistent with the study by Lieb and colleagues.[93]

Although more data would be preferable, there is agreement among the meta-analyses that little evidence suggests that psychotropic medications are effective in reducing the overall severity of borderline PD itself. Given the ambiguity of the current literature and the potential side-effect burden of atypical antipsychotics, it makes sense to use them primarily for PD domains such as psychotic-like symptoms, impulsivity, anger, and aggression when there is a comorbid Axis I disorder with an indication for an atypical antipsychotic. It would also seem reasonable to use them off-label in the absence of Axis I comorbidity, when patients are experiencing severe symptoms in those domains and psychotherapy has been ineffective or is not readily available.

Khalifa and colleagues[95] conducted a Cochrane Database review of pharmacotherapy for antisocial PD. They examined 4 studies that included 274 participants, and concluded that the body of evidence is currently insufficient to allow any conclusions to be drawn regarding the use of medications to treat antisocial PD.

Many primary studies and subsequent reviews and guidelines have examined the role of various classes of medications for patients with mood disorders, but the primary studies generally have excluded patients with prominent PDs. In studies that may not have explicitly excluded patients with a mild PD, the subanalyses of patients with PD features generally are lacking. Attempting to merge the literature of pharmacotherapy for mood disorders with the evidence for pharmacotherapy in patients with PDs results in indirect comparisons of unknown validity.

Combination therapy for the treatment of personality disorders

A recent randomized trial examined whether the combination of modified interpersonal therapy (IPT) and fluoxetine would be better than fluoxetine alone in treating patients with borderline PD.[96] Duration, but not type of treatment, had a significant effect on a variety of outcome measures and the authors concluded that combined therapy was superior to pharmacotherapy alone for some of the core features of borderline PD. This trial, although limited by a small sample size and the fact that there was no psychotherapy-alone arm, represents a model for future studies that may examine the comparative effectiveness of combination therapy compared with monotherapy approaches in treating borderline PD.

Treatment of patients with concurrent mood and personality disorders

Bellino and colleagues[97] conducted a study that specifically examined the provision of combination treatment—medication and psychotherapy—in patients with both MDD and borderline PD. They treated patients with either fluoxetine and cognitive-behavioral therapy (CBT) or fluoxetine and IPT. Although they found that combination treatment that included CBT was associated with greater changes on the Hamilton Anxiety Rating Scale and combination therapy that included IPT was more effective on some domains of social functioning, overall there were no differences in outcomes on measures such as the Hamilton Depression Rating Scale or the Social and Occupational Functioning Assessment Scale. The study was limited, however, by its small sample size and examination of a large number of variables without appropriate statistical controls. Despite its limitations, the study highlighted the need for further investigation of combination treatment options in patients with comorbid mood and personality pathology.

Preston and colleagues[98] retrospectively assessed DSM-IV dimensions of borderline PD pre- and post-treatment with lamotrigine in 35 patients with BD. The investigators reported that dimensions of borderline

PD improved with treatment in patients with and without a diagnosis of borderline PD and corresponded with response in bipolar symptoms. The authors acknowledged that the retrospective assessments used in the study represented a limitation of the design.

Swartz and colleagues[99] compared medication treatment outcomes in a sample of patients who met standardized diagnostic criteria for both BD I and borderline PD (n = 12) to those who met criteria for BD I only (n = 58). Only 3 (25%) BD and borderline PD patients achieved stabilization compared with 43 (74%) BD-only patients; dropout rates in the comorbid group were high. The authors noted that some of the patients with comorbid illness improved substantially over longer periods of time with pharmacotherapy and interpersonal and social rhythm therapy, consistent with Bellino's suggestion that the combination of medication and psychotherapy should be considered for patients with comorbid mood and personality pathology.[97]

As a result of the paucity of studies investigating whether certain pharmacologic agents are better suited for patients with mood disorders comorbid with PDs, and because as a general rule there can be no effectiveness without efficacy, a primary consideration in the selection of medications is demonstrated utility for the Axis I condition. It is important for clinicians to recognize that although mood disorders comorbid with a PD may impart a more guarded prognosis in the short term, patients with borderline or other PDs improve substantially with treatment, and the presence of a PD is no reason for therapeutic nihilism.[100] This message should be communicated to the patient and to others who are involved in the patient's care, such as health care professionals and those who have personal relationships with the patient.

CONCLUSIONS

There is a paucity of RCTs that have primarily evaluated pharmacotherapeutic or psychosocial interventions in individuals with MDD or BD with a comorbid PD. Consequently, for this section, we do not include hierarchical levels of evidence. Instead, we provide clinical recommendations reflecting authorship consensus and extrapolation of study results involving individuals with PDs.

- Clinicians treating patients with mood disorders should systematically screen for clinical presentations suggestive of PDs.
- Given the considerable comorbidity of PDs and mood disorders, clinicians treating PDs should routinely screen for comorbid Axis I mood disorders.
- A more complete assessment for comorbid PDs is warranted in patients who do not respond to first-line treatment for their mood disorder or who display characteristic features of an Axis II disorder.
- Although it is observed that depressive symptoms may alter the presentation and severity of a PD, it is not necessary to defer a personality assessment until the person has recovered from an Axis I diagnosis if structured interviews are used. Otherwise, it is better to reassess for PD after the Axis I disorder has been stabilized.
- It is important to obtain a collateral history from others who can confirm whether or not any PD features occur exclusively in the context of an Axis I condition or are long-standing from childhood.
- If collateral history indicates that the PD features are not long-standing, then it suggests that such features may be secondary to the Axis I diagnosis. Practitioners should be mindful that no matter how characterological the presentation, the diagnosis is unlikely to be a PD if there is no supportive evidence from earlier in life. In such patients, PD-like behaviors may reflect a combination of refractory or recurrent mood disorder on personality expression in concert with demoralization and/or situational crises. These patients need active and often robust management of their Axis I disorders, and reassessment of Axis II features after remission of the Axis I disorder has been achieved.
- Although there are some divergent signals, the outcome literature generally indicates that PDs can negatively affect outcome in mood disorder treatment. PDs can influence elements of treatment such as the development of a therapeutic alliance, adherence to treatment, estimated probability of improvement, and other issues such as self-harm or substance abuse. Therefore, the presence of PD comorbidity should be carefully considered in any prospective treatment plan. Monitoring treatment response is warranted in patients with comorbid mood disorders and PDs, in part because treatment response is likely to be less robust, at least initially, in this group.
- Because patients with comorbid PDs, particularly borderline PD or other Cluster B disorders, are at risk of being impulsive and engaging in self-harm behaviors, particular consideration should be given to the lethality of medications prescribed to this group. Although a guiding principle in managing all patients is careful appraisal

in the surveillance of risk and harm, individuals with comorbid PDs may be at higher risk because of impulsivity, poor frustration tolerance, and occasional reality testing disturbances. Consequently, clinicians should arrange for an appropriate locus of care, frequent visits, appropriate supports, and prescription of suitable medication; dosing should be based on an individual case assessment. In general, medications may need to be prescribed in smaller quantities and, if possible, use of prescription and over-the-counter medications with lower lethality should be considered. Given the increased concern regarding impulsive behaviors, careful assessment and documentation of self-harm risk is important.

- Patients with both mood disorders and concurrent PDs should be offered treatment for both conditions. However, there are few primary studies that determined whether a sequential or concurrent approach is superior to focusing treatment on either the mood disorder or the PD. In many cases, a concurrent approach is encouraged, while in others a sequential approach is more appropriate.
- Patients with mood disorders and concurrent PDs should be treated with a combination of diagnosis-specific pharmacotherapy and psychotherapy. Carefully reviewing past medication interventions with regards to dose, duration, benefit, and adverse effects is essential. Similarly, reviewing past psychotherapy interventions with regard to type of therapy, frequency, duration, benefit, and adverse effects is useful.
- Clinicians also should focus treatment on those PD-related behaviors that may disrupt Axis I treatment negatively, affecting the treatment alliance and/or risking the safety of the patient. Such management would include psychotherapy strategies and medication considerations. Given the current mixed signals from the literature as noted above,[76,78] and given the frequency of comorbid Axis I conditions in PD patients, it remains preferable to use pharmacotherapy for the Axis I condition. Using medications for specific Axis II symptom domains should be reserved for consideration after assessing and treating Axis I disorders.
- For patients not receiving concurrent combination treatment directed at both the mood disorder and the PD, stabilization of the Axis I disorder should be followed expeditiously by considering adjunctive treatment for the PD; ideally, this would include offering efficacious psychotherapy for PD (eg, DBT or cognitive analytic therapy for borderline PD).

Absent the level of evidence that would be preferred for treating this difficult patient population, the clinician is left to follow best clinical practices. Attention must be paid to careful diagnostic assessment considering whether PD comorbidity complicates the Axis I diagnosis, and in other situations considering whether patients with a PD have an undiagnosed Axis I diagnosis that may be more readily amenable to treatment. Careful monitoring and management of treatment alliance, adherence, and countertransference are special challenges in working with these patients. It is observed that some patients will "outgrow" their PD condition and/or exhibit less comorbidity with longitudinal observation.[86] ■

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