Staging in bipolar disorder: from theoretical framework to clinical utility

Michael Berk[1-5], Robert Post[6], Aswin Ratheesh[3,4], Emma Gliddon[1], Ajeet Singh[1], Eduard Vieta[7], Andre F. Carvalho[8,9], Melanie M. Ashton[1], Lesley Berk[1,2], Susan M. Cotton[3,4], Patrick D. McGorry[3,4], Brisa S. Fernandes[1], Lakshmi N. Yatham[10], Seetal Dodd[1-3]

[1]IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia; [2]Department of Psychiatry, University of Melbourne, Melbourne, Australia; [3]Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia; [4]Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia; [5]Florey Institute for Neuroscience and Mental Health, Melbourne, Australia; [6]Department of Psychiatry and Behavioral Sciences, George Washington University School of Medicine and Health Sciences, Washington, DC, USA; [7]Bipolar Disorders Program, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain; [8]Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, Brazil; [9]Institute for Clinical Research and Education in Medicine, Padua, Italy; [10]Department of Psychiatry, University of British Columbia, Vancouver, Canada

Illness staging is widely utilized in several medical disciplines to help predict course or prognosis, and optimize treatment. Staging models in psychiatry in general, and bipolar disorder in particular, depend on the premise that psychopathology moves along a predictable path: an at-risk or latency stage, a prodrome progressing to a first clinical threshold episode, and one or more recurrences with the potential to revert or progress to late or end-stage manifestations. The utility and validity of a staging model for bipolar disorder depend on its linking to clinical outcome, treatment response and neurobiological measures. These include progressive biochemical, neuroimaging and cognitive changes, and potentially stage-specific differences in response to pharmacological and psychosocial treatments. Mechanistically, staging models imply the presence of an active disease process that, if not remediated, can lead to neuroprogression, a more malignant disease course and functional deterioration. Biological elements thought to be operative in bipolar disorder include a genetic diathesis, physical and psychic trauma, epigenetic changes, altered neurogenesis and apoptosis, mitochondrial dysfunction, inflammation, and oxidative stress. Many available agents, such as lithium, have effects on these targets. Staging models also suggest the utility of stage-specific treatment approaches that may not only target symptom reduction, but also impede illness neuroprogression. These treatment approaches range from prevention for at-risk individuals, to early intervention strategies for prodromal and newly diagnosed individuals, complex combination therapy for rapidly recurrent illness, and palliative-type approaches for those at chronic, late stages of illness. There is hope that prompt initiation of potentially disease modifying therapies may preclude or attenuate the cognitive and structural changes seen in the later stages of bipolar disorder. The aims of this paper are to: a) explore the current level of evidence supporting the descriptive staging of the syndromal pattern of bipolar disorder; b) describe preliminary attempts at validation; c) make recommendations for the direction of further studies; and d) provide a distillation of the potential clinical implications of staging in bipolar disorder within a broader transdiagnostic framework.

Key words: Bipolar disorder, clinical staging, early intervention, neuroprogression, neuroprotection, cognitive functioning, biological markers, kindling, treatment outcome, lithium, transdiagnostic framework

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Clinical staging models are extensively used in medicine, especially in oncology and cardiology, where they are major determinants of prognosis and drivers of treatment choice. The utility of staging in these specialties is aided by clear biomarkers of the staging process. In cancer, for example, the "tumour, node, metastasis" (TNM) model of disease staging uses three easily operationalized and objective domains.

In contrast, psychiatry, lacking objective markers, has not been able to empirically define the critical components of stage definitions. The field has tentatively begun to use staging models as a template to model the sequence of vulnerability, at-risk states, prodrome, onset, progression, and end-stage chronicity, and to link these to outcome and choice of specific treatments.

The body of data on this topic in bipolar disorder and other mental illnesses is steadily increasing[1,2], allowing closer examination of the evidence supporting or refuting the theoretical underpinnings of the construct, and refining its applicability to targeted and individualized diagnostic, prognostic and therapeutic domains.

The first hint supporting clinical staging in psychiatry came from Kraepelin[3], whose detailed observations of the course of mental disorders over time suggested that this might be a useful validator of diagnostic assignment. However, his hard and largely tactical distinction between dementia praecox and manic depressive illness proved to be an oversimplification, and he did not define therapeutically useful stages or patterns of illness.

A century later, Fava and Kellner[4], focusing on mood and anxiety disorders, called staging the "neglected dimension in psychiatric classification", presaging current developments. Staging of mental disorders was formalized and operationalized by McGorry et al[5], who aimed to move beyond diagnostic silos to develop a widely used transdiagnostic model. Staging models have subsequently been adapted to bipolar disorder[6-9], depression[10,11], eating disorders[12], and anxiety disorders such as agoraphobia[13], where they share the same essential elements as the original models[14].

It needs to be emphasized that the early stages of most of these syndromes are non-specific and overlapping, favouring the application of transdiagnostic models of staging[15]. Models which focus on traditional diagnostic categories are largely used to describe the syndromal patterns emerging after a first full-threshold episode.

Whether transdiagnostic or disorder-specific staging models are more appropriate for mental illness has been debated. The relative concentration of specific diagnoses in some family histories and the differences in course and treatment outcomes across disorders support the latter approach, while the lack of specificity of genetic and biomarker findings, the extensive comorbidity between disorders, the similarity in effective treatments, and the symptomatic overlap between several disorders lend support to the former approach[16].

In broad terms, transdiagnostic staging models are probably optimal for the study of the at-risk and prodromal phases as a "trunk", while disorder-specific models can contribute to the understanding of the later phenomenon of syndromally expressed "branches". Individual psychiatric disorders, as currently defined, may not turn out to be discrete entities if and when their pathophysiology is identified, and are likely syndromal patterns only. Furthermore, the link between any syndromal phenotype and the underlying neurobiology remains tenuous[17].

MODELS

Clinical staging describes where an individual's presentation can be placed on a temporal spectrum of disorder progression. Staging models in psychiatry have generally adopted the numerical system that is used in medical staging models, being operationalized to begin with stage 0 (defined as an at-risk or latency stage), followed by stage 1 (defined as a prodrome), stage 2 as a first episode, and stage 3 of single or multiple recurrence, and ending with stage 4 of chronic disease[5].

This model captures the aggregate course and evolution of bipolar disorder (see Figure 1). However, some individuals may have a more severe and deteriorating presentation and course from the outset, while others may have an episodic illness with full inter-episode recovery. Linear stepwise progression through serial phases may not be applicable to the course of illness in all patients.

Moreover, developmental approaches examining the heterogeneity in evolution of bipolar disorder among youth at high familial risk have argued for different phases in the prodrome. Sleep disturbances, anxiety, psychotic symptoms, depression and impairments in cognition may be indicative of substages prior to the onset of classical or mixed/psychotic mania[18]. Similarly, a definition of stages based on functioning has been developed to attempt to clarify the latter end of the staging spectrum, based on inter-episodic recovery, comorbidity and ability to live independently[19].

These descriptions of clinical stages of bipolar disorder still need operationalization, specification of cut-off points, and consensus on terminology, and would greatly benefit from external validation through biomarkers.

This would ideally follow what has happened for cancer. First came the documentation of the progression from genetic and environmental vulnerability (including double hits) to precancerous histology to malignant lesions (small, localized to larger, more invasive) to metastases (local to distant, single to multiple). Then predictive validity was delineated by linking these descriptive stages of tumour progression to prognosis and outcome (1 and 5 years survival rates). Discriminant validity subsequently emerged from linking stages to the effectiveness or not of different treatments and to the correspondence

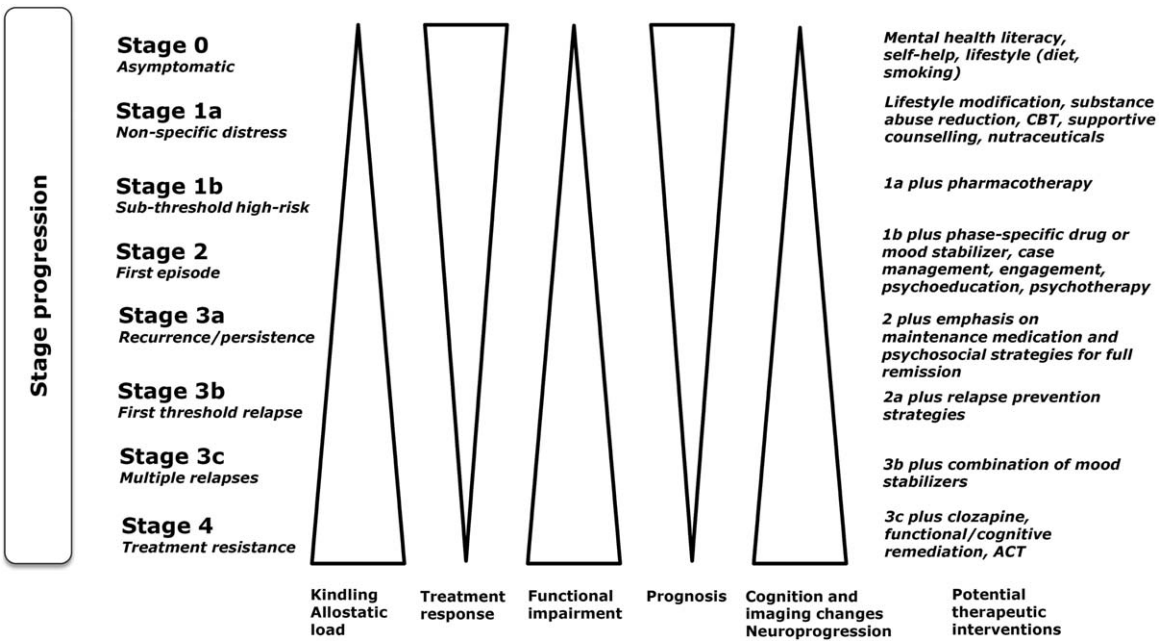

Figure 1 Staging in bipolar disorder. CBT – cognitive behaviour therapy, ACT – assertive community treatment

of numbers and sequences of somatic mutations (those driving cell replication and those reflecting loss of tumour suppressor factors) and other biological measures.

The attainment of many of the aforementioned steps in cancer is an aspiration for mental disorders[20]. This would permit relating descriptive stages to prognosis and ultimately to variables like survival (loss of years of life expectancy). The best validation would come from linking stages to neurobiological alterations and effectiveness (or not) of specific treatments. The task ahead is therefore to cluster clinically observable phenomena and label them as identifiable stages, and then proceed with demonstrating reliability, validity and clinical utility[21].

This model lends itself to further detailing and subdividing. For example, stage 0 could contain more refined characterization of risk based on genetic/familial loading; prenatal factors such as maternal infection or drug exposure; and perinatal factors such as infection, head trauma, neglect and psychosocial abuse. As vulnerability genes such as calcium voltage-gated channel subunit alpha1 C (CACNA1C) and others are better defined and validated, these could be incorporated into this stage.

TESTABLE HYPOTHESES

The model of staging begs the testable hypothesis that the natural history of the disorder progresses through an aggregate and stepwise temporal progression. If staging is to be clinically useful, it needs to demonstrate the same kinds of utility seen in medicine, particularly oncology and cardiology (i.e., to have clinical validity). It needs to be documented that treatments can be identified which have differential value across illness stages. Established examples in schizophrenia include the appropriate use of clozapine for the later stages of treatment, while atypical antipsychotics with a lower adverse event burden are used to treat acute symptoms in early and intermediate stages. Transdiagnostic approaches such as public health interventions, nutraceuticals, Internet-based self-help or indicated prevention could target asymptomatic or at-risk stages[22].

The staging model for bipolar disorder assumes that treatments chosen for earlier stages should have a more favourable risk-benefit ratio than those used for the later stages. Furthermore, treatments suited for clear diagnostic categories, such as antipsychotic and mood stabilizing medications, are less justifiable in the earliest stages of illness, where psychotic symptoms or mood swings are not overtly manifest, and their efficacy has not been systematically assessed[23]. Symptoms of psychological distress may be evident early in the illness course, and preliminary evidence supports intervention with psychotherapeutic strategies such as family-focused treatment for high-risk children with symptoms of depression, cyclothymia, and other specified and unspecified bipolar and related disorders[24]. In these circumstances, low-risk medicines and putative neuroprotective agents[25] may also be more appropriate in term of safety (see Figure 1), but ultimately demonstration of efficacy in these early stages is required[26]. More evidence is needed to determine if prognosis would be more favourable with earlier diagnosis and intervention, as predicted.

FROM NEUROPROGRESSION TO NEUROPROTECTION

The elements of the progressive underlying neuropathology in bipolar disorder appear to include epigenetics, telomere shortening, inflammation, oxidative and nitrosative stress and mitochondrial dysfunction, leading to decreased neurotrophins and consequent deficient neurogenesis and increases in cell shrinkage and apoptosis, ultimately compromising neuronal function and structure. The construct of neuroprogression has been proposed to incorporate the influence of the operative biological elements on the progressive course and outcome of the disorder[27,28]. The impact of neuroprogression may also go some way to explaining treatment non-responsiveness[29].

Social, psychological, environmental, behavioural, biological and genetic variables can be either risk or protective factors that interact in a complex and often unpredictable manner to mediate or moderate the process of disease progression. These factors vary from person to person within a disorder, and also may vary in terms of their impact on different stages. Some risk factors may operate across all stages and some may be stage-specific. For instance, physical or sexual abuse or early attachment disruption may increase risk for the onset phase of a disorder, substance abuse may be noxious across all stages, while adherence and engagement might positively impact by lowering the risk of progression to later stages and improving prognosis[30].

It is theoretically possible to modify an individual's trajectory of disease progression. Early intervention may have potential to alter the distribution of the stages in a given population over time[5,6]. A premise of staging is to define the earliest potential intervention window at any stage of disease evolution in order to prevent progression to the more advanced stages of a disorder and even engage the "reverse gear" towards more benign earlier stages. A person may move from a resistant stage 4 phenotype to a clinically improved and responsive stage 3 pattern. Strategies include primary prevention for those at highest risk, effective intervention in heterotypic and homotypic prodromes (secondary prevention), and attempts at limiting later stages of illness progression (tertiary prevention)[31] (see Figure 1).

The aspiration that appropriate therapy can both prevent neuroprogression and have neuroprotective effects is supported by observational studies indicating that lithium treatment might increase grey matter volume in hippocampus and cortex, increase the length of telomeres, prevent the accumulation of some medical comorbidities, and prevent the progression to

dementia[32-34]. While further evidence is needed, it is plausible that some agents (such as atypical antipsychotics) may avert episodes but may or may not secondarily prevent progression, while others such as lithium not only prevent episodes but might also impede neuroprogression[35].

Prevention of disease progression (i.e., stopping episodes) may differ mechanistically and prognostically from an impact on neuroprogression. As a recent example, lithium and quetiapine were compared in the first year following a first episode of psychotic mania, and lithium but not quetiapine was associated with both decreases in manic and depressive episodes and protection against white matter changes over that time period[36]. Observational data similarly suggest that lithium use may be associated with a greater protective effect on thalamic and grey matter volume than other mood stabilizers[37].

It is noteworthy that medications widely used for bipolar disorder – including lithium, valproate and some antipsychotics – appear to influence inflammation, oxidative biology, neurotrophins, neurogenesis and apoptosis[38]. However, a new generation of medications that may more specifically target these pathways are being investigated, including erythropoietin, minocycline, N-acetylcysteine and anti-inflammatory drugs[39]. Agents more specifically acting on epigenetic mechanisms may also become viable therapeutic options for bipolar disorder, as they have in oncology[40].

THEORETICAL PREMISES UNDERPINNING THE STAGING MODEL

Post et al[11] defined the constructs of sensitization and kindling to capture and describe the progression of bipolar disorder. That model incorporated an increase in primary pathological factors and a failure of endogenous compensatory mechanisms associated with illness progression. Kindled seizure episodes progress from early partial seizures to full blown seizures triggered by stimulation of the amygdala to seizures that occur spontaneously. Here, stage-specific anticonvulsant medications are clearly delineated, with some agents and not others working on the initial stages of seizure development, middle stages of triggered seizures, or late stage spontaneous seizures.

The construct of allostatic load, pioneered by McEwen and Stellar[41], was adapted to bipolar disorder by Kapczinski et al[42]. Allostatic load is the accumulated attempts to re-establish homeostasis after perturbations caused by, for example, stressors and abused substances. The compensatory adaptations required to achieve the new balance are generated at a cost to the organism. More stressors, mood episodes, and bouts of substance use provoke further adaptations, increasing allostatic load. This can generate a potential vicious cycle which can further impact brain circuits required for mood regulation and cognition and amplify vulnerability to recurrent episodes of illness. As an example, cortisol dysregulation could play a role in both the primary pathology and allostatic adaptations, leading to illness progression and cognitive dysfunction[43]. Gut dysbiosis may play a role in these inflammatory processes[44], although evidence for bipolar disorder remains limited[45].

WHAT IS THE EVIDENCE SUPPORTING STAGING?

The evidence supporting the descriptive components of staging in bipolar disorder is initially derived from observational studies of the course and natural history of the illness. Kraepelin was the first to observe that, with each successive episode, periods of euthymia in people with bipolar disorder become shorter[3]. His seminal observations have been repeatedly verified. More recent data derived from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study support the utility of staging, as the number of episodes was positively associated with more severe mania and depression, and poorer functioning and quality of life[46].

Considerable evidence supports the view in psychosis that: a) treatment earlier in the full-blown illness (i.e., after a shorter duration of untreated psychosis) is more effective; b) continuous treatment may be more effective than intermittent treatment; and c) response to an antipsychotic medicine decreases as the number of medication trials increases[47].

Similar evidence exists for lithium in bipolar disorder, as this medication is generally more effective if used earlier in the illness course, and response is poorer in those with multiple prior episodes. A number of observational studies have suggested that the efficacy of lithium declines with successive episodes[48-50]. A similar pattern appears to occur with atypical antipsychotics in the treatment of bipolar disorder, with data for both olanzapine[51] and cariprazine[52]. Lamotrigine is less effective as a function of the number of prior depressive episodes, and so is treatment in general[53].

A cross-sectional examination of differences in medication prescription patterns found that monotherapy was common in stage 1, two drug combinations were common in stage 2, while the later stages were characterized by polypharmacy, with social and occupational functioning inversely correlated with number of medications[54].

The pattern seen in pharmacological studies is also seen in studies of psychological treatments for bipolar disorder. In one of the largest trials of cognitive behaviour therapy (CBT) for this disorder to date, while negative on the primary outcome measure, the therapy was found in post-hoc analyses to be more effective in people who had the fewest prior episodes, but appeared to aggravate outcomes of those who had more than 30 episodes[55]. Similarly, data from psychoeducation studies showed that participants who had the fewest prior episodes had the greatest benefit from the intervention[27,56].

Neuroimaging evidence also supports the staging construct. The available data suggest, although with some inconsistencies, that brain structure is relatively preserved during the early stages of bipolar disorder[57,58]. It appears that progressive

structural changes develop as the disorder evolves[59]. Among a cohort of individuals with a first episode of mania, ventricular size was comparable to controls, while individuals with recurrent illness had ventricular enlargement[60]. Over time, there is also progressive loss of grey matter[61,62] in those who have a recurrence compared with those who remain episode free[58].

Some studies show smaller amygdala and insular volumes among ultra-high risk individuals prior to a threshold first episode of mania, suggesting that these potentially represent vulnerability markers[63]. Some of these differences may be neurodevelopmentally mediated and interact with neuroprogression[64].

A decline in cognition is apparent in bipolar disorder. Cognitive dysfunction is also a major driver of the functional disability seen in the disorder[65] and may correlate to some extent with the structural changes noted above. There is strong evidence that cognitive changes are associated with the number of prior episodes of illness[66,67]. That the number of episodes determines the magnitude of cognitive impairment was confirmed in a prospective cohort study, which showed that those who had a recurrence of a mood episode within a year after a first manic episode continued to show cognitive impairment, while those who remained episode free had significant improvements in cognition, suggesting that early intervention has the potential to reverse cognitive deficits[68].

Further, in a study that compared cognitive functioning among people who had had a first, second and third episode, participants who had a first or second episode showed relatively preserved cognitive functioning compared to controls, but subjects with three or more episodes performed more poorly compared to both controls and early-episode bipolar patients[59]. Another study found that cognition was significantly worse than healthy control groups only for persons with stage 3 (recurrent) or 4 (chronic, late illness) bipolar disorder, while it was not in those in earlier illness stages[69].

A combination of cognitive measures such as verbal intelligence and cognitive control, along with episode density and level of residual depressive symptoms, were the best predictors of classification of persons with bipolar disorder into those with good and poor function[70]. Similarly, a cluster analytical study of a historical cohort identified two subgroups of persons with bipolar disorder categorized as early and late stages based on differences in their functioning, age of onset, number of episodes and time from the onset of their first episode[71].

Overall, the use of such a "reduced" or simplified staging such as "good or poor" outcome or "early or late" stages in bipolar disorder is likely to most easily show relationships with neurobiological markers. However, to be truly useful, more refined definitions of sub-stages may be required to define relationships to neurobiological markers and association with clinical response.

Some biochemical alterations are putative markers of an underlying disease process. For example, measures of inflammation, in particularly cytokines, are among the most robustly established correlates of both depression and mania[72]. The first study of biomarkers and staging found that pro-inflammatory cytokines, notably interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα), were raised in both early and late stage participants, but the increase of TNFα was more accentuated in the late stage, while that of IL-6 was more marked in the early stage. Anti-inflammatory cytokines such as interleukin 10 (IL-10) were increased in the early stage, with no differences from controls in the late stage. Brain-derived neurotrophic factor (BDNF) levels were normal in the early stage but decreased in the late stage participants[73]. There are further data showing that BDNF and TNFα could be useful peripheral blood biomarkers aiding in the discrimination of the early from the late stage of bipolar disorder with an accuracy of 0.95 and 0.96, respectively[74]. The fact that patients at a later stage have lower levels of IL-6 possibly indicates underlying differences in inflammation or allostatic load[71].

Stage dependent changes in redox markers have been studied, particularly the glutathione pathway, where the activity of glutathione reductase and glutathione transferase appeared increased in late stage participants[75]. A recent study that examined the differences between those at early and later illness stages showed that matrix metallopeptidase 9 and soluble intracellular adhesion molecule (sICAM) levels were significantly different across stages, even when patients were euthymic[76]. While these biomarkers were associated with measures of functioning, cognition and subthreshold symptoms, the gross separation of early and later stages offered a pragmatic first-pass system to categorize participants into meaningful subgroups for biomarker analyses.

Neurotrophins may similarly display stage-related changes, with normal levels found in the early stages of the disorder, and decreases later in the illness course[73,77].

It is unclear whether these stage-related changes in biomarkers – including neurotrophins, oxidative stress and inflammatory measures – reflect the primary progression of the disorder or the failure of adaptive homeostatic mechanisms.

CAVEATS AND LIMITATIONS

The biochemical, cognitive and structural markers highlighted in the previous section do not have replicated sensitivity and specificity, which limits their clinical utility. The operationalization of staging, therefore, remains a challenge.

The staging model is at this point heuristic, and remains an exploratory framework. In contrast to staging in medical illnesses, where anatomic extent and impact of the disease determine stage, staging models in psychiatry remain largely based on a course-based definition of illness, using number of episodes and relapse criteria in defining stages[8]. A clear limitation of a course-based approach is that some individuals can have a benign course of illness with excellent inter-episode functioning despite multiple episodes, while others have a

seemingly malignant course from the outset[78]. Any staging model needs to account for the between-individual as well as the within-individual variability over time in people with bipolar disorder. Staging, therefore, is an aggregate construct.

The difficulties in defining boundaries between hypomania and mania, and between mood episodes in general, have been described as representing a challenge to the staging model[79,80], but could potentially be overcome with precise definitions and criteria. Furthermore, the question whether persons with hypomania and depression of varying severity fit into stages 1b or 2 needs further clarification.

Research exploring the staging model has been so far largely cross-sectional, while longitudinal prospective cohort studies are necessary. The moderating effects of personality and temperament, environmental influences such as societal networks and supports, and occupational and environmental resources, have not been adequately explored.

Furthermore, comorbid physical and psychiatric diseases are not currently incorporated in staging models, although they are drivers of outcome and an almost universal feature of most mental disorders. More detailed sub-staging of illness evolution could include the presence or absence of prominent comorbidities such as anxiety and substance abuse, psychosis and other phenotypes. Not only will this be appropriate to refine the relationship to neurobiological markers, but the descriptors of effective therapeutic strategies in those with and without these comorbidities remains to be better defined and is clearly an unmet need for the field.

IMPLICATIONS AND DIRECTIONS

There are a number of implications of the staging model. The presence of a demonstrable process of disease progression moving along a definable temporal trajectory suggests the presence of targets that could be amenable to intervention and a focus for health services and providers. The progressive evolution of clinical phenotypes implies that the best opportunity for effective treatment may be the earliest. The staging model therefore logically segues to that of early intervention and hence a transdiagnostic approach.

Intervention is theoretically possible at a public health level focusing on the general population through strategies operating on identified risks, as with smoking for heart disease and cancer prevention. For bipolar disorder, lifestyle, diet, exercise and well-being interventions, including meditation and mindfulness, could be employed at a public health level, taking into consideration that these would be of value across emerging clinical phenotypes and other non-communicable medical disorders[81]. Indicated prevention targeted to people identified as being at high risk is feasible, as is targeting the "at-risk" or ultra-high risk stage[82,83].

Some heterotypic prodromes are by definition non-specific, with inattention symptoms, substance use, mood lability, anxiety, depression, sleep symptoms and non-specific behavioural change documented[84-86], and these may require different interventions. Once a homotypic prodrome or syndrome occurs, with manic-like symptoms, especially when accompanied by added risk factors such as family history loading and psychosocial adversity in childhood, one is at extremely high risk for evolution to full-blown illness and other specified and unspecified bipolar and related disorders[87-89]. The morbidity and dysfunction accompanying other specified and unspecified bipolar and related disorders is considerable, and clearly deserves concerted therapeutic efforts.

An essential first step in preventing the progression of the disorder, therefore, is accurate and timely diagnosis. The diagnosis of bipolar disorder is complex, and the disorder is often initially misdiagnosed, since the diagnosis is predicated on the presence of mania, yet the index presentation is more commonly depression. Mania, and even more so hypomania, can be missed, as it is often not associated with subjective distress and easily misinterpreted or misattributed, for example, to substance abuse. Full-blown mania can present with psychosis and be difficult to distinguish from schizophrenia. The affective storm and extreme mood lability of borderline personality disorder is a frequent diagnostic confounder[90]. Another set of confounders accompany childhood onset bipolar disorder, a diagnosis which appears more common in the US than in many other countries, where the disorder is rarely seen before late adolescence or early adulthood[91]. The delay to first treatment is inversely associated with an earlier age of onset of bipolar disorder, and both early onset and treatment delay are independent predictors of a poor outcome in adult-hood.

There are very few clinical trials that use staging to stratify recruits. Conus et al[92] compared chlorpromazine and olanzapine in a first-episode mania cohort. They found that there was a shorter time to stabilization with the atypical agent, an interesting finding given that the extant literature generally shows atypical and typical agents to have broadly similar efficacy in mania[92]. More recently, a first-episode mania cohort stabilized on lithium plus quetiapine was randomized to one-year continuation with either agent alone[93]. Unlike head-to-head studies in non-stage stratified cohorts, where no major differences between these agents were seen[93], lithium was superior to quetiapine on most clinical measures. It remains uncertain whether this superiority of lithium over quetiapine reflects the effects of staging (i.e., treating early after the first episode), primary efficacy differences, or methodological factors. A few other studies have targeted the later stages of the disorder. Murray et al[94], for example, have developed online acceptance and commitment approaches to people with chronic stages of the disorder.

Early intervention promises to prevent or minimize the secondary consequences of recurrent episodes[95]. Kessing et al[96] documented that randomization to two years of comprehensive, expert, special clinic treatment after a first manic hospitalization not only led to fewer relapses than treatment as usual for the first two years, but its effect persisted and was

magnified over the next four years (even though all patients received treatment as usual during those years). This is important evidence that early high-quality intervention can change the trajectory and course of illness for the better in the intermediate term, if not indefinitely. Further, early intervention at first episode has been shown to reverse cognitive deficits and preserve grey matter volumes, especially in those that remain episode free[58,68]. Similar benefits of early intervention programs are documented in first-episode psychosis[97].

With multiple recurrences, relationship, employment and financial difficulties erode self-esteem, corrode supports and coping strategies, and lead to guilt and loss. These are powerful stressors that can further perpetuate and exacerbate the illness[55]. As the disorder typically begins in adolescence or early adulthood, it interrupts critical emotional, educational and psychosocial developmental goals and milestones, again acting as a secondary stressor. The earlier the illness begins, the poorer the outcomes in adulthood are[91].

Early intervention strategies should aim to minimize disruption to normal developmental trajectories. It is likely that multifaceted strategies will be required, ones that integrate effective psychopharmacology with stage-specific and evidence-based psychosocial interventions. New research is beginning to emphasize the value of cognitive remediation and vocational recovery for late stage illness[98]. Given the impact of the disorder on families, and the secondary consequences of family dysfunction, assisting with family and caregiver support is invaluable[99-101].

Staging models can also encourage help-seeking and improve access. A critical avenue is via service reform, especially the creation of early intervention services[102]. They can also provide further impetus to study the efficacy of potential primary and secondary preventive strategies where evidence is so far scant[103]. Education campaigns may help ill persons or those at risk to seek help in earlier stages, and service changes that welcome persons at earlier illness stages may lead more timely delivery of effective interventions.

There is a clear need to study which treatments actually work for the early stages. Delivering care for more persons at an earlier stage may lead to a better resolution for those who would otherwise be "pre-destined" to have an adverse illness course, and an amelioration of the course for those who would go on to develop later stages.

CONCLUSIONS

The staging model is supported by observations that, with some exceptions, the clinical course of untreated or poorly treated bipolar disorder evolves in a complex but progressive fashion. Poorer response to treatment (principally lithium) occurs in the later stages of illness, and preliminary biomarker data (primarily neuroimaging) supports stage-specific brain changes.

A fundamental proposition of the staging model is that early intervention is more effective and needs to be less complex than later intervention. Early intervention implies that optimal use of biological and psychosocial interventions in at-risk, prodromal, and first-episode phases of bipolar disorder could mitigate some of the clinical and neurobiological consequences of the illness. These include markers of neuroprogression such as brain volume loss and cognitive and physical impairment.

It is hoped that some effective therapies for preventing episodes might also be neuroprotective and reduce the physical burden and reduced life expectancy that accompanies bipolar disorder. Defining and validating the staging of bipolar disorder is part of ongoing research efforts to improve management of this all too often destructive illness.

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