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Bipolar disorder is heterogeneous in phenomenology, illness trajectory, and response to treatment. Despite evidence for the efficacy of multimodality interventions, the majority of persons affected by this disorder do not achieve and sustain full syndromal recovery. It is eagerly anticipated that combining datasets across various information sources (e.g., hierarchical "multi-omic" measures, electronic health records), analyzed using advanced computational methods (e.g., machine learning), will inform future diagnosis and treatment selection. In the interim, identifying clinically meaningful subgroups of persons with the disorder having differential response to specific treatments at point-of-care is an empirical priority. This paper endeavours to synthesize salient domains in the clinical characterization of the adult patient with bipolar disorder, with the overarching aim to improve health outcomes by informing patient management and treatment considerations. Extant data indicate that characterizing select domains in bipolar disorder provides actionable information and guides shared decision making. For example, it is robustly established that the presence of mixed features – especially during depressive episodes – and of physical and psychiatric comorbidities informs illness trajectory, response to treatment, and suicide risk. In addition, early environmental exposures (e.g., sexual and physical abuse, emotional neglect) are highly associated with more complicated illness presentations, inviting the need for developmentally-oriented and integrated treatment approaches. There have been significant advances in validating subtypes of bipolar disorder (e.g., bipolar I vs. II disorder), particularly in regard to pharmacological interventions. As with other severe mental disorders, social functioning, interpersonal/family relationships and internalized stigma are domains highly relevant to relapse risk, health outcomes, and quality of life. The elevated standardized mortality ratio for completed suicide and suicidal behaviour in bipolar disorder invites the need for characterization of this domain in all patients. The framework of this paper is to describe all the above salient domains, providing a synthesis of extant literature and recommendations for decision support tools and clinical metrics that can be implemented at point-of-care.

Key words: Bipolar disorder, clinical characterization, phenotyping, subtypes, mixed features, cognition, rapid cycling, trauma, comorbidity, social determinants, stigma, stressors, resilience, bipolar I disorder, bipolar II disorder, mania, depression, personalization

Bipolar disorder is a common, chronic and highly debilitating condition[1]. Notwithstanding evidence of effective and safe pharmacological and psychosocial treatments, the majority of persons affected by this disorder do not achieve and sustain full syndromal recovery from either a clinician or patient perspective[2]. Multiple modifiable factors contribute to suboptimal outcomes in bipolar disorder, including – but not limited to – the insufficient characterization of the presenting phenotype as well as interpersonal, social and personality factors.

The strategic framework and imperative of personalized/precision medicine posits that biophenotyping an individual can enhance therapeutic outcomes and/or cost-effectiveness by informing bespoke treatment selection[3]. However, notwithstanding the promise of biomarkers/biosignatures as a tactic to assist diagnosis and treatment selection in bipolar disorder, clinical utility is hitherto not established[4]. Consequently, the "near-term" opportunity to improve health outcomes for persons diagnosed with this disorder is deep *in vivo* granular characterization across multiple domains at the point-of-care. It is expected that refining clinical characteristics across multiple salient domains will also inform biomarker research.

It is recognized that bipolar disorder is highly heterogeneous between and within individuals throughout the developmental trajectory. It is also acknowledged that the pleomorphic clinical characteristics of the disorder are moderated by both extrinsic (e.g., social, economic, cultural) and intrinsic (e.g., genetic) factors in dynamic interplay[1]. Moreover, the foregoing domains are also relevant insofar as they moderate illness course and outcomes

Table 1 *In vivo* phenotyping of bipolar disorder: salient domains

1. Psychopathological components of mania/hypomania
2. Psychopathological components of depression
3. Suicidality
4. Clinical subtypes
5. Onset and clinical course
6. Neurocognition
7. Social functioning
8. Clinical staging
9. Temperament and personality
10. Other antecedent and concomitant psychiatric conditions
11. Physical comorbidities
12. Family history
13. Early environmental exposures
14. Recent environmental exposures and relapse triggers
15. Protective factors and resilience
16. Internalized stigma

of the disorder (e.g., higher rate of suicidality in bipolar patients with a history of adverse childhood experiences) as well as inform treatment selection[5,6].

During the past two decades, the number of treatment options proven effective and/or approved by regulators for various aspects of bipolar disorder has significantly increased. Additional treatment options provide opportunity for a more favourable health outcome in bipolar disorder, especially amongst individuals who are motivated to consider further steps when the initial treatment is not found to be helpful[7]. The unavailability of biomarker decision support at point-of-care should not lead to the conclusion that management of the bipolar patient cannot be personalized.

Similar to previously published clinical characterization papers in this journal[8-10], the overarching aim of this report is to identify salient domains for clinical characterization in an individual who is currently diagnosed with bipolar disorder. We have adopted a pragmatic guiding principle insofar as we prioritize domain characteristics that substantively inform case formulation, care planning, and treatment selection (see Table 1).

In addition to synthesizing available evidence across relevant domains, we also provide practical recommendations for measurement-based care and decision support that are scalable, validated and implementable. This paper is not intended to consider bipolar disorder in children and adolescents or in the elderly, as they are comprehensively reviewed elsewhere[11,12]. It is also not aimed to supplant clinical practice guidelines for bipolar disorder, which are considered complementary to the clinical characterization process.

PSYCHOPATHOLOGICAL COMPONENTS OF MANIA/HYPOMANIA

Bipolar I disorder is defined by the presence of at least one lifetime manic episode, whilst bipolar II disorder is defined by the presence of at least one hypomanic episode and one depressive episode. The essential feature of mania as identified by the DSM-5-TR is "a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy", lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)[13].

Notwithstanding the rich phenomenological literature describing euphoric, expansive, dysphoric and irritable mood states, there is little evidence that further differentiating the foregoing quality of mood, with the exception of identifying mixed features, substantively influences treatment outcomes in bipolar disorder[1].

However, it is probably useful to acknowledge that mood in mania is often also labile (i.e., varying in response to internal or external stimuli). Persistent mood lability can be associated with unpredictably variable behavioural manifestations, including suicidality[14].

The ICD-11 is similar to the DSM-5-TR insofar as not only mood disturbance, but also increase in perceived energy and activity, are regarded as essential features of mania (this was not the case in the ICD-10 and the DSM-IV)[15]. Actually, it has been reported that the inclusion of increased energy along with disturbance of mood enhances the specificity of the diagnosis of mania[16-21], and that speeding of movements, speech and thoughts is even more typical of manic patients than elevated or expansive mood[22].

In both the DSM-5-TR and ICD-11, the diagnosis of mania requires the presence of additional symptoms (at least three – or four if mood is irritable – in the DSM-5-TR; "several" in the ICD-11), including inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity, and excessive involvement in activities with a high potential for painful consequences. The impulsive nature of reckless behaviour in mania is explicitly mentioned only in the ICD-11. The above symptoms should be present to a significant degree and represent a noticeable change from the individual's usual behaviour. Furthermore, the mood disturbance should cause marked impairment in social or occupational functioning, or necessitate hospitalization to prevent harm to self or others, or psychotic symptoms should be present.

The criteria for hypomania are similar to those for mania with respect to essential and additional symptomatological features. In both the DSM-5-TR and ICD-11, hypomania is differentiated from mania only on the basis of functional outcome, insofar as it is "not severe enough to cause marked impairment", nor does it require hospitalization or include psychotic features.

Clinicians may disagree about whether functional impairment in a patient is or is not "marked", in the absence of further specification (justified by the lack of relevant research evidence). This may contribute to the difficulties recently noted in the differentiation between bipolar I and II disorder[23]. Furthermore, clinical judgement about the degree of functional impairment is likely to be influenced by cultural and even gender considerations, especially when the domain of social relationships is considered. Impairment in work functioning is probably the most reliable indicator in this respect.

There are additional phenomenological domains in mania that are not explicitly recognized in either the DSM-5-TR or the ICD-11 definitions, such as social disinhibition, leading to meddlesome and intrusive behaviour; enhanced perceptions; and impaired insight and judgement[24]. Furthermore, motor symptoms other than agitation may occur in mania: an example is catatonia, which has been reported in some studies to occur in up to one third of manic inpatients and is regarded as an indicator of a poor prognosis[25].

The clinical picture of mania varies from patient to patient and may vary in the same patient from time to time. This heterogeneous, multi-faceted and dynamic presentation invites the need for systematic psychopathological assessment, which is also essential to monitor the effect of treatment. Multiple clinician- and self-rated scales are available.

The most frequently used scale is the clinician-rated Young Mania Rating Scale (YMRS)[26], which takes 15-30 min to complete. The scale includes 11 items, of which four (irritability, rate and amount of speech, thought content, and disruptive/aggressive behaviour) are rated from 0 to 8, and seven (elevated mood, increased motor activity-energy, sexual interest, sleep, language-thought disorder, appearance, and insight) from 0 to 4.

Other available tools are the 44-item Bipolar Inventory of Signs and Symptoms Scale (BISS) (which captures both manic and depressive symptoms)[27], the self-rated 5-item Altman Self-Rating Mania Scale (ASRM)[28], the 16-item Internal States Scale (ISS)[29], the 47-item Self-Rating Mania Inventory (SRMI)[30], and the 9-item Patient Mania Questionnaire (PMQ-9)[31].

Notwithstanding concerns about the validity of self-ratings in mania wherein insight may be compromised, the foregoing self-rated scales have demonstrated sufficient concurrent validity with clinician-rated measures[32]. Shared decision making and patient self-management justify their inclusion as part of the characterization of the adult with bipolar disorder.

In a patient fulfilling the symptomatological criteria for mania, it is imperative to rule out substance abuse or withdrawal, the effects of medications, or a general medical or neurological condition as a possible explanation of symptoms. This is actually recommended by both the DSM-5-TR and ICD-11, but not always implemented in ordinary clinical practice.

It is reported that psychotic symptoms affect from 40 to 70% of individuals during a manic episode. They manifest as delusions (most frequently grandiose or religious, but not rarely paranoid), hallucinations (often of a fragmented and fleeting nature) and/or formal thought disturbances[33,34].

Formal thought disorder has been understudied in mania, but there have been attempts to distinguish it from thought disorder in schizophrenia that may be clinically relevant. In particular, emphasis has been laid on the occurrence in manic patients of "combinatory thinking" (i.e., "the tendency to merge percepts, ideas or images in an incongruous fashion"[35]) as well as the presence of an affective component marked by flippancy and playfulness.

Psychotic symptoms during mania are a medical emergency, indicate greater severity of illness, increase risk for intentional or unintentional harm to self and others, and may lead to inpatient admission. Clinical practice guidelines for adults with mania generally recommend including antipsychotic treatment when psychotic symptoms are present[36-38].

In addition to psychotic symptoms, the presence of mixed features during mania or hypomania should be ascertained[39]. They are defined as three or more intra-episodic depressive symptoms (including prominent dysphoria or depressed mood, diminished interest or pleasure in all or almost all activities, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt; suicidal ideation, attempts or plans)[39,40]. The frequency of mixed features in mania has been variably reported between 20 and 80%[41,42].

The impetus to identify mixed features within mania is provided by observation of the higher risk of suicidality, psychiatric and physical comorbidity, functional impairment, post-mania depression, and chronicity in bipolar patients with these features[43]. Discontinuation of antidepressants in an individual with mania and mixed features is essential, as is the discontinuation of illicit substances and alcohol[39].

The acute efficacy of valproate in mania with mixed features is reported to be higher than lithium[44]. There is no compelling evidence that the presence of mixed features attenuates antimanic efficacy amongst first- and second-generation antipsychotics[45].

Anxiety symptoms are also often observed during mania[46]. "Anxious mania" was described by Kraepelin[47], but does not appear as a codified diagnosis in the DSM-5-TR or ICD-11. Instead, the DSM-5 introduced the specifier "with anxious distress", which may apply to mania or hypomania[13].

Anxious distress is defined as the presence of two or more of the following symptoms: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, or feeling that the individual might lose control of himself or herself[13]. The DSM-5-TR uses an ordinal schema wherein severity of anxiety is rated mild to severe as a function of the number of symptoms. The ICD-11 also includes the qualifier "with prominent anxiety symptoms", which can apply to both mania and hypomania[15].

It has been reported that anxiety affects at least 25% of persons during a manic episode[22]. Patients presenting with mania and mixed features are more likely to show anxiety symptoms, which predict longer time to recovery. Moreover, anxiety symptoms during mania are associated with a higher risk of suicidality and aggressive behaviour[48,49]. Anxiety is observed to fluctuate in severity and is frequently a residual symptom after resolution of mania (post-mania anxiety)[46].

Rating scales for anxiety are the 14-item clinician-rated Hamilton Anxiety Rating Scale (HAM-A)[50], the 14-item clinician- and/or self-rated Hospital Anxiety and Depression Scale - Anxiety (HADS-A)[51], the 7-item Generalized Anxiety Disorder (GAD-7)[52], the 40-item self-rated State Trait Anxiety Index (STAI)[53], and the 21-item Beck Anxiety Inventory (BAI)[54].

There are no randomized trials specifically targeting anxiety in an individual presenting with mania. If anxiety is severe, clinical wisdom suggests the use of verbal de-escalation techniques and short-term benzodiazepines (e.g., sublingual lorazepam) or rapidly acting second-generation antipsychotics. The adjunctive

use of anticonvulsants with anxiolytic efficacy may also be considered (e.g., gabapentin). For persistent anxiety symptoms in bipolar disorder, manual-based psychoeducation and cognitive behavioural therapy (CBT) are treatment considerations[55].

A "delirious" variety of mania has been classically described[56], marked by a profound clouding of consciousness. Kraepelin also noted that some manic patients appear "stupefied, confused, bewildered"[47]. Modern descriptions of this variety of mania[57] also exist, emphasizing the sudden onset; the poor orientation for place, date and time, as well as restlessness, fearfulness, confabulation and paranoia. Although this form of mania may be now rare, clinicians should be alerted to consider it in the differential diagnosis with delirium and some substance-induced states of excitement, confusion and agitation, especially in emergency settings.

PSYCHOPATHOLOGICAL COMPONENTS OF DEPRESSION

The DSM-5-TR and ICD-11 provide identical diagnostic criteria/requirements for a depressive episode, with the exception that the ICD-11 also includes "hopelessness about the future" among the symptoms that can be considered (five out of nine are required for the diagnosis in the DSM-5-TR; five out of ten in the ICD-11)[15]. There are no features of depression in the DSM-5-TR or ICD-11 that distinguish and/or are pathognomonic of bipolar disorder. Notwithstanding, replicated evidence indicates that bipolar patients are more likely to manifest atypical, melancholic, psychotic as well as mixed features during a depressive episode when compared to those with major depressive disorder[58,59].

For example, hyperphagia, hypersomnia and profound fatigue are more commonly reported in bipolar depression, and may be associated with obesity and binge eating behaviour[60,61]. Melancholic symptoms during depression in bipolar patients frequently manifest as psychomotor disturbance, anhedonia and non-reactive mood. The psychological component of psychomotor disturbance is generally expressed as inattentiveness, or subjective "fogginess" with difficulty in registering and retaining information. The motor component usually comprises aspects of retardation and/or agitation[62].

Those with psychomotor retardation almost invariably affirm anergia (most commonly evidenced by physical difficulty in getting out of bed), and move and speak minimally and/or slowly. Those with psychomotor agitation generally have epochs of pacing, rubbing their hands, showing facial apprehension or a furrowed brow (the "omega sign") and, in severe instances, stereotypic movements (e.g., hand rubbing, skin picking) and importuning (with a characteristic repeated coda of "What's going to become of me?" that is resistant to reassurance).

Similar to a manic episode, psychotic symptoms are not infrequent during a depressive episode, and influence treatment selection and patient care planning. Delusions are commonly weighted to themes of guilt, but nihilistic or penury themes may be present, as well as somatic ones, with the often associated constipation providing a nidus to develop a delusion of bowel cancer. Delusions are best identified by the clinician inquiring about "guilt"

and whether the patient has any sense that he/she "deserves to be punished". Hallucinations are less common (although they may occur in the absence of delusions), being most frequently experienced as a voice telling the individual that he/she deserves to die or would be better off dead. Illusions are common (e.g., seeing a silhouette on the wall), but alone do not establish a diagnosis of psychotic depression. Non-psychotic suprasensory phenomena (e.g., accentuated smell, taste or hearing) may occur.

Mixed features during a depressive episode (i.e., intra-episodic manic symptoms) affect 20-80% of persons with bipolar depression, depending on definitions[39]. They often co-occur with anxiety, agitation, irritability, indecision and insomnia, and are frequently a focus of clinical attention[1]. The foregoing features are not included in the DSM-5-TR mixed features specifier criteria, whereas the ICD-11 lists irritability and increased activity among common contrapolar symptoms in mixed depression[15,63,64].

Individuals presenting with mixed features during a depressive episode are less likely to achieve full syndromal recovery, show higher health service utilization, and frequently manifest treatment-emergent mania when exposed to conventional antidepressants[65]. If depression is severe, a subtle fluctuation in activation or the emergence of racing thoughts may trigger suicidality.

Multiple clinician- and self-rated scales for the assessment of depressive symptoms in adults with bipolar disorder are available, including – but not limited to – the 21-item Hamilton Rating Scale for Depression (HAM-D)[66], the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS)[67], the 21-item self-rated Beck Depression Inventory (BDI)[68], the 20-item Center for Epidemiological Studies - Depression (CES-D)[69], the 16-item Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR-16)[70], the 30-item Inventory of Depressive Symptoms (IDS)[71], the 20-item Zung Self-Rating Depression Scale (SDS)[72], the 20-item Bipolar Depression Rating Scale (BDRS)[73], and the 9-item Patient Health Questionnaire (PHQ-9)[74].

A self-report measure of DSM-5 mixed features during depression – the Clinically Useful Depression Outcome Scale - Mixed features specifier (CUDOS-M)[75] – has been validated and demonstrated high internal consistency and test-retest reliability, as well as high correlation with self-report measures of mania and depression.

The common presence of atypical symptoms in bipolar depression underscores the importance of prioritizing treatments less susceptible to induce weight gain, somnolence or sedation[76]. Psychotic symptoms invite the need for integrating antipsychotic medication as part of the treatment regimen. Long-standing injunctions about not using antidepressants for treating bipolar depression now appear less absolute: in severe bipolar depression, the initial use of an antidepressant (while warning the patient to be aware of switching and mixed states), in conjunction with a mood stabilizer, may be actually needed. Any current mood stabilizer should be reviewed in terms of dose, serum level and adherence, to determine whether it should have its dose adjusted or a different medication should be introduced.

Mixed features identify a subgroup of patients who should not be prescribed conventional antidepressants during the depressive episode, as they increase the risk for treatment-emergent mania[39]. Observational data indicate that anxiety symptoms,

which are often associated with mixed features and frequently occur during bipolar depression, often lead to the prescription of antidepressants, which is not recommended[77].

Relatively few treatment options have proven efficacious for managing anxiety symptoms during bipolar depression. They may include psychological interventions (e.g., CBT), second-generation antipsychotics and, in some circumstances, gabapentin[78].

SUICIDALITY

Psychological autopsy studies have determined that approximately 50-66% of all suicides involve persons affected by a mood disorder[79]. A separate study determined that, among individuals who completed suicide during a depressive episode, 53% had a diagnosis of major depressive disorder and 47% of bipolar disorder[80]. It is estimated that up to 19% of bipolar patients die from suicide, and up to 60% report at least one suicide attempt during their lifetime[80].

In a 40-year follow-up study of 406 patients with bipolar I or II disorder, 11% died from suicide[81]. The risk of suicide is 10-30 times greater for individuals affected by bipolar disorder relative to the general population[82]. Psychological autopsy studies have determined depressive episodes to be more frequently associated with suicide than mixed episodes, while suicide during euphoric mania or euthymia is less common[83].

A rapid-cycling course and a depressive polarity predominance are both associated with a higher suicide risk in persons with bipolar disorder[84]. Some studies report that bipolar II disorder carries a higher risk of suicide than bipolar I disorder[1]. In a 9-year follow-up study of 163 bipolar patients who had been hospitalized, 6% of those with bipolar I and 18% of those with bipolar II disorder died from suicide during the follow-up period[85]. Agitated depression, comorbid anxiety disorders, and a predominant depressive course of illness are characteristic of bipolar II disorder which may account for the elevated suicide rate.

Serious suicide attempts have been reported to be more common early in the course of the illness, especially during the first depressive episode[86]. An early onset of illness also seems to be associated with a higher suicide risk[87]. Recent discharge from hospital is also a risk factor.

A genetic contribution to suicide risk has been reported, and a significant association has been found between first-degree family history of suicide and suicide in bipolar disorder[88]. Twin studies confirm that there is an estimated heritability of approximately 40% for suicide[89]. Studies which have aimed to identify associations between suicidality and specific genes and/or neurobiological substrates have been inconclusive to date.

Socio-demographic factors contribute to suicide insofar as the risk is relatively greater for individuals in both the youngest and oldest age groups. Social isolation or being single/divorced are both associated with a higher suicide risk[90]. Other risk factors include history of childhood abuse, family history of mental disorders, exposure to suicide attempts or completions, traumatic loss of people (e.g., death of a family member), ill health, employment and/or financial insecurity. All the foregoing risk factors should be evaluated in any person with bipolar disorder presenting for care.

Multiple screening and rating instruments for the assessment of suicidality are available for implementation at point-of-care, including the Beck Scale for Suicidal Ideation (BSS)[91], the Beck Hopelessness Scale (BHS)[92], the Columbia Suicide Severity Rating Scale (CSSRS)[93], the InterRAI Mental Health Assessment Tools: Severity of Self-harm Scale (interRAI SOS)[94], the Suicidal Behaviors Questionnaire (SBQ)[95], and the Suicide Intent Scale (SIS)[96].

The clinical management of patients at risk for suicidal behaviour is a challenging task for health care professionals. Risk factor modification should be a priority therapeutic objective in any person with bipolar disorder. Along with assuring safe environment, access to emergency services as needed, and supportive interpersonal contacts, a strong perceived meaning of life and hyperthymic temperament have been linked with reduced risk of suicide, as has receiving active treatment for the disorder.

Currently, there is no proven anti-suicidal effect of antidepressants in bipolar disorder, and some studies have even reported an increased risk of suicidal ideation associated with antidepressant use, although this trend is not observed for completed suicide[82].

Lithium is a mainstay of treatment for bipolar disorder which has been reported to lower the risk of life-threatening attempts and death from suicide by as much as 60-80%[97], although large prospective controlled trials are still needed. Notably, the anti-suicidal effect of lithium has been also demonstrated in patients with otherwise poor treatment response[98]. Preliminary evidence suggests that the anti-suicide effect may not be found in those with low serum lithium levels[99]. The anticonvulsants valproate and carbamazepine have in some studies demonstrated reduction in suicidal ideation, but not in the rate of completed suicide. Antipsychotics, including clozapine, have not been proven to reduce suicide risk in bipolar disorder[1].

Ketamine has been studied primarily in major depressive disorder, where a short-term reduction of suicidal ideation has been reported. Preliminary evidence suggests that similar effects can occur in adults with bipolar disorder[100], although further research is needed in this respect[101]. Electroconvulsive therapy has been found to be effective in treating acute suicidality[82]. Although CBT has been shown to reduce suicidal behaviour in major depressive disorder, such effects are not established in bipolar disorder[102].

Suicidality should be assessed in all individuals with bipolar disorder at initial consultation as well as throughout the illness course. Locus of care is guided by ongoing assessment, especially as it relates to the risk of imminent harm. Clinicians are reminded that suicide risk is increased across all ages in bipolar patients, and that it should be a prioritized part of the assessment during both acute and maintenance treatment phases.

CLINICAL SUBTYPES

The DSM-5-TR and ICD-11 provide diagnostic criteria/requirements for both bipolar I and II disorder. Although bipolar II disorder has been conceptualized as a less severe phenotype, extant evidence suggests that its chronicity and severity are similar to bipolar I disorder. As stated earlier, some evidence indicates that

bipolar II disorder is associated with a higher suicide risk[103,104].

While some debate has occurred regarding the validity of the concept of bipolar II disorder, the weight of evidence supports it as a valid subtype within the bipolar spectrum. Its course of illness is similar to bipolar I disorder, with the distinction that it shows a greater predominance of depression, especially during the early trajectory of illness[105].

The predominance of depression invites the need to assess all persons presenting with depressive symptoms in clinical settings for the possibility of an underlying bipolar II disorder. In probing for a history of hypomania, it is advisable to focus more on hyperactivity than on mood change, and to collect information from people who know the patient well, because patients may not identify the hypomanic periods as pathological.

Treatment considerations in bipolar I and II disorders overlap, but have points of dissimilarity. For example, recent studies suggest that antidepressant monotherapy may be an effective and safe treatment for depression (in the absence of mixed features) in some persons with bipolar II disorder[36,106,107]. Clinical practice guidelines are limited due to the paucity of controlled trials. Quetiapine and lumateperone have demonstrated acute efficacy via replicated studies including subpopulations with bipolar II disorder[108,109], while there is less strong evidence for lithium, lamotrigine and antidepressants[36].

Further clinically relevant subtypes of bipolar disorder are those marked by anxiety and panic attacks, mixed presentations, psychosis, peripartum mood changes, seasonality, and unipolar mania. As reviewed earlier, anxiety is codified by an anxious distress specifier in the DSM-5-TR, which can apply to mania, hypomania or depression. The ICD-11 includes an anxiety qualifier as well as a separate qualifier for panic attacks. The latter should be used only if the panic attacks have occurred specifically in response to depressive ruminations or other anxiety-provoking cognitions[15].

The DSM-5-TR and ICD-11 have taken different approaches on how to define mixed presentations, though both recognize the existence of mixed symptoms in bipolar disorder. The DSM-5-TR includes a specifier "with mixed features" applicable to manic, hypomanic and depressive episodes, whereas the ICD-11 differentiates mixed episodes from mania and depression, consistent with the ICD-10 and the DSM-IV[15].

Mixed states are usually treated with a second-generation antipsychotic as either monotherapy or in combination with a mood stabilizer. Valproate and carbamazepine are effective in mixed episodes, whereas the efficacy of lithium is questionable[110].

A separate subpopulation of persons with bipolar disorder are women with peripartum mood changes. It is of critical importance to screen for mood symptoms in pregnant women and new mothers, to ensure the health of both the mother and the baby[111]. It is well recognized that persons with established bipolar disorder have greater risk for relapse during pregnancy and the peripartum period, and the risk may be higher in women with bipolar II disorder[112-114]. Some women who have experienced prior depressive episodes may develop a first manic episode following childbirth[115,116].

The use of pharmacological treatment is critical in many cases during pregnancy and, if discontinued, should be reinitiated immediately after, or even before, parturition[112,117]. The evidence unequivocally indicates that the use of medication during the peripartum period significantly reduces relapse vulnerability in women at risk for peripartum depression[117].

The seasonal subtype is estimated to affect 15-25% of persons with bipolar disorder[118,119]. It is defined by a regular seasonal pattern of at least one type of episode (mania, hypomania or depression) during the last two years[13]. The most frequent variety is marked by depressive episodes beginning in fall or winter and remitting in spring, often characterized by hypersomnia and overeating.

The seasonal pattern may be more common in females, patients with bipolar II disorder, and those with a family history of bipolar disorder[118,120-122]. It has been reported that bipolar individuals with a seasonal pattern have a higher rate of overweight and obesity when compared to those with a non-seasonal pattern[123].

It is relevant to identify a seasonal pattern insofar as it invites the need for alteration of treatment intensity during periods at higher relapse risk. The additional risk for some comorbidities (e.g., obesity) as well as suicidality is a further rationale for characterizing the seasonal pattern. A validated measure of seasonality in mood disorders is the Seasonal Pattern Assessment Questionnaire (SPAQ)[124]. There is no convincing evidence that any specific treatment modality (including light therapy) is uniquely effective in seasonal bipolar disorder[36].

In addition to the foregoing classic subtypes of bipolar disorder, some additional ones have been proposed. For example, unipolar mania (defined as mania without history of depressive episodes) is a subtype described in both contemporary and classical writings on bipolar disorder[125]. It is estimated that approximately 5% of persons with bipolar I disorder experience this condition[125,126].

Taken together, the subtyping of bipolar disorder, especially the differentiation of bipolar I vs. II disorder, is essential for patient care planning and treatment selection.

ONSET AND CLINICAL COURSE

The onset of bipolar disorder usually occurs in late adolescence or early adulthood, with more than 75% of affected persons exhibiting clinical characteristics of the disorder before the age of 25[1,127]. According to a recent meta-analysis of 40 cohort studies, the modal age at onset of bipolar disorder is 19.5 years[128].

The age at onset of the disorder is clinically relevant, insofar as it affects the clinical presentation, pattern of comorbidity, illness course trajectory, and possibly response to treatment. In particular, a younger age at onset has been found to be associated with a higher prevalence of mixed and rapid-cycling presentations, a greater frequency of family history of the disorder and of substance abuse comorbidity, a higher risk for suicide attempts, and lower levels of treatment response[129-132].

The age at onset of bipolar disorder differs depending on whether the illness is defined by the initial presentation of symptoms, the first onset of functional impairment, the first contact

with health services, or the first codified diagnosis and/or initiation of treatment. Moreover, a proportion of persons affected with the disorder manifest clinically significant psychopathology as a phenomenological antecedent to an index depressive, manic and/or hypomanic episode[133-138]. For example, learning disorders, externalizing behavioural disorders – such as attention-deficit/hyperactivity disorder (ADHD) and substance use disorders – and anxiety disorders frequently manifest prior to initial mania[133,139-145]. The foregoing observation raises a fundamental conceptual and clinical question as to whether such disturbances are "comorbidities" or represent heterotypic continuity of bipolar disorder[146].

Replicated evidence indicates that depressive symptoms/episodes are the most common initial presentation of bipolar disorder[134,147-154]. A separate observation is that a large percentage of persons with the disorder manifest "prodromal" symptoms prior to the initial or subsequent mood episode. For example, a meta-analysis of 11 studies (N=1,078) reported that prodromal symptoms were observed for an average of 27.1±23.1 months prior to an initial mood episode and 1.0±0.9 months prior to a recurrent mood episode[150]. Commonly reported prodromal symptoms are largely consistent with a subthreshold presentation of the subsequent mood episode[150]. Identifying and addressing prodromal symptoms may contribute to preventing episodes, and working collaboratively to identify prodromes can increase mastery of the illness by the patient and engagement of key relatives.

Some rating scales have been developed and validated to specifically assess and quantify prodromal manic or hypomanic symptoms. The Bipolar Prodrome Symptom Interview and Scale - Prospective (BPSS-P)[155] has demonstrated good internal consistency, convergent and discriminant validity, as well as interrater reliability. In addition to the foregoing clinician-rated scale, the BPSS Abbreviated Screen for Patients (BPSS-AS-P)[156] has been developed and validated as a simple self-administered screening tool.

A clinically relevant course feature in bipolar disorder is the predominant polarity of the mood episodes. Predominant polarity has been defined as a >2:1 ratio of either depressive episodes (depressive predominant polarity) or manic episodes (manic predominant polarity)[157,158]. The proportion of bipolar patients in whom the predominant polarity can be ascertained has been variously estimated from 28 to 100%.

Clinical correlates of manic predominant polarity include – but are not limited to – male gender, longer duration of mania, residual manic symptoms, longer duration of euthymia, cyclothymic or hyperthymic temperament, irritability, and cognitive impairment. Clinical correlates of depressive predominant polarity include – but are not limited to – female gender, bipolar II disorder, traumatic events, mixed episodes, higher number of prior mood episodes, and residual depressive symptoms[157,158].

The clinical relevance of predominant polarity is incompletely established[159,160]. Nevertheless, extant evidence indicates that some treatments for bipolar disorder are more effective at preventing and/or forestalling mania (e.g., lithium), whereas other agents are more effective at preventing and/or forestalling depression (e.g., lamotrigine)[129,161]. For antipsychotics proven effective in bipolar disorder (i.e., quetiapine, cariprazine, lurasidone, lumateperone, olanzapine-fluoxetine combination), it is not known if they are preferentially effective in persons with depressive vs. manic predominant polarity.

A separate but related issue is the polarity sequence – i.e., mania-depression-free interval (MDI) vs. depression-mania-free interval (DMI)[162]. The MDI sequence and absence of rapid cycling have been identified as significant predictors of lithium response[132], whereas the DMI sequence may be associated with a higher risk of treatment-emergent mania when exposed to conventional antidepressants[163].

Persons with an MDI pattern should be carefully monitored for the emergence of depression following resolution of a manic episode. There is evidence that conventional antipsychotics are associated with a higher risk for post-mania depression when compared to lithium or atypical antipsychotics[164].

Rapid cycling is defined as four or more acute mood episodes within the past 12 months. Although this pattern is transitory for some individuals, for others it is a more enduring longitudinal course feature[132]. Establishing the presence of rapid cycling is clinically relevant insofar as it is associated with mixed symptoms, suicidality, comorbidity (e.g., substance use disorder), history of adverse childhood experiences, greater risk of treatment-emergent mania with antidepressants, greater psychosocial impairment, and suboptimal pharmacological treatment response[132,165-167].

In addition, individuals with a rapid-cycling course pattern should not be prescribed conventional antidepressants and/or stimulants, as they can accelerate cycling rate. Although the conceptual framework of kindling posited that anticonvulsants may be preferred in individuals with rapid cycling, there is no compelling evidence that either valproate or carbamazepine are more efficacious than lithium in rapid-cycling bipolar disorder.

The systematic assessment of the course of bipolar disorder is advisable in ordinary clinical practice. The Life Chart Method[168] is a flexible and easily usable approach for mapping the course of the disorder, facilitating capture of episodes that might be missed. The assessment may be retrospective or prospective or both, and information may be collected from patients as well as key relatives (with the patient's permission).

NEUROCOGNITION

Despite the use of the term "dementia praecox" by Kraepelin to differentiate schizophrenia from manic-depressive (bipolar) illness, the presence of neurocognitive impairment across different mood states was identified by the end of last century as a core feature of bipolar disorder[1].

Cognitive disturbances may be present during manic, depressive and mixed states, as well as during periods of remission[169]. They may include deficits of attention, learning and memory, executive functions, and processing speed, amongst other domains[170]. Cognitive functions may improve in some affected persons, whereas in others impairment may persist and progress.

Cognitive deficits in bipolar disorder are moderated by multiple variables, including – but not limited to – number of prior episodes, chronicity of illness and exposure to psychotropic agents[171].

There is considerable heterogeneity across persons with bipolar disorder with respect to the type and magnitude of cognitive deficits. For example, 2-40% of patients display global cognitive deficits, 29-40% show selective decline in attention and psychomotor speed, and 32-48% are cognitively intact[172,173]. Cognitive problems are common in both bipolar I and II disorder, with a greater degree of cognitive impairment reported in the former condition, particularly among persons with psychotic symptoms[174,175].

The clinical relevance of assessing cognitive impairment in bipolar disorder is mostly due to its direct mediational effects on patient-reported outcomes (e.g., quality of life, psychosocial functioning)[176]. Some individuals with bipolar disorder may be more insightful than others about their cognitive problems. Therefore, the correlation between objective and subjective deficits is relatively weak[177].

The assessment of cognitive impairment is imperative in bipolar patients. The Screen for Cognitive Impairment in Psychiatry (SCIP)[178] can be recommended as a brief measure of objective deficits, and the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) for subjective deficits[179]. It should be noted that the foregoing assessments do not replace a full neuropsychological battery, but are applicable to clinical practice due to their relative brevity and ease of use. When formulating a personalized management plan, it is advisable to assess objective and subjective cognition when persons are not acutely ill.

The presence of cognitive impairment may be influenced by several modifiable factors. For example, it is often recognized that many persons with cognitive dysfunction also have subthreshold depressive symptoms. Hence, treating these symptoms when present is the first priority towards attenuating cognitive deficits[180].

Moreover, targeting comorbidity is critical, insofar as many types of physical and psychiatric comorbid conditions are also associated with cognitive impairment. Substance abuse, anxiety disorders, ADHD, as well as physical disorders – including obesity, diabetes mellitus, hypertension and hypothyroidism – may adversely affect cognitive performance in adults with bipolar disorder[181-183].

It is well established that persons with bipolar disorder exhibit unhealthy behaviours with respect to lifestyle and diet. Insufficient or poor sleep quality, sedentarism and a suboptimal diet can be addressed, and this may benefit cognitive performance[184]. In addition, many psychotropic agents prescribed to bipolar patients (e.g., topiramate, anticholinergic agents, anticonvulsants, D2 binding agents, benzodiazepines, lithium) may exert adverse effects on cognition[185].

It is well recognized that cognitive deficits are progressive in several bipolar patients[186]. Conceptually, the foregoing observation is hypothesized to reflect a neurodegenerative process.

When cognitive deficits are identified and quantified, and potentially treatable causes are addressed, patients who fail to achieve full functional recovery may benefit from specific interventions. The management of cognitive deficits in individuals with bipolar patients includes cognitive and functional remediation, aerobic exercise, as well as possibly neuromodulation techniques and chronotherapeutic approaches[180,186-189].

SOCIAL FUNCTIONING

Bipolar disorder has a modal onset during late adolescence or young adulthood, affecting the ability to achieve education, obtain a job, and create long-lasting interpersonal relationships and overall settling in life[190].

Social functioning is often impaired in bipolar patients during and between episodes. In a recent Danish nation-wide population-based longitudinal register study, social functioning and interpersonal relationships were systematically investigated in 19,955 bipolar patients, their siblings, and gender, age and calendar matched control individuals from the general population[191]. Compared to individuals from the general population, persons with a diagnosis of bipolar disorder had lower odds of having achieved the highest educational level (45% vs. 54%, odds ratio, OR=0.75); were less often employed (58% vs. 88%, OR=0.16); less often achieved the highest category of personal income (55% vs. 71%, OR=0.33); less often resided with others (36% vs. 54%, OR=0.44); and less often were married (37% vs. 49%, OR=0.54). Bipolar patients demonstrated a substantially decreased ability to enhance their socio-economic status during the 23-year follow-up period when compared to controls[191].

The Global Assessment of Functioning (GAF)[192] is the most frequently employed scale for the assessment of social dysfunction in psychiatric patients, but its scores have been found to correlate more with symptom severity than functional impairment[193]. The Functional Assessment Short Test (FAST) is currently recommended as the standard scale for assessing social functioning in bipolar disorder[194]. It involves a simple 20-30 min interview specifically designed to assess functioning both globally and across six domains previously identified as the most impaired in bipolar patients (i.e., autonomy, occupational functioning, cognitive functioning, finances, interpersonal relationships, and leisure time)[194].

All FAST items are rated from 0 (no difficulties) to 5 (severe difficulties). The instrument has a high test-retest reliability and has been validated against the GAF. Due to its brevity and ease of use, it has been widely adopted in clinical settings[195].

A systematic review of clinical studies investigating social functioning in individuals with bipolar disorder using the FAST demonstrated global and broad functional impairment that often persists during periods of remission[193]. The prevalence of functional impairment in euthymic persons with bipolar disorder has been reported as follows: global, 58.6%; occupational, 65.6%; cognitive, 49.2%; autonomy, 42.6%; interpersonal relationships, 42.1%; leisure, 29.2%; and financial issues, 28.8%[193]. Residual depressive symptoms are the most frequently cited mediational variable associated with functional impairment, followed by impaired cognition[193].

Marriages of untreated or treatment-refractory bipolar patients are often turbulent. Both patients and their spouses regard violence as the most troubling manifestation of mania, and suicide

threats and attempts as the most worrying aspects of depression. Furthermore, they both complain about financial difficulties, unemployment and social withdrawal due to depression[196].

Most interventional studies in bipolar disorder have primarily aimed to alleviate acute symptoms, as well as to prevent recurrence of illness. Relatively fewer studies have primarily sought to determine whether an intervention can improve functional outcomes. Functional remediation, comprising neurocognitive training, psychoeducation and problem-solving, has evidence of being effective in bipolar patients[188].

The perniciousness of social dysfunction in bipolar disorder invites the need for early detection and intervention. It has been reported that early diagnosis and treatment may prevent aspects of social impairment, with an improved functional trajectory as evidenced by greater education attainment, gainful employment in early adulthood, and economic security[197,198].

There is an unmet need for large-scale early intervention studies in bipolar patients with social functioning as a primary outcome measure, including real-world data on education, employment, income, and interpersonal relationships (i.e., cohabitation, marriage). Furthermore, it is important to address, both at the individual and societal levels, the psychological and social barriers that bipolar patients encounter in their daily lives, which contribute to problems in social functioning[199].

It is recommended that bipolar patients have, as part of their clinical characterization during acute as well as maintenance phases of treatment, their overall functioning assessed by using the FAST. Furthermore, initiatives and behavioural steps to improve daily and social functioning should be integrated into clinical treatment plans. Functional remediation, including occupational and cognitive rehabilitation, should be implemented more broadly in clinical care, providing the basis for these persons to have more fulfilling lives.

CLINICAL STAGING

Clinical staging originated in psychiatry as a conceptual framework for schizophrenia, but has been extended to bipolar disorder, with several overlapping proposed staging models[200-205]. These models have generally adopted the numerical system used in medical staging, with stage 0 defined as an at-risk stage, stage 1 as the prodrome, stage 2 as the first episode, stage 3 as single or multiple recurrences, and stage 4 as chronic or refractory disease[200].

These models capture the aggregate evolution of bipolar disorder, but some bipolar patients may have a severe and deteriorating presentation and course from the beginning, whereas others may have an episodic course with full inter-episode recovery. A linear stepwise progression may not be applicable to all bipolar patients[200]. Furthermore, the diagnosis of bipolar disorder requires the occurrence of a manic episode, but substantial depressive morbidity may precede the first episode of mania.

There is some evidence supporting the construct validity of clinical staging in bipolar disorder. First, there is strong evidence that cognitive impairment is associated with the number of episodes of illness[206]. In a prospective cohort study, patients who had a recurrence within the year after a first manic episode continued to show cognitive impairment, whereas those who remained episode-free had significant improvement in cognition[207]. In another study, patients with a first or second mood episode had relatively preserved cognitive functioning compared to controls, whereas those with three or more episodes had a poorer performance than both controls and early-episode bipolar patients[171]. Finally, cognitive performance was significantly worse than in healthy controls in stage 3 or 4 bipolar disorder, but not in bipolar patients in earlier illness stages[208].

A further evidence is provided by treatment response. Lithium has been found to be more effective earlier in the course of bipolar disorder, while response is poorer in those with multiple prior episodes[209]. A similar pattern has been reported with olanzapine[210] and cariprazine[211]. Lamotrigine has also been found to be less effective as a function of prior depressive episodes[201].

A cross-sectional assessment of prescription patterns in bipolar disorder found that monotherapy or combination of two drugs was common in earlier stages of the disorder, while later stages were characterized by polypharmacy. Social and occupational functioning were inversely correlated with the number of medications[212].

The same pattern of response has been observed in some psychotherapy studies conducted in bipolar patients. For example, it has been reported that manual-based psychotherapy (e.g., CBT) exhibits inferior efficacy in persons with multi-episode (i.e., >12) bipolar disorder as compared to individuals with fewer episodes[213]. However, there is no adequately designed study that has primarily evaluated manualized psychotherapy-based treatment in populations dichotomized as a function of fewer- versus multi-episode bipolar disorder[214].

Some psychoeducation studies found that bipolar patients with the lowest number of prior episodes had the greatest benefit from the intervention[215], while there are data suggesting that functional remediation is effective in individuals with late-stage chronic tertiary presentations of the disorder[216].

Further evidence supporting the clinical staging model is the observation of higher rates of psychiatric and physical comorbidity in individuals with multi-episode/chronic bipolar disorder when compared to individuals who are first-episode. In addition, it is observed that individuals with multi-episode bipolar disorder present lower rates of recovery and quality of life when compared to those with fewer episodes[200]. Multi-episode bipolar disorder has been also found to be associated with progressive brain volumetric changes[217].

Relatively few clinical trials in bipolar disorder have recruited individuals stratified *a priori* using a staging framework. In a first-episode mania study, Conus et al[218] compared chlorpromazine and olanzapine as add-on to lithium and reported a relatively shorter time to acute episode stabilization with the latter. A separate first-episode mania cohort study[219] found that, in patients acutely treated with a combination of lithium and quetiapine, continuation treatment with lithium rather than quetiapine was superior in terms of mean levels of symptoms during a one-year follow-up.

Notwithstanding the conceptual appeal of the clinical staging model in bipolar disorder (as well as the indirect support from cognitive, neurostructural and interventional studies), its clinical application with respect to patient care planning and treatment selection is not sufficiently established. However, the observation that bipolar patients with a higher number of episodes exhibit a more complex illness presentation, higher rates of co-morbidity, decreased rates of recovery and quality of life, and diminished treatment responses invites the need for integrated, timely implementation of evidence-based treatments early in the course of illness to positively affect its trajectory.

TEMPERAMENT AND PERSONALITY

Kraepelin operationalized specific affective temperament types, including cyclothymic, dysthymic, hyperthymic and irritable. The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS) questionnaire[220] extends Kraepelin's proposal by adding a fifth type of temperament (i.e., anxious).

The clinical value of measuring temperament is incompletely determined in bipolar disorder. Specifically, there is insufficient evidence that implementing any of the established dimensional quantitative measurements of temperament meaningfully informs illness prognostication or treatment selection.

However, preliminary evidence suggests that quantitative characterization of temperament using the TEMPS may inform suicide risk in bipolar disorder. In fact, risk of suicide attempts in persons with either major depressive disorder or bipolar disorder was associated with elevated scores of four factors in descending order (i.e., anxious, cyclothymic, irritable, and dysthymic) and relatively low ratings for hyperthymic temperament[221,222].

An additional consideration is whether assessing aspects of temperament is relevant to prediction of adherence to treatment. It has been reported that lower rates of adherence in bipolar disorder are associated with higher TEMPS-evaluated cyclothymic and anxious personality dimensions and lower hyperthymic measures[223].

Replicated evidence indicates that the rate of personality disorders in bipolar patients is significantly elevated. For example, approximately 70% of persons with bipolar disorder have traits of borderline personality disorder, with 20% meeting full diagnostic criteria[224]. It is also observed that co-occurring personality disorders in bipolar disorder are associated with a more severe and complex illness presentation, as well as with higher rates of suicidality, non-adherence to treatment, health service utilization, and comorbidity (e.g., alcohol use disorder)[224].

The assessment of personality pathology (as well as temperament) in bipolar patients should be conducted during euthymic periods, taking into account the overlap between several symptoms of bipolar disorder – in particular affective instability, exaggerated emotional expression and intense irritability – with histrionic and borderline personality pathology.

The hazards posed by comorbid personality disorders in bipolar patients justify the careful clinical assessment of these disorders and of maladaptive personality traits at point-of-care. Some evidence suggests that the use of a self-reported screening tool (e.g., the McLean Screening Instrument for Borderline Personality Disorder, MSI) may help identify borderline personality disorder in a person with a diagnosis of bipolar disorder[225].

For individuals with borderline personality disorder, psychotherapeutic approaches (e.g., dialectical behavioural therapy) are considered the cornerstone of treatment, and can be integrated with evidence-based treatments for bipolar disorder[226].

OTHER ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

Persons with bipolar disorder have high rates of psychiatric comorbidity[227]: up to 90% of them meet criteria for one other comorbid condition, and approximately 50% for two or more comorbid conditions[228-231]. However, there is significant under-recognition and, consequently, under-treatment of this comorbidity, reflecting the insufficient characterization of the bipolar patient in ordinary clinical practice.

Population-based and clinical studies indicate that, in many circumstances, co-occurring conditions are antecedent to a first lifetime episode of mania. These antecedent conditions may contribute to bipolar disorder risk. For example, cannabis consumption and other illicit drug utilization may predispose and portend earlier age at onset of bipolar disorder[232]. Preliminary evidence also suggests that antecedent substance use disorder in bipolar patients identifies a different subpopulation (illness presentation and course trajectory) when compared to persons whose substance use disorder is coterminous or follows the onset of bipolar disorder[233].

The presence of comorbidity in bipolar disorder is associated with a younger age at onset and a worse long-term outcome, including increased suicidality and self-harm, a poor adherence to treatment and a less favourable response to lithium. The rate of psychiatric comorbidity is higher in persons with multi-episode bipolar disorder and possibly in persons presenting with the depressive predominant polarity pattern[234].

Clinically significant anxiety disorders are commonly encountered, often antecedent, comorbid psychiatric conditions in bipolar patients[235]. Generalized anxiety disorder, panic disorder and social phobia all differentially affect bipolar patients and are associated with suicidality, greater illness severity and the presence of mixed features. As reviewed earlier, anxiety symptoms at point-of-care can be evaluated with clinician- and/or self-rated anxiety measures (e.g., GAD-7).

Post-traumatic stress disorder (PTSD) also commonly occurs in persons with bipolar disorder. Among the contributing factors are the higher risk of trauma in bipolar patients (mostly due to impulsivity and poor judgement) and the sharing of risk factors between the two disorders. One of the consequences of overarousal in PTSD is sleep disturbance, which can have a direct impact on the course of bipolar disorder. Furthermore, avoidance can lead to social isolation, which may worsen the depressive component of the disorder. The assessment of PTSD at point-of-

care can be made using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[236] or the Davidson Trauma Scale (DTS)[237].

Obsessive-compulsive disorder (OCD) and obsessive-compulsive symptoms are common in bipolar disorder[238]. It has been reported that the course of OCD associated with bipolar disorder tends to be more frequently episodic, and that sexual and religious obsessions may be more frequent, and checking rituals less common[239]. The morbidity associated with OCD warrants direct clinical assessment and initiation of integrated guideline-concordance pharmacotherapy, as well as psychological treatments (e.g., CBT). The assessment of OCD and obsessive-compulsive symptoms can be performed by using the clinician-administered Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[240].

Persons presenting with OCD, PTSD and anxiety disorders are candidates for manual-based psychotherapies. The use of antidepressant treatments to target the foregoing concurrent conditions has to balance the potential benefit with the risk of mood destabilization.

Replicated evidence from both epidemiological and clinical studies has identified an increased prevalence of ADHD in persons with bipolar disorder. As mentioned earlier, ADHD in bipolar patients may be a phenomenological antecedent and is associated with additional comorbidity (e.g., substance use disorder, binge eating disorder)[241]. As the phenomenology of ADHD overlaps with bipolar disorder, careful clinical characterization complemented by informant reports can assist in disambiguating the diagnosis. Also, evaluating ADHD in bipolar patients can be assisted by the use of the Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 (ASRS)[242]. The treatment of ADHD in bipolar disorder integrates CBT approaches along with, in select cases, pharmacological interventions[243].

Approximately 60% of individuals with bipolar disorder meet criteria for alcohol or substance use disorders. Alcohol use disorder is the most common concurrent problem, followed by cannabis use disorder[244]. The assessment of substance/alcohol use disorder in the bipolar patient could include the NIDA Drug Use Screening Tool (NM ASSIST)[245] and/or the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) scale[246].

Despite the common occurrence of substance/alcohol use disorders in bipolar patients, relatively few treatments have demonstrated level 1 evidence (i.e., large rigorous randomized double-blind controlled trials) of efficacy at improving such disorders in these patients[247].

Bipolar patients with concurrent substance/alcohol use disorders should be considered at higher risk for a more complicated illness presentation and a worse outcome, in part related to poorer treatment adherence. The difficulties in personal relationships and occupational functioning related to substance abuse may add to those associated with bipolar disorder, and the effects of the substances may mimic or worsen the side effects of medications, contributing to impair treatment adherence.

A future research vista is to empirically establish whether integrating psychosocial treatments for substance use disorders with guideline-concordant care for bipolar disorder results in improved health outcomes.

Behavioural addictions are reported to be several fold more common in individuals with bipolar disorder relative to controls, with pathological gambling, compulsive buying, sexual and work addictions being the most commonly encountered conditions[248]. The social, legal, occupational and interpersonal consequences of the foregoing addictions are significant. Psychosocial interventions are the treatment of choice for individuals who have behavioural addictions, and should be integrated with the management of bipolar disorder[249].

Eating disorders are frequent, with close to half of bipolar patients reporting significant loss of control concerning food consumption[250]. It is reported that a rapid-cycling course of illness and comorbid substance use disorders are more common in bipolar adults with eating disorders. Preliminary evidence suggests that bipolar II disorder is more likely to be associated with eating disorders than type I disorder. The Eating Disorder Diagnostic Scale (EDDS)[251] can be implemented during clinical assessment to determine whether eating disorders are present and clinical targeting is required.

In addition to the morbidity and mortality associated with eating disorders, they also influence the clinical presentation (e.g., greater complexity of depression), course and outcome of bipolar disorder. Moreover, treatment selection, especially as it relates to pharmacotherapy, may be affected by the presence of eating disorder comorbidities, with some treatments potentially contraindicated (e.g., bupropion in persons with comorbid bulimia nervosa). The treatments for individuals with eating disorders are largely psychological, with an emphasis on CBT.

Tourette's syndrome is estimated to be approximately four times more frequent in bipolar patients relative to the general population[252]. Similarly, impulse control disorders are more common in persons with bipolar disorder, with the overlapping of symptoms being a significant problem for the differential diagnosis. Examples of impulse dyscontrol include fire-setting behaviour, aggressive behaviour, and shoplifting. Targeted psychosocial interventions (e.g., CBT) are indicated in these cases.

Premenstrual dysphoric disorder is reported to be more frequent in bipolar II patients[253]. The assessment of this disorder should be made using the Premenstrual Tension Syndrome Visual Analogue Scale (PMTS-VAS), a validated 12-item scale[254]. The treatment should be based on the cautious administration of a selective serotonin reuptake inhibitor (SSRI) as add-on to the ongoing mood stabilizer.

Taken together, the characterization of the patient with a diagnosis of bipolar disorder in all circumstances should carefully ascertain whether concurrent psychiatric conditions are present. Clinicians are reminded that these conditions may manifest as antecedent, coterminous or later declared disorders. The presence of comorbidity is associated with a more complex illness presentation, greater illness severity (e.g., suicidality), suboptimal response to treatment, and a more unfavourable illness trajectory.

All individuals with psychiatric comorbidity will require either sequential or contemporaneous management of the concomitant condition(s), and it can be anticipated that the longitudinal course of bipolar disorder is more likely to be recurrence prone in the

context of comorbidity.

PHYSICAL COMORBIDITIES

Multiple physical comorbidities occur at a higher rate in bipolar disorder, including – but not limited to – obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, thyroid dysfunction, and inflammatory bowel disease[255-257]. Moreover, there is increasing awareness of the higher rate of non-alcoholic fatty liver disease in persons with bipolar disorder, which is associated with obesity, exposure to psychotropic medication, and number of prior mood episodes[258].

This higher rate of physical comorbidities is a consequence of risk factor clustering in this population[259-261]. For example, persons living with bipolar disorder often have relatively less access to timely, high-quality, primary and preventive health care. Moreover, they are more likely to report economic, housing as well as food insecurity, each of which is associated with adverse physical health outcomes[262-264]. Adverse childhood experiences, which are reported in a significant percentage of these persons, are associated with obesity, metabolic disturbances and cardiovascular disease[265].

Unhealthy behaviours and psychiatric comorbidities associated with bipolar disorder (e.g., cigarette smoking, substance and alcohol use disorders) are additional risk factors for both non-communicable and communicable physical diseases. Smoking has also been identified as a risk factor for bipolar disorder and a predictor of an unfavourable clinical outcome[266]. Finally, contemporary models of disease pathogenesis in bipolar disorder implicate disturbances in immunoinflammatory systems, insulin signalling, mitochondrial function, autonomic regulation, as well as hypothalamic-pituitary-adrenal axis function, each of which may be causative of comorbid physical disorders[1,267-271].

A separate body of literature implicates bipolar disorder as an independent risk factor for cardiovascular disease[272]. For example, in younger populations with the disorder, an increased frequency of subclinical vascular disease has been found[273]. It is also reported that the disorder is an independent risk factor for immune-based non-communicable (e.g., hyperthyroidism)[274] as well as communicable (e.g., COVID-19 infection)[275] diseases. The relationship between bipolar disorder and thyroid dysfunction is complex and reciprocal; subclinical hypothyroidism has been associated with rapid cycling and treatment-resistant depression. Bipolar patients, in particular women, are more likely to suffer from migraine than the general population.

An established modifiable risk factor for some comorbid physical conditions (e.g., obesity, type 2 diabetes mellitus, dyslipidemia) is exposure to psychotropic medications (e.g., lithium, valproate, second-generation antipsychotics)[276-278].

Bipolar patients with obesity are more likely to present suicidality, impaired reward processing, relapse and chronicity[260,279]. It is also established that obesity and related metabolic disorders in bipolar patients are associated with cognitive dysfunction, mixed features, impaired quality of life and psychosocial dys-

function[261,280-282].

Cardiovascular disease is the most common cause of premature mortality and shortened life expectancy in bipolar patients, with approximately 8-12 years of life lost[283,284]. The shorter life expectancy is not observed in unaffected first-degree relatives of bipolar patients, implicating factors specifically related to the disorder[285].

All bipolar patients should be evaluated for the presence of risk factors for physical comorbidities. Several risk factor calculators are available, which may inform and quantify prognostic risk for cardiovascular disease – e.g., the Framingham Risk Factor for Cardiovascular Disease (FRS-CVD)[286], the Systematic Coronary Risk Evaluation (SCORE)[287]. Some risk calculators are able to prognosticate risk for type 2 diabetes and by extension cardiovascular disease[288].

Emphasis should be given to primary prevention of physical comorbidities, especially in newly diagnosed individuals with bipolar disorder. Lifestyle modification, dietary education, sleep hygiene, and stress management should be components of a larger psychoeducational program for any person diagnosed with the disorder.

It is established that approximately 50-70% of persons with bipolar disorder smoke cigarettes daily or regularly. This is associated with depressive symptoms, suicidality, alcohol and substance use disorder, and shorter life expectancy[289,290]. The foregoing hazards of smoking invite the need for smoking cessation programs.

Available evidence indicates that, although bipolar patients may have higher dropout rates from smoking cessation programs, a considerable proportion of them can reasonably expect abstinence from smoking with concordance to the foregoing treatment interventions[291]. Web-based programs – such as acceptance and commitment therapy combined with WebQuit Plus – have been found to increase the likelihood of smoking cessation when combined with nicotine replacement[292].

As part of a comprehensive assessment, all persons with bipolar disorder should have a physical examination with attention paid to blood pressure, weight, and body mass index. Measurement of waist circumference is also encouraged, as it has greater predictive utility of cardiovascular risk when compared to body mass index[293]. Laboratory tests should include assessment of lipid parameters, cholesterol fractionation, blood glucose, and glycated hemoglobin[1]. The evaluation of the thyroid function is particularly advisable in patients with rapid cycling and treatment-resistant depression.

When comorbid physical conditions are present, they should be managed in parallel with the psychiatric disorder. Care pathways for patients should integrate multidisciplinary expertise and implement best practice recommendations longitudinally. Pharmacological strategies targeting concomitant physical disorders should be adopted with attention to potential for drug-drug interactions. Treatments for the psychiatric disorder that do not adversely influence risk and course of concurrent physical conditions should be prioritized[294].

Available evidence indicates that effective management of physical comorbidities has salutary effects on the clinical course

and outcome of bipolar phenomenology[295].

FAMILY HISTORY

Family history is a critical aspect of diagnostic assessment and treatment selection, as well as being pertinent to the risk of suicide and comorbid conditions in bipolar patients.

Bipolar disorder is highly familial, with heritability estimates of approximately 70%[1]. The risk to first-degree relatives of bipolar probands is approximately 8-10 times higher compared to the general population[296]. In addition to an elevated risk of bipolar disorder, family members are at increased risk of other mental disorders (e.g., major depressive disorder, psychotic disorders)[297]. A number of susceptibility loci for bipolar disorder have been identified via genome-wide association studies, but family history remains the best proxy of the genetic liability to the disorder.

Multiple studies suggest an association between a favourable response to lithium and family history of bipolar disorder. It is reported that response to lithium is higher in bipolar probands who have a family history of lithium-responsive bipolar disorder (i.e., approximately 67%)[298].

The suicide risk in bipolar disorder is among the highest of any medical condition, and results from meta-analysis indicate that suicide clusters in families (i.e., OR=1.69)[299]. This finding, however, may under-estimate the risk, insofar as a separate analysis that included systematic assessments of multiple family members reported a much higher risk of suicide in families of bipolar patients (i.e., hazard ratio=6.6)[300].

The modality by which family history is routinely documented by clinicians may be imprecise and have little clinical utility. Frequently, the history is collected by a few questions such as "Did anyone in your family have any similar conditions?". However, in order to have clinical utility, family history should include additional information such as the specific diagnosis, history of comorbid psychiatric conditions, history of physical disorders, and response to treatment(s) including adverse effects. In addition, features such as the presence of psychosis and rapid cycling should be explored as far as possible.

When assessing family history, a useful approach is to draw the family tree and proceed with collection of information systematically, starting with the patient's parents, siblings and children. Various structured tools – including the Family Interview for Genetic Studies (FIGS)[301], the Family History Research Diagnostic Criteria (FH-RDC)[302] and the Family History Screen (FHS)[303] – can aid clinicians in collecting and documenting patients' family history in a comprehensive and systematic manner.

Reviewing individual family members also provides the clinician with an opportunity to probe about family dynamics and gain insight into how the family views psychiatric illness (i.e., are they supportive, do they aid in maintaining treatment adherence, are they interested in psychoeducation, can they be involved in relapse prevention planning?).

While structured approaches to documenting family history can generate useful information beyond routinely collected data, they remain of limited value in patients who were adopted, those who do not keep in close contact with their relatives, and/or in families which hold negative/stigmatizing views of mental illness. Similarly, the advantage of family history is reduced in small families, due to increased random variation[1].

EARLY ENVIRONMENTAL EXPOSURES

Adverse childhood experiences are common in persons with bipolar disorder. It is frequent for these persons to report multiple forms of abuse (e.g., verbal, physical, sexual, emotional) and/or neglect, and cumulative measures and severity of abuse and/or neglect have been found to be associated with a more complicated course and outcome of the disorder[1]. This includes an earlier age of onset; greater levels of anxiety, substance abuse, and comorbid personality disorder; more episodes and rapid or ultra-rapid cycling; and treatment resistance. Adverse childhood experiences are also associated with the occurrence of more physical illnesses in adulthood[304].

The hazards posed by adverse childhood experiences, as well as their frequent occurrence, provide the impetus for recommending that all bipolar patients be assessed for history of these experiences. A careful clinical history is often sufficient to elicit reports of the experiences. Self-report scales, such as the Childhood Trauma Questionnaire (CTQ)[305], may additionally be used[306]. The type, severity and timing of the experiences should be ascertained and documented.

Available research suggests that physical and sexual abuse, rather than verbal abuse, may have more hazardous effects for persons with bipolar disorder. However, verbal abuse alone (i.e., in the absence of physical and sexual abuse) is reportedly associated with an earlier age at onset and a worse course of the disorder[307].

When there is a convergence of adversity in early childhood and a positive family history of bipolar disorder, the incidence of early onset and suicide attempts is significantly greater relatively to when either risk factor is exhibited in isolation[308]. Several lines of evidence indicate that a history of sexual abuse is associated with the highest rate of subsequent suicide attempts[6,309].

A history of childhood adversity may have a priming or sensitizing effect insofar as experiencing subsequent stressful life events. It has been reported that patients with such a history experienced more stressors (in multiple domains including interpersonal support, economic difficulties, and inadequate access to psychiatric and physical health care) in the year prior to the onset of the first episode of bipolar disorder[310].

There is also evidence for a cross-sensitization between the experience of early adversity, mood episodes and bouts of substance use. Early adversity is associated with an increased proclivity to substance use and abuse, and mood episodes can induce stressful life events and further increase the risk for substance abuse. Thus, the experience of early adversity can precipitate a cascading effect of sensitization to further stressors, mood episodes and substance misuse, each of which further drives illness progression[311].

Persons with bipolar disorder reporting adverse childhood experiences should receive treatment that integrates evidence-based pharmacotherapy with manual-based psychotherapies (e.g., CBT). It is not known whether trauma-focused psycho-therapies (e.g., eye movement desensitization and reprocessing therapy) are differentially effective in individuals with bipolar disorder[312].

RECENT ENVIRONMENTAL EXPOSURES AND RELAPSE TRIGGERS

Replicated evidence indicates that recent stressors across the exposome (e.g., environmental, economic, interpersonal, vocational, cultural, and social factors) moderate the presentation, course and outcome of bipolar disorder[313].

Commonly encountered recent stressors in adults with bipolar disorder derive from interpersonal relationships and occupational insecurity. Indeed, bipolar patients report shorter duration of relationships as well as divorce rates 2-3 times greater than the general population[314]. They are also more likely to report maladaptive interpersonal experiences (e.g., bullying) which are associated with symptom intensification, suicide and psychosis, especially in younger populations[315].

Individuals with bipolar disorder are also more likely to report job stress, employment insecurity and dislocation, and need for disability payment when compared to the general population[316]. Moreover, job-related stress is often identified as an antecedent of relapse and chronicity of illness.

Taken together, each of the foregoing stressors should be a focus of clinical inquiry given their established association with illness destabilization.

Social determinants of health (e.g., poverty) are increasingly recognized as modifiable environmental factors that also predispose to relapse in bipolar disorder[317]. In addition, comorbidities (both medical and psychiatric) may also represent recent stressors (as well as chronic stressors) and are reported to be more common in persons with multiple-episode unstable bipolar disorder[227].

Life events that cause disruption to sleep/wake cycles are often associated with recurrences of mania, suggesting the importance of keeping regular daily and nightly routines following a disruptive event[318]. Positive "goal attainment" events, such as getting a job promotion or developing a new romantic relationship, promote drive, ambition and self-confidence in bipolar patients, and may result in excessive engagement in goal pursuit and manic symptoms.

Several scales assessing the presence and magnitude of stressors/life events have been validated. The Longitudinal Follow-Up Evaluation (LIFE)[168] and the LIFE Range of Impaired Functioning Tool (LIFE-RIFT)[319] are examples of scales that identify and measure stressors/life events. At point-of-care, recent environmental stressors in bipolar patients can be evaluated with the Perceived Stress Scale (PSS)[320], a patient-administered, 10-item scale measuring self-appraisal of life stress.

Critical elements when assessing life events are the frequency and the individual perception of impact of the stressor. Evaluating stressors in bipolar patients has conventionally focused on critical time points across the course of illness, such as the premorbid period, the first year of illness, and the most recent episode. The lifetime trajectory approach recognizes that the potential for substance misuse, psychosocial supports, financial/employment difficulties, medical comorbidities, and access to health care may differ across the life span[309].

There is increasing interest in tracking daily behavioural patterns, bipolar symptoms, and exposomic stressors with mobile technology such as actigraphy and ecological momentary assessment devices[321-324]. The foregoing technology is a capability which allows for real-time assessment of illness-related dimensions (e.g., circadian rhythms, psychomotor activity) akin to digital fingerprinting of the disease state[325]. Notwithstanding the promise of this technology, it has not yet been established that it positively affects health outcomes, treatment selection, health service utilization, concordance with best practices, and/or cost-effectiveness of treatment in bipolar disorder[322,326,327].

All individuals with bipolar disorder should be queried about recent stressors across multiple domains of the exposome. Problems with access to timely primary and specialty health care as well as disruption to medication availability represent both intrinsic and environmental stressors that should also be explored. Social rhythm therapy[328] should be considered in patients in whom disruption of sleep/circadian rhythms appears to contribute to relapses.

In addition to the foregoing, all individuals with bipolar disorder should be queried about their economic, employment, housing and food security. Characterization of a patient's socio-economic status, as well as spatial/structural stressors (e.g., racism, residency in a high-crime neighborhood) also add to the characterization of the bipolar patient.

PROTECTIVE FACTORS AND RESILIENCE

Although few studies have systematically examined protective factors or resilience in bipolar disorder, randomized trials of psychosocial interventions have provided some insight.

Patients with caregivers who show low levels of expressed emotion (EE) are at a lower prospective risk for relapse than patients with high EE caregivers[329]. Low EE families are able to curtail negative patient/caregiver interchanges before they become destructive, whereas high EE families are characterized by frequent "point-counterpoint" arguments[330]. Low EE families are also more cohesive and adaptable than high EE ones[331]. Differences among patients may moderate the foregoing associations: those who report less distress when criticized by parents or spouses show lower levels of depression and more days of wellness over one year[332].

Family conflict and relationship quality can be assessed via the Conflict Behavior Questionnaire (CBQ)[333] and/or the Family Adaptability and Cohesion Scale (FACES)[334]. EE among caregivers can be difficult to assess in practice, due to the extensive train-

ing required to administer and score interviews. Proxy measures can be obtained with the Five-Minute Speech Sample (FMSS)[335] or the patient-report Perceived Criticism Measure (PCM)[336], a 10-point rating of the amount of criticism from relatives and the causal degree of distress[337,338].

Family relationships are not static entities, and can change considerably as the patient cycles through recurrence and recovery from episodes. Additionally, family environments are influenced by whether relatives are affected by mood disorders themselves, and whether these disorders are stable at the time of assessment.

The duration of depressive episodes is mitigated by social support networks, an important protective factor in maintaining self-esteem[339]. Patients who are low in rejection sensitivity are also buffered against the effects of negative events[340]. Bipolar patients with better emotion regulation (i.e., ability to reappraise negative situations) are less likely to ruminate about their moods after negative events[341]. Bipolar patients who have difficulties with cognitive flexibility are more likely to use maladaptive regulation strategies (e.g., emotion suppression) in emotionally charged situations compared to healthy controls[342].

Insight – i.e., the recognition that one is ill and needs treatment – has been found to be a protective factor for some outcomes of bipolar disorder and a risk factor for others. Higher insight is associated with better medication adherence[343] and better symptomatic outcomes over 1-2 years[344]. However, among patients who have been highly recurrent, increased illness awareness may contribute to feelings of hopelessness about the future as well as suicidality[345].

Illness literacy – i.e., having an understanding of etiology, prognosis, treatment, and self-management – contributes to resilience in bipolar disorder. In a randomized trial of a brief form of individual psychoeducation, patients with higher post-treatment scores on an illness knowledge test had more weeks in remission over the next year[346]. Patients' health beliefs, such as whether medications are likely to have beneficial or disadvantageous effects on moods or functioning, influence treatment adherence[347,348]. Illness literacy in caregivers is also protective: a longitudinal study found that patients with lower ratings of perceived criticism from caregivers, and more caregiver knowledge of bipolar disorder, were 9.5 times more likely to be free of hospital admissions over 1 year than patients without the foregoing factors[349].

Most adjunctive psychosocial treatments for bipolar disorder have a psychoeducational component, in which patients and/or key relatives explore their beliefs about the illness, learn to recognize prodromal signs of recurrences, and practice preventive strategies (e.g., requesting rescue medications). A network meta-analysis of 39 randomized clinical trials of adjunctive psychotherapy for bipolar disorder indicated that guided practice of illness management skills (e.g., self-monitoring of symptoms), conducted in a family or group format, was associated with lower rates of recurrence over one year than the same practice conducted in an individual format[350]. Thus, involving collaterals in pharmacological or psychosocial treatment sessions often leads to better ad-

herence and outcomes.

Clinicians treating bipolar patients should be aware of the potential role of protective factors in informing the choice of treatments and affecting their success. For example, patients in families with high levels of criticism and conflict show greater responses to family-focused therapy than those in more benign family environments[351]. When psychotherapy is successful in encouraging patients to keep consistent daily routines and sleep/wake habits, recurrences occur less frequently[352]. Brief motivational enhancement therapy – a person-centered approach that addresses illness awareness and readiness for change – has been demonstrated to have a strong impact on pharmacological adherence and depression in patients with bipolar disorder[348].

Absent from the literature are well-operationalized, illness-specific definitions of protective and resilience processes. Patient-centered definitions of recovery (e.g., having a satisfying life despite symptoms or impaired functioning) may be more meaningful than traditional endpoints such as symptom remission[353]. Digital tracking of illness coping strategies and their relationship to symptom fluctuations may help clarify whether protective factors are more important in certain phases of the illness (e.g., during acute episodes vs. recovery periods), or in earlier vs. later stages of the disorder.

INTERNALIZED STIGMA

Internalized stigma is defined as a subjective state "characterized by negative feelings (about self), maladaptive behaviour, identity transformation, or stereotype endorsement resulting from an individual's experiences, perceptions, or anticipation of negative social reactions on the basis of their mental illness"[354].

The magnitude of stigma associated with bipolar disorder is comparable to that reported in persons living with schizophrenia[355]. Stigma is identified by persons living with this disorder and their families as a priority concern and therapeutic target[356].

The need for the assessment of internalized stigma in bipolar patients is underscored by its association with decreased health service utilization and concordance with guideline-recommended treatments[357].

A derivative of stigma related to treatments for bipolar disorder is the perceived impact on self-rated measures of creativity. It is well established that bipolar disorder is more common in individuals who are creative, and the disorder is over-represented among persons in the creative professions[358]. Notwithstanding stigma and patient concerns, there is no convincing evidence that psychotropic agents prescribed to persons with bipolar disorder, as well as other modalities of treatment (e.g., neurostimulation), attenuate aspects of creativity[359].

Further evidence instantiating the clinical relevance of internalized stigma as part of the clinical assessment of bipolar disorder is provided by data indicating that higher stigma ratings are associated with increased symptom severity, reduced functioning, greater concealment of illness, social withdrawal and social anxiety[360,361].

Internalized stigma can be assessed via clinical interview by soliciting feedback from the patient regarding his/her experience of living with bipolar disorder. This clinical assessment can be supplemented by several quantitative measures. For example, the Internalized Stigma of Mental Illness (ISMI) is suitable for use in bipolar patients[362,363]. The ISMI scale is comprised of 29 items and has high internal consistency as well as test-retest reliability.

Evidence suggests that stigma reduction initiatives are more likely to be effective when tailored to the clinical profile of specific conditions, yet few stigma interventions targeted towards bipolar disorder have been developed. Although most modalities of psychotherapy for bipolar patients address aspects of internalized stigma, their anti-stigma impact has not been established[364].

In the interim, the clinical characterization of bipolar disorder should query all affected persons about internalized stigma and its impact on the person's experience of mental illness, overall functioning, concordance with treatment, and motivation to participate in chronic disease management. Moreover, where applicable, an evidence-based conversation with bipolar patients expressing concerns about the adverse effects of medications on creativity should take place.

DISCUSSION

In this paper, we have systematically described salient domains for the clinical characterization of the person with a diagnosis of bipolar disorder, and provided suggestions for clinical metrics that can be implemented in both high- and low-resource environments.

Pharmacological discovery and development across phases of bipolar disorder are primarily designed to seek regulatory approval for subsequent marketing authorization. The treatment development process gives greater emphasis to large, randomized, double-blind, placebo-controlled trials. These trials enroll patients that are often not representative of those encountered in clinical practice, limiting their ecological validity. Clinical practice guidelines in bipolar disorder are thus largely comprised of algorithms based on trials that were not primarily designed to identify differences between pharmacological agents and classes or patient characteristics moderating treatment response. Consequently, treatment choices across acute mania, depression, mixed states and maintenance are often not informed by the multiple clinical characteristics of the person living with bipolar disorder seeking health care.

Taken together, compelling evidence indicates that improving health outcomes from a clinician, patient and societal perspective in bipolar disorder is possible with existing treatments informed by deep *in vivo* characterization across salient domains. However, implementation research indicates that most recommendations for patients with chronic disease are not implemented at the point-of-care[365]. As a derivative of the foregoing observation, clinicians should be familiar with enablers and barriers to implementing evidence-based treatment approaches in ordinary practice.

It is apparent that an asymmetric body of evidence exists with respect to which domains should be priorities for clinical characterization by professionals providing care to a person with bipolar disorder. Compelling evidence exists that subtyping the disorder as a function of types I and II has relevant clinical implications. In addition, the identification of mixed features, and history of trauma/maltreatment have demonstrable impact on treatment selection, illness presentation, course and outcome of the disorder. Suicidality should be assessed in all individuals throughout the illness trajectory, and appropriate risk mitigation strategy implemented in high-risk patients. Despite its conceptual appeal, there is less evidence that staging is a clinically useful construct in bipolar disorder, although individuals with multi-episode disorder generally exhibit less favourable responses to pharmacological treatment when compared to those with single-episode mania.

During the past decade, replicated epidemiological and clinical data have underscored the prevalence and clinical implications of physical and psychiatric comorbidities in bipolar disorder. Moreover, the available evidence indicates that cardiovascular disease is the most common specific cause for premature and excess mortality in bipolar patients[366]. Clinician evaluation of comorbidity and its risk factors should be an integral component of every patient assessment[367]. The elevated risk for COVID-19 infection and its complications amongst persons with bipolar disorder illustrates the confluence of innate and social/economic determinants of medical risk in this population[275]. Health systems and organizations are often not configured to sufficiently address both physical and mental health comorbidities in the adult with bipolar disorder. Notwithstanding, scalable risk factor modification, and medical health education including aspects of diet and lifestyle change are cost-effective and should be part of general education aiming to enhance patients' illness literacy and self-management[368,369].

Despite the plethora of research on temperamental characterization in bipolar disorder, there is limited evidence indicating that quantitative assessment of temperament dimensions can inform treatment decisions or other aspects of clinical care. The high rate of personality pathology in bipolar disorder is a replicated observation. The co-occurrence of bipolar disorder and borderline personality disorder, in particular, is a common occurrence in clinical practice and identifies a subgroup especially at risk for self-harm, comorbidity (e.g., alcohol and substance use disorder), maladaptive interpersonal function, and suicide[224].

Despite the ubiquity of comorbidities in bipolar disorder, there is a relative lack of large randomized controlled trials informing treatment decisions in persons presenting with either psychiatric or physical concomitant conditions. Notwithstanding a large and compelling body of evidence describing disparate aspects of resilience and its relevance to wellness and adaptation, this area has been greatly understudied in bipolar disorder. Validated scales for resilience in bipolar patients are currently available, but implementation research has not documented meaningful effects of their use on health outcome.

Furthermore, the robust literature describing the relationship between interpersonal conflict and the course of bipolar disorder stands in contrast to the lack of data evaluating measures of loneliness in persons with this disorder and whether aspects of loneliness influence the presentation and should be measured at point-of-care[370]. A replicated body of evidence has identified an association between validated measures of loneliness (e.g., the UCLA Loneliness Scale[371]) and risk for depression, anxiety, medical comorbidity (e.g., obesity), cognitive impairment, and decreased quality of life[370]. A separate body of evidence also indicates that higher self-reported loneliness measures are associated with an increase in psychotropic drug prescription (e.g., antidepressants, hypnotics, benzodiazepines) in older populations[372].

Subjective measures of loneliness have been insufficiently applied to adults with bipolar disorder. Preliminary evidence suggests that loneliness in bipolar patients is associated with decreased measures of self-efficacy with respect to managing their illness[373]. It is, however, unknown whether loneliness influences relapse vulnerability, phenomenological presentation, illness trajectory, and/or response to treatment. In the interim, clinicians are encouraged to carefully characterize interpersonal networks and supports in each person presenting with bipolar disorder. Future research vistas should ascertain whether loneliness has to be specifically measured at point-of-care and, if so, what are the appropriate measures and what is the impact on health outcomes and cost-effectiveness of treatment.

A compelling body of literature indicates that clinicians' implicit biases influence diagnostic considerations as well as treatment choices in psychiatry[374]. For example, individuals from ethnic and racial minorities with bipolar disorder are more likely to be misdiagnosed with a primary psychotic disorder[375]. It is also reported that male physicians are more likely to prescribe benzodiazepines to female patients when compared to female physicians[376]. The potential for bias to portend discordance with diagnosis and/or best treatment practices amongst persons with serious mental illness provides impetus for contemplation at point-of-care. Future research should attempt to empirically quantify the extent to which implicit biases as well as aspects of equity, diversity and inclusion moderate health outcomes in persons with bipolar disorder, and what are potential measures and mitigation strategies at point-of-care[377].

Personalizing a management plan for an individual diagnosed with bipolar disorder starts with determining locus of care[378]. Lack of timely access to high-quality, integrated, longitudinal care is a modifiable structural barrier to optimal outcome for a large percentage of persons living with bipolar disorder. Digital psychiatry is an opportunity to address access gaps and possibly assist in momentary assessment of disease activity, "just in time care", suicide risk assessment, and monitoring of psychosocial outcomes and response to treatment, as well as to provide a platform for psychoeducation and peer support[322]. End user satisfaction and clinical outcomes achieved with Internet-based manualized psychotherapeutic approaches for depression are compelling and, in some circumstances, comparable to in-person outcomes[322].

Moreover, Internet-based approaches are potentially more cost-effective and destigmatizing and are especially appealing in low-resource environments with minimal access to timely psychiatric care. It is, however, unknown whether digital capabilities meaningfully influence long-term health outcomes in individuals with bipolar disorder – a further research vista priority[379].

The guiding principle of deep *in vivo* clinical characterization emphasized herein is to be integrated with shared decision making and other aspects of chronic disease management[380]. Research into innovative treatments for bipolar disorder will also benefit from thorough characterization of the phenotype as the field endeavours to identify relevant biomarkers[3,268]. It is additionally expected that the future of clinical psychiatry will use big data and machine learning approaches integrating the characterization of the patient informed by clinical assessment with electronic health records and sensor recordings.

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