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Stage managing bipolar disorder

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Abstract

Objectives—Clinical staging is widespread in medicine—it informs prognosis, clinical course and treatment, and assists individualized care. Staging places an individual on a probabilistic continuum of increasing potential disease severity, ranging from clinically at-risk or latency stage through first threshold episode of illness or recurrence and finally to late or end-stage disease. The aim of this paper was to examine and update the evidence regarding staging in bipolar disorder, and how this might inform targeted and individualized intervention approaches.

Methods—We provide a narrative review of the relevant information.

Results—In bipolar disorder, the validity of staging is informed by a range of findings that accompany illness progression, including neuroimaging data suggesting incremental volume loss, cognitive changes, and a declining likelihood of response to pharmacological and psychosocial treatments. Staging informs the adoption of a number of approaches, including the active promotion of both indicated prevention for at-risk individuals and early intervention strategies for

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newly diagnosed individuals, and the tailored implementation of treatments according to the stage of illness.

Conclusions—The nature of bipolar disorder implies the presence of an active process of neuroprogression that is considered at least partly mediated by inflammation, oxidative stress, apoptosis and changes in neurogenesis. It further supports the concept of neuroprotection, in that a diversity of agents have putative effects against these molecular targets. Clinically, staging suggests that the at-risk state or first episode is a period that requires particularly active and broad-based treatment, consistent with the hope that the temporal trajectory of the illness can be altered. Prompt treatment may be potentially neuroprotective and attenuate the neurostructural and neurocognitve changes that emerge with chronicity. Staging highlights the need for interventions at a service delivery level and implementing treatments at the earliest stage of illness possible.

Keywords

bipolar disorder; clinical staging; depression; early intervention; mania; neuroprogression; treatment

Introduction

In a range of medical specialities, including cardiology and oncology, clinical staging forms the basis of assessment, prognosis, and choice of therapies. In contrast, psychiatry has only recently begun to use staging as a construct to understand the onset, progression and outcome of psychiatric disorders. However, of late, there has been a substantial body of emerging data on this topic. The purpose of this paper is to examine and update the evidence regarding staging in bipolar disorder, and how this might inform targeted and individualized intervention approaches.

Staging is widely used in medicine, particularly for disorders such as cancer, heart and liver disease. According to this model, illnesses progress through identifiable phases that have specific features and consequently require tailored interventions. For example, in breast cancer, the *Tumour, Node, Metastasis (TNM)* staging model ties the clinical phenotype and extent of disease progression in three related domains; this is documented to refine diagnosis, tighten prognosis and assist in treatment selection. Staging in cancer highlights the imperative of early diagnosis and intervention, as survival may depend on the timely application of effective treatment. In medicine, clinical staging describes where an individual's presentation exists on a temporal spectrum of disorder progression. The models generally begin at stage 0 (defined as an at risk, or latency stage) through to stage IV, operationalized as late stage disease (1). There is acceptance that this concept reflects an aggregate picture, and that stepwise progression through serial phases may not be applicable to all patients with a particular disorder (Table 1).

Staging implies a number of potentially testable hypotheses, which have been largely validated in medicine, particular oncology and cardiology. The first is that the natural history of the disorder moves through a predictable temporal progression. Secondly, provision of timely and stage appropriate treatment can modify the individual's pattern of disease progression. Thirdly, prognosis is more favourable with earlier diagnosis and

treatment, and treatments used earlier have a more favourable risk-benefit ratio than those used later. Lastly, the effects of early intervention can alter the distribution of the stages in the population over time (1, 2).

The clinical stages define the extent of disease progression at any particular point in time as well as where a person currently lies along a continuum of the described course of an illness. A staging template refines clinical choice, assisting clinicians to choose treatments relevant to a particular stage of illness. For example, in the treatment of schizophrenia, clozapine is typically used in the later stages of treatment, while public health interventions or indicated prevention is adapted to the asymptomatic or at risk stages. Such interventions address potentially plastic risk factors for the genesis or progression of disorders (3). The model assumes that interventions will be simultaneously more effective and less harmful if delivered earlier in the treatment course.

An implicit aim of staging is to prevent progression to advanced stages of a disorder and facilitate regression to earlier and more benign stages. The hope, supported by evidence for example that lithium increases grey matter volume, is that appropriate therapy can both prevent neuroprogression, and have neuroprotective effects (4). It is thus necessary to understand the diverse and interacting genetic, environmental, social, biological, and psychological protective and risk factors that mediate or moderate the process of disease progression (2, 5, 6). These factors need to be understood in aggregate for a particular disorder, as well as for an individual person, in order to develop personalised approaches to care. Risk factors may vary in their impact on different stages; some may impact all stages, whereas others may be stage-specific. For example, sexual abuse may increase risk in a non-specific manner for the onset phase of diverse disorders, and operate across several or all stage transitions; with adherence and engagement potentially influencing risk of transition to later stages (7).

Clinical evidence supporting staging

Staging in psychiatry has a long history. A century ago, Kraepelin first suggested that psychiatric disorders had a staged progression, and his view of their progressive nature was reflected in his nomenclature of *dementia praecox*. In 1993, Fava and Kellner (8) described staging as a “neglected dimension in psychiatric classification”. Staging was subsequently operationalized around schizophrenia, and staging models have been adapted and proposed for bipolar disorder (2, 5, 9), unipolar depression (10, 11), eating disorders (12), and agoraphobia (13). However, in contrast to staging in medical illnesses where anatomic extent and impact of the disease determine stage, staging models in psychiatry have been based on a course-based definition of *phase* of illness, using duration and relapse criteria in defining stages (9).

In psychiatry, staging models described categories in a model compatible with medical staging models. These categories ranged from Stage 0 (describing an at-risk phase for a disorder without any clear symptoms), through Stages 1a and 1b (reflecting mild, non-specific and identifiable prodromal symptoms respectively), Stage 2 (defined as the first episode), Stages 3a, 3b, and 3c (defined as subthreshold, threshold, and persistent relapses

respectively), to Stage 4 (reflecting persisting unremitting symptoms that are potentially non-responsive to treatment) [for a review, see (1)]. There is a twist in this model for bipolar disorder, as according to the DSM system, one has to have a manic or hypomanic episode to be bipolar. Since depression usually is the index episode, there is a consequent mismatch between the model and the DSM classification of the disorder. It is therefore prudent that we allow index depression, under a unipolar rubric, to be added to the broader phenotype.

A number of clinical lines of evidence support the validity of staging. The first data showing that psychiatric disorders having a progressive and potentially deteriorating course were those of Kraepelin, who observed with each episode, that periods of wellness between relapses in bipolar disorder often become shorter and that each recurrence catalyses vulnerability to further illness. This finding that has been robustly replicated prompted the suggestion of a progressive underlying neuropathology, the nature of which has only recently begun to be elucidated.

The second key line of evidence are studies that show stage related differences in the efficacy of therapies at differing phases in the temporal course of bipolar disorder. Gelenberg et al. (14), Swann et al. (15), and Franchini et al. (16) have shown that the efficacy of lithium is consistently reduced with successive episodes. A similar pattern has been shown with atypical antipsychotics, where a study examined pooled data of 4,346 participants in twelve studies of an atypical antipsychotic in the treatment of bipolar disorder. Those at the earliest stages of illness consistently had a more favourable response to treatment on measures of mania, depression, overall global impression, and relapse (17). In the Systematic Treatment Enhancement Program for Bipolar Disorder database, number of episodes was robustly related to ratings of mania, depression, functioning and quality of life. In addition, the suggestion of possible efficacy of antidepressants in early stage illness was not seen in later stages (18).

A similar pattern is seen in studies of psychological treatments for bipolar disorder. While Lam et al. (19) suggested that cognitive behavioral therapy (CBT) is effective in preventing or delaying relapse independent of the number of previous episodes, other studies for example, the largest trial of CBT for bipolar disorder to date, Scott et al. (20), challenge this. Specifically this study revealed that psychological intervention was more effective in those in the early stages, between episodes 1–6, and that CBT led to higher relapse rates compared to treatment as usual amongst people who had more than 30 episodes. Similarly, Reinares et al. (21) and Colom (22) showed that those who had the smallest number of previous episodes had the greatest benefit from psychoeducation.

Neuroprogression

At the foundation of the staging model is the concept of neuroprogression, which has been demonstrated as a characteristic of numerous psychiatric disorder (21, 46). This has its origins in the work of Post and colleagues (11), who first coined the concept of neurosensitisation, and adapted the concept of *kindling* to apply to mood disorders in 1986. Early attempts to understand the underlying neurobiological mechanisms focussed on cortisone and the monoamines, but this has broadened considerably in recent years.

Neurogenesis, apoptosis, oxidative, mitochondrial, and inflammatory mechanisms are gaining traction as key components of the phenomena underlying the progression of psychiatric disorders including bipolar disorder, and the consequences including treatment non-responsiveness (23). These shared novel pathways may also go some way to explaining the effectiveness of medications as different as lithium, valproate and antipsychotic medications, which have all been found to influence neurotrophins, neurogenesis, apoptosis, inflammatory pathways and oxidative biology (24). These pathways will be discussed in more depth in succeeding sections of this paper.

Perhaps the most important neurobiological biomarker of staging is neuroimaging evidence of structural changes. In contrast to research in schizophrenia, which has shown that hippocampal volume loss and ventricular dilatation may occur prior to the first episode of schizophrenia, the data suggests, albeit with inconsistencies, that in bipolar disorder, gross brain structure is relatively preserved during its early phases (25). Paralleling this, progressive neuropsychological changes unfold during the course of the disorder (26), supporting the presence of neuroprogressive changes over time. Strakowski et al. (27) has shown that individuals with a first-episode of mania had ventricular size comparable to controls, whereas individuals with recurrent illness showed ventricular enlargement. With chronicity, progressive loss of grey matter thickness over time is also described (27, 28). There is however conflicting data, in that ‘ultra-high risk’ individuals prior to a threshold first-episode of mania had reductions in amygdala and insular volume (A. Bechdolf, personal communication). There may thus be both early differences that are neurodevelopmentally mediated (29), in addition to regionally specific neuroprogressive changes.

A consequence of the structural changes in bipolar disorder is the decline in cognitive functioning, which is a well-documented feature, and a major driver of secondary disability (30). Cognitive change may be related to the number of prior illness episodes (31, 32). López-Jaramillo et al. (26) compared cognitive functioning in first, second and third episode groups, and showed that people who have had a first- or second-episode displayed minimal cognitive differences from controls, whereas individuals with three or more episodes diverged on most measures of cognition compared to both early-episode patients with bipolar disorder and controls.

That multiple episodes can result in long term alterations in neuronal systems was first described by Goddard and adapted by Post in his kindling model (33). With the progression of illness, it was thought that there is a failure of endogenous compensatory mechanisms (10). McEwan’s concept of allostatic load hypothesis similarly captures a progressive “wear and tear” process, in which life stressors and genetic load, interact with aggravating factors such as substance abuse (34), setting up a vicious cycle capable of aggravating the core neuropathology of the disorder, which can further disrupt the brain circuits that are responsible for mood regulation and cognition, which further increases vulnerability to illness. The operative elements of this biochemical process of neuroprogresssion include the dopaminergic system, oxidative stress, inflammatory cytokines, endoplasmic reticulum stress, mitochondrial dysfunction and neurotrophins including brain-derived neurotrophic factor (BDNF) (10, 35, 36).

Elevated levels of cytokines are one of the best established biomarkers of both depression and mania (36). Kauer-Sant'Anna et al. (37) first described stage related changes in cytokines, noting specifically that the pro-inflammatory cytokines IL6 and TNFα were elevated in both early and late stage disorder, while the anti-inflammatory cytokine IL10 was increased in the early stage, but not the late stage of the disorder. Conversely, TNFα, was higher in the later stages. Similar stage dependant changes in oxidative biology have been found at later stages of the illness such that in individuals with bipolar disorder compared to those in the early stages and controls, the activity of glutathione reductase, and glutathione transferase, which are key enzymes in the glutathione pathway, are increased (38). Further, neurotrophins such as BDNF, which play a key role in neuronal survival and proliferation, also show stage dependant changes, and while maintaining normal levels in the early stages of the disorder, measurably decrease in its later stages (37, 39). These stage related changes in the neurotrophins, oxidative and inflammatory system may be due to either failure of adaptive homeostatic mechanisms as part of neuroprogression, or progression of the primary underlying disease process.

Methodological caveats

A number of methodological caveats are necessary in interpreting the data. The concept of staging is heuristic, and is an exploratory framework. Almost all studies are cross sectional in nature, and prospective studies that follow cohorts over time are necessary to definitively confirm the results of the cross sectional findings. Importantly, individuals' illness trajectories can vary widely, with some people having a good or poor outcome at the onset of disorder; some individuals only having a single episode of illness, and others manifesting a malignant pattern from the outset. A challenge confronted by the staging model is the necessity to account for the inter- as well as intra-individual variability in functional outcomes in individuals with bipolar disorder. Many individuals with substantial illness burden continue to function at a high level as well as the converse. There are important moderator effects of temperament, social networks and support and occupational complexity and environmental resources. There is a risk of tautology, inasmuch as those people belong to either pattern might cluster in different stages of the model. It is therefore unclear to what extent this influences classification, and to what extent true illness progression accounts for in the model, as both are likely to be simultaneously operative. While we do have intriguing biomarker data suggesting stage related changes, this is not yet of a nature that allows an analogue of the TNM model to be developed.

Substantive clinical heterogeneity exists; biomarker and neuroimaging structural changes may vary for different individuals with similar clinical histories, and individuals who have experienced the same number of illness episodes may have different clinical presentations and different levels of functioning. The role of comorbid illness in the staging model is not defined, but is a feature of most mental illness.

Clinical implications of staging

If the thesis holds that there is plastic process of disease progression, and that this is amenable to intervention, then the best opportunity for effective treatment may be that of

early intervention. For this to occur, the first necessary step is accurate diagnosis. Intervention may be theoretically possible as early as in the ultra-high risk stage, and criteria to identify such individuals have been validated (40, 41). Bipolar disorder is however often initially misdiagnosed, largely because the index presentation is that of depression, and the prodrome is even more non-specific, with anxiety, substance use, mood lability, sleep change and diffuse behavioral change typical; in contrast, mania, which usually occurs some years later, is required for diagnosis (42, 43). Mania, which can be ego-syntonic, or can present with psychosis, is consequently not always easy to diagnose (44). As a result, 69% of people with bipolar disorder are misdiagnosed at least once (9), and there is a delay over 12 years between initial onset of symptoms and commencement of treatment (10).

Early intervention has the potential to prevent or minimise the secondary morbidity that arises because of progressive episodes (45). A clinical course marked by multiple episodes is associated with consequent employment and financial difficulties, a deleterious impact on relationships, and the development of self-esteem issues, guilt and loss, which serves as a secondary stressor, perpetuating illness (20). As a disorder with an onset in adolescence or early adulthood, it occurs during a normative and critical phase in an individual's emotional, educational and psychosocial development. One of the goals of age- and stage-dependant intervention is to minimise disruption to a person's normal developmental trajectory. This can be achieved through an integrated approach combining effective psychopharmacology and evidence-based psychosocial interventions, including CBT, social rhythm based approaches, psychoeducation, medication adherence, relapse prevention, social and vocational recovery, and assisting with family and caregiver adaptation to the disorder (46-48).

Conclusions

Concordant with established use in medicine, and following initiatives in psychosis research, staging models are now of value on the basis of the clinical trajectory of bipolar disorder, differences in response to therapies and biomarkers including neuroimaging, cognition and biochemistry. Staging suggests that interventions may have differential utility at different phases of the disorder, and that treatments should be tailored, amongst other factors, to the phase of the disorder. This paradigm is inherently optimistic. It suggests deployment of appropriate biological and psychosocial interventions in the early phases of bipolar disorder as they could prevent the secondary consequences of the illness, including neuroprogression and secondary morbidity, and might have neuroprotective potential, as well as the promise of preventing or reducing stage progression. This is predicated on timely and accurate diagnosis, and highlights the importance of service initiatives to allow implementation of these goals.

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Table 1

A potential clinical staging model for bipolar disorder[a]

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder (e.g., family history, abuse, substance use) No specific current symptoms	Mental health literacy Self-help
1a	Mild or non-specific symptoms of mood disorder	Formal mental health literacy Family psychoeducation Substance abuse reduction Cognitive behavioral therapy, supportive counseling
1b	Prodromal features: ultra-high risk	*1a* plus therapy for episode: phase specific or mood stabilizer
2	First episode threshold mood disorder	*1b* and case management, vocational rehabilitation, specific psychotherapy
3a	Recurrence of sub-threshold mood symptoms	*2* and emphasis on maintenance medication and psychosocial strategies for full remission
3b	First threshold relapse	*2a* and relapse prevention strategies
3c	Multiple relapses	*3b* and combination mood stabilizers
4	Persistent unremitting illness	*3c* and clozapine and other tertiary therapies, social participation despite disability

[a] Adapted with permission from McGorry et al. 2006 (1).