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REVIEW ARTICLE

Managing medical and psychiatric comorbidity in individuals with major depressive disorder and bipolar disorder

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BACKGROUND: Most individuals with mood disorders experience psychiatric and/or medical comorbidity. Available treatment guidelines for major depressive disorder (MDD) and bipolar disorder (BD) have focused on treating mood disorders in the absence of comorbidity. Treating comorbid conditions in patients with mood disorders requires sufficient decision support to inform appropriate treatment.

METHODS: The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force sought to prepare evidence- and consensus-based recommendations on treating comorbid conditions in patients with MDD and BD by conducting a systematic and qualitative review of extant data. The relative paucity of studies in this area often required a consensus-based approach to selecting and sequencing treatments.

RESULTS: Several principles emerge when managing comorbidity. They include, but are not limited to: establishing the diagnosis, risk assessment, establishing the appropriate setting for treatment, chronic disease management, concurrent or sequential treatment, and measurement-based care.

CONCLUSIONS: Efficacy, effectiveness, and comparative effectiveness research should emphasize treatment and management of conditions comorbid with mood disorders. Clinicians are encouraged to screen and systematically monitor for comorbid conditions in all individuals with mood disorders. The common comorbidity in mood disorders raises fundamental questions about overlapping and discrete pathoetiology.

KEYWORDS: bipolar disorder, major depressive disorder, comorbidity, obesity, anxiety disorders, personality disorders, substance use disorders, attention-deficit/hyperactivity disorder, cardiovascular disease, hypertension, dyslipidemia

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INTRODUCTION

Understudied and priority research vista

Notwithstanding the prevalence, persistence, and hazards posed by comorbidity in MDD and BD, relatively few studies have aimed primarily to characterize treatment response on the basis of stratifying individuals as a function of comorbidity. A chasm exists between the reality of clinical medicine where comorbidity is the rule rather the exception and registration trials that consistently exclude individuals with comorbid conditions. A major criticism of evidence-based guidelines for treating MDD and BD is that they have been formulated based on non-comorbid patients.

The aim of the CANMAT task force recommendations for treating MDD and BD was to provide a preliminary management framework for practitioners and to identify areas that have been studied insufficiently and need empirical evidence.[1-7] Levels of evidence were specified based on criteria from the 2009 CANMAT Guidelines for the Treatment of Major Depressive Disorder and Bipolar Disorder and revised to reflect consensus opinions about quantitative reviews[8,9] (**TABLE 1**). The levels of evidence represent the quality of the studies that have been conducted. Recommendations also were graded according to line of treatment based on criteria we used for our previous guidelines (**TABLE 2**). A first-line treatment represents an optimal balance of efficacy, tolerability, and clinical support. When creating these comorbidity recommendations, there was insufficient evidence for most comorbid conditions and as such, there was an increased emphasis on expert opinion of the CANMAT committee. The CANMAT committee's opinions were intended to enhance utility for practitioners. Second-line treatments represent those strategies wherein the first-line treatment was deemed to be inefficacious or not appropriate for the patient.

Developing the task force recommendations was an iterative process wherein manuscripts were circulated among subsection committee members for revision and consensus. The CANMAT comorbidity task force recommendations did not receive any financial support from the pharmaceutical industry or any other external funding body. The potential conflicts of interest of each author are listed in the CANMAT recommendations.[1-7]

The comorbid conditions selected for these recommendations reflect those conditions most commonly encountered in clinical practice. The task force recommendations are comprised of 6 sections emphasizing the treatment of MDD or BD with comorbidity. The comorbid conditions were: anxiety disorders; substance use disorders; personality disorders; cardiometabolic disorders; attention-deficit/hyperactivity disorder (ADHD); and other medical comorbidity. Several other psychiatric and medical comorbidities were not reviewed simply because our aim was to be relevant yet succinct. Indeed there are many other disorders that are relevant, including, but not limited to, eating disorders, sleep disorders, impulse control disorders, and somatoform disorders.[10-14] Providing comprehensive recommendations for the management of MDD and BD comorbid for each of these conditions was not feasible. Therefore, we focused on the management of mood disorders and the most common and disabling comorbid conditions.

TABLE 1
Criteria for level of evidence

Level	Criteria
1	At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
2	At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals
3	Non-randomized, controlled prospective studies or case series or high quality retrospective studies
4	Expert opinion/consensus

RCT: randomized controlled trial.

As with all guidelines, these CANMAT comorbidity task force recommendations represent a combination of evidence and consensus opinion. Admittedly these recommendations are weighted heavily on consensus and are not intended to be used as an inflexible algorithm for treatment selection and sequencing. Instead, the recommendations are intended to inform clinical practice where the individual needs of each patient are considered separately. Our hope is that creating these recommendations will not only inform treatment decisions, but also will provide the impetus for evaluating disparate interventions for persons with mood disorders and other comorbid conditions.

Comorbidity prevalence in mood disorders

National Comorbidity Survey-Replication (NCS-R) estimated a 16.2% lifetime prevalence of MDD and 6.6%

TABLE 2
Criteria for lines of treatment[a]

Line of treatment	Criteria
First-line	Level 1 or level 2 evidence, plus clinical support
Second-line	Level 3 evidence or higher, plus clinical support
Third-line	Level 4 evidence or higher, plus clinical support

[a]Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are realistic and applicable for clinical practice, in order to enhance the utility of the guidance for clinicians. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment because of clinical issues such as side effect or safety profile.

prevalence of MDD in the 12 months before the interview.[13] Lifetime prevalence estimates of BD were 1.0% for bipolar I disorder (BD I), 1.1% for bipolar II disorder (BD II), and 2.4% for subthreshold BD (4.4% overall). The 12-month prevalence estimates were 0.6% for BD I, 0.8% for BD II, and 1.4% for subthreshold BD (2.8% overall).[13]

Comorbidity generally is defined as the joint occurrence of multiple disorders. Feinstein introduced the term "comorbidity" into medicine, and suggested that multiple disorders have distinct pathoetiology.[15] Results from community epidemiological surveys and clinical studies indicate that the majority of individuals with MDD or BD will meet criteria for at least 1 other DSM-IV-TR psychiatric disorder.[16-21]

The majority of community epidemiological respondents with lifetime bipolar spectrum disorders meet comorbidity criteria, with higher comorbidity rates seen in individuals with threshold BD compared with subthreshold BD.[22,23] The NCS-R reported that 63.1% to 86.7% of respondents with lifetime BD also met criteria for at least 1 lifetime comorbid anxiety disorder and 35.5% to 60.3% met criteria for at least 1 lifetime comorbid substance use disorder.[24] The high rates of psychiatric comorbidity in population-based epidemiological settings offsets the Berkson's bias (the differential representation of comorbidity in clinical cohorts) in clinical samples but does not sufficiently deal with the artifact of overlapping diagnostic criteria.[25,26]

The prevalence of psychiatric comorbidity in cohorts using health services is similar. For example, the Stanley Foundation Bipolar Treatment Outcome Network reported that 65% of patients with BD also met DSM-IV criteria for at least 1 comorbid lifetime Axis I disorder.[16] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported that 65.2% of patients enrolled had at least 1 comorbid psychiatric disorder (social phobia was the most common comorbid psychiatric disorder, 31.3%); 38.6% of patients had ≥2 comorbid psychiatric disorders. Moreover, the mean number of medical conditions endorsed in the STAR*D cohort was 3.3.[27]

High rates of medical comorbidity also have been reported in patients with BD. For example, a descriptive study of 4,310 veterans who received at least 1 inpatient or outpatient BD diagnosis reported a high prevalence of comorbid medical conditions including cardiovascular (hypertension), endocrine (hyperlipidemia, diabetes), pulmonary (chronic obstructive pulmonary disease), infectious (hepatitis C), and musculoskeletal (eg, low back pain) conditions. More than one-third of BD patients were diagnosed with ≥3 comorbid medical conditions. Individuals with BD had a greater burden of medical comorbidity at a younger age than the general veteran population.[28]

Persistence of comorbidity

Another observation pertaining to comorbidity in mood disorders is its stability across time. Results from the 15-year prospective Zurich cohort demonstrated that anxiety comorbid with MDD is more persistent than either syndrome alone.[24,25,29] This greater persistence is thought to contribute to the greater functional disability described in comorbid populations.[24,25,29]

Implications of comorbidity in mood disorders

At the individual level, comorbidity affects evaluation, course, and treatment, as well as social and economic costs of psychiatric disorders.[25] A replicated observation is that psychiatric and medical comorbidity is associated with an earlier age of onset, intensified symptomatology, suicidality, poor symptomatic and functional recovery, diminished acute response to pharmacologic and psychosocial treatment, decreased quality of life, a more complex affective disorder presentation, lower rate of recovery, and unfavorable course and outcome.[25]

For example, individuals with BD and medical comorbidity exhibit a longer duration of lifetime depression and lifetime inpatient depression treatment, higher baseline depression severity scores, higher service utilization for depressive episodes, and increased suicidal behavior.[30] Moreover, ADHD in individuals with

MDD or BD is associated with more frequent affective episodes, antisocial personality disorder, and substance use disorders.[31] Taken together, the composite of comorbidity provides the impetus for careful screening, detection, treatment, and management of co-occurring conditions.

The cost of mood disorders involves not only health care costs for the primary condition, but also costs related to psychiatric and medical comorbidity. Individuals with BD and medical comorbidity incur costs approximately 40% higher than individuals with BD and no medical comorbidity.[32] The increased costs incurred by the comorbid BD patient are mediated largely by increased health care utilization and decreased role functioning (eg, occupational impairment).

Shared pathophysiology

Several factors contribute to comorbidity in mood disorder patients. Results from epidemiological, clinical, family, and brain volumetric studies indicate that mood and anxiety disorders share pathophysiological and causative factors.[33] Evidence suggests that disturbances in reward circuits implicated in affective disorders also subserve other "comorbid" addictive disorders including substance use disorders and excess food intake (ie, food addiction).[34-37] For example, excess food intake might be a phenotypic expression of addictive behavior subserved by similar circuits implicated in illicit substance misuse.[35]

BD linkage studies indicate that panic comorbidity may proxy a genetically distinct BD subtype. Building on reports of a possible genetic link for BD on chromosome 18, significant variation between linkage scores were reported across sets of families when researchers stratified genetic linkage results by proband panic diagnoses.[38-40] Families at risk for panic were linked to markers on the long arm of chromosome 18, while families of probands without panic exhibited no evidence of linkage.

Other factors contributing to the co-occurrence of mood and other disorders can be categorized as organizational (eg, economic, access to primary and preventative health care, educational attainment), behavioral, neurobiological, and iatrogenic.[41] For example, individuals with mood disorders often have relatively less access to public and private health care systems compared with individuals without a psychiatric disorder. Moreover, a comorbid condition has a lower rate of detection, treatment, and management in an individual with a chronic psychiatric disorder compared with persons with a single medical condition.[42]

Mood disorders are associated with a host of negative health behaviors including smoking, poor diet, overeating, and a sedentary lifestyle.[43] The high prevalence of medical disorders in mood disorder populations is related to an increased rate of merging risk factors (eg, inflammation, oxidative stress) as well as established risk factors (eg, hypertension, diabetes mellitus).[44]

Implications for diagnoses

The high prevalence of lifetime comorbidity in mood disorder patients has emboldened the perspective that comorbid conditions are not validated as distinct. Discriminant validity has not been established for psychiatric disorders and comorbidity.[45] The prevailing system of rule-based classification and diagnostic criteria may inflate the prevalence of comorbidity. For example, the diagnostic criteria for ADHD in adults overlap considerably with criteria for a manic episode, therefore increasing the probability of *comorbidity*.

Moreover, comorbidity studies often cannot distinguish between homotypic continuity (the same diagnosis at different assessments) and heterotypic continuity (continuity of disorder but a different diagnosis). Homotypic continuity suggests that a disorder has a similar manifestation independent of age at assessment whereas heterotypic continuity suggests a broad-based underlying vulnerability with heterogeneous manifestations at different ages.[46,47] An example would be pediatric ADHD as a phenotypic variant of BD. This scenario may be coded as comorbidity when in fact heterotypic continuity may be operating, indicating that comorbidity is imprecise.

The temporal association of the co-occurring conditions may help dissect and unravel the complex relationship between mood disorders and comorbidity. For example, when evaluating alcohol abuse or dependence in patients with BD, researchers determined that individuals with BD who reported alcohol use disorders before BD onset (ie, alcohol first) had characteristics consistent with a less severe form of affective illness compared with "bipolar first patients." Specifically, these patients had a later age of BD onset, symptomatically recovered more rapidly, spent less time in affective episodes, and had a relatively rapid recovery rate.[48] These observations (ie, that the sequence of onset of bipolar

and substance use disorders would differentially affect outcome) also were reported for co-occurring cannabis use disorders.[49]

Principles of treatment

1. Establish the diagnosis. Treating comorbidity in mood disorder populations begins with identifying the mood disorder. Notwithstanding extensive education and public awareness programs pertaining to mood disorders, an estimated 50% of individuals with MDD are not diagnosed, furthermore there remains a high rate of false positives in primary care settings.[50] Moreover, deficiencies in BD diagnosis lead to a high rate of false positives, false negatives, and delay in diagnoses. It is estimated that <25% of mood disorder patients receive guideline-concordant care for the mood disorder.[51]

2. Risk assessment. All individuals with mood disorders need to be assessed for self-harm, suicide ideation, and plan. A thorough inventory of previous suicide or self-harm attempts and ongoing surveillance for factors that heighten risk is essential for each patient. Several psychiatric and medical conditions are associated with increased suicidality in mood disorders.[52-56]

3. Establish the appropriate treatment setting. The least restrictive setting should be sought when managing comorbidity. The assessment process needs to include symptom severity, functionality, supports, risk assessment, and comorbidity.

4. Chronic disease management. Mood disorders are chronic medical syndromes that have been identified as national health priorities. The routine inclusion of chronic disease management components (eg, decision support) is encouraged for all patients. Integrating treatment and multi-disciplinary professionals services increases the probability for full recovery. Patient psychoeducation and family involvement in the care process is encouraged.[57,58]

5. Concurrent or sequential treatment. Treatment needs to determine whether the co-occurring condition should be treated concurrently or sequentially. Evidence indicates that integrated treatment of mood disorders and comorbidities concurrently increases the probability of recovery from both conditions (eg, substance use disorders, diabetes mellitus). The sequential treatment of comorbidity would be preferred in some situations, for example, when treating an adult with comorbid BD and ADHD, mood stabilization should be considered before introducing psychostimulants. Determining the sequence of treating comorbid conditions should be based on a hierarchical assessment that gives priority to the level of harmful dysfunction. For example, when treating individuals with symptomatic BD, active illicit substance abuse, and panic disorder, the primary focus should be mood stabilization and abstinence. When these therapeutic objectives are achieved, then attention to panic disorder would be warranted.

6. Measurement-based care. Structured evaluation of symptoms, functioning, and side effects at each visit is encouraged. Measurement-based care has been demonstrated to enhance the quality and consistency of care and increase the probability of remission.[27]

CONCLUSIONS

Individuals with mood disorders are differentially affected by psychiatric and medical comorbidity. The presence of a co-occurring condition in an individual with a mood disorder is associated with a more complex illness presentation, lower rate of recovery, and generally unfavorable course. In many cases, comorbidity may antedate the onset of mood disorders, while in most cases it seems to follow the onset of mood disorders. Evaluating individuals with comorbid conditions introduces a research opportunity to refine disease models by identifying points of pathoetiological commonality. For practitioners, the evidence unequivocally supports recommendations for routine surveillance of comorbid conditions. When comorbidity is present, guideline-concordant care as part of an integrated, coordinated, and continuous care model is recommended for both the mood disorder and the comorbid condition. The CANMAT task force recommendations on the treatment of comorbid conditions is intended to offer decision support and foster further research in the study of these commonly encountered conditions. ■

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